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Hypertension and Electrolyte Disorders in Patients with COVID-19

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The worldwide coronavirus disease 2019 (COVID-19) pandemic is still in progress, but much remains unknown about the disease. In this article, we review the association of hypertension or the renin-angiotensin system (RAS) with COVID-19 and the correlation between electrolyte disorders and disease severity. Underlying hypertension is likely to be associated with severe or critical COVID-19, but the relationship is not clear owing to confounding factors. Angiotensin-converting enzyme 2 (ACE2) plays an important role in the non-classical RAS pathway and binds to a receptor binding domain of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The RAS blockade is known to increase ACE2 levels, but controversy remains regarding the effect of RAS blockade therapy in the course of COVID-19. Some reports have indicated a protective effect of RAS blockade on COVID-19, whereas others have reported an association of RAS blockade therapy with the occurrence of severe complications such as acute kidney injury and admission to the intensive care unit. Electrolyte disorders are not uncommon in patients with COVID-19, and severe COVID-19 has frequently shown hypokalemia, hyponatremia, and hypocalcemia. Electrolyte imbalances are caused by alteration of RAS, gastrointestinal loss, effects of proinflammatory cytokines, and renal tubular dysfunction by the invasion of SARS-CoV-2.

Key Words: Angiotensin-converting enzyme 2, COVID-19, Electrolyte, Hypertension, Hypocalcemia, Hypokalemia, Hyponatremia, Renin-Angiotensin system

INTRODUCTION

As the worldwide coronavirus disease 2019 (COVID-19) pandemic continues, morbidity and mortality have increased[1,2]. The pathogen responsible for COVID-19, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a novel coronavirus belonging to the betacoronavirus genus and causes severe pneumonia in humans[2,3]. There have been many studies to research SARS-CoV-2 around the world, and new information about this virus is continuously being updated.

Comorbid diseases such as diabetes and cardiovascular disease are known to increase the severity of COVID-19[1,4]. Hypertension has also been reported to be associated with severe or critical disease in several studies[5-7]. It is presumed that the relationship between hypertension and severity of COVID-19 is related to angiotensin-converting enzyme 2 (ACE2)[7]. The spike protein of SARS-CoV-2 binds to ACE2 and causes depletion and downregulation of ACE2[8].

Early epidemiological studies reported that electrolyte disorders are not uncommon in patients with COVID-19[9,10]. Subsequent studies indicated that electrolyte imbalances were associated with more severe COVID-19[11-13]. However, an individual study has limitations in interpretation owing to small sample sizes and ethnic differences. In the current study, we reviewed the latest information of COVID-19 to evaluate the association of hypertension or the renin-angiotensin system (RAS) with COVID-19 and the correla-

tion between electrolyte disorders and disease severity of COVID-19.

Pathophysiology of COVID-19

The entry of SARS-CoV-2 into target cells is facilitated by ACE2. Transmembrane ACE2 plays a role as an entry receptor by binding to the receptor binding domain of the virus's spike protein, thus allowing virus entry[14]. In addition, transmembrane protease serine subtype 2 (TMPRSS2) activates the spike protein to facilitate binding with ACE2, increasing virus invasion[8]. ACE2 is a new isoform of ACE discovered in 2000[15] and has a crucial role in the non-classical RAS pathway, ACE2/angiotensin (Ang)-(1-7)/Mas receptor axis, which counteracts the classical RAS pathway. ACE2 is not directly inhibited by conventional RAS inhibitors, such as ACE inhibitors (ACE-I) or angiotensin receptor blockers (ARB)[16]. The binding affinity of SARS-CoV-2 has been identified 10 to 20 times higher than SARS-CoV[17]. Therefore, ACE2 would play a more important role on infectivity in COVID-19. ACE2 is highly expressed on the colon, gall bladder, heart, kidney, and lung; therefore, these organs can be vulnerable to SARS-CoV-2 infection18). Serine protease, TMPRSS2, is highly expressed in epithelial cells in the prostate, colon, small intestine, kidney, and lung, and it is known to be upregulated by androgen[8]. ACE2 and TMPRSS2 coexpressed cells such as type 2 lung pneumocytes and ileal absorptive enterocytes are primary targets for virus invasion[8].

Pathophysiological mechanisms of virus-induced multiorgan dysfunction have been identified as follows: (1) direct cytotoxicity of virus; (2) altered regulation of RAS by depletion and downregulation of ACE2; (3) endothelial cell injury, apoptosis, and thromboinflammation; and (4) dysregulation of immune response such as over-release of proinflammatory cytokines that cause cytokine storm[14].

Relationship between blood pressure and COVID-19

Early epidemiological studies reported that hypertension is common in patients with COVID-19 and is associated with disease severity[5,6]. Of 1,099 patients with COVID-19 in China, hypertension was prevalent in nonsurvivors and severe COVID-19 patients (survivor vs nonsurvivor, 13.7% vs 35.8%; mild to moderate disease vs severe disease, 13.4% vs 23.7%)[9]. A meta-analysis of 2,552 Chinese patients with COVID-19 also reported that hypertension was associated with increased severity (odds ratio [OR], 2.49; 95% confidence interval [CI], 1.98-3.12) and mortality (OR, 2.42; 95% CI, 1.51-3.90)[19]. However, this evidence is still insufficient, mainly because of the retrospective design of the study and the presence of other comorbidities. Son et al. analyzed Korean population-based data and reported that the overall mortality rate of COVID-19 was 2.3% and that the mortality rate increased to 4.0% in COVID-19 patients with hypertension[20]. However, when comparing patients with hypertension who test negative for COVID-19, the mortality rate was not different between the 2 groups (hypertension with COVID 19 vs without COVID-19, 4.0% vs 3.9%; p=0.84)[20]. Patients with hypertension are usually older and often experience other comorbidities such as diabetes, cardiovascular disease, and obesity, which are also risk factors for disease severity in COVID-19[1,4,21,22]. Therefore, it is difficult to interpret the independent effect of hypertension on severity of COVID-19. For these reasons, the Centers for Disease Control and Prevention (CDC) has not defined hypertension as a risk factor for severe COVID-19[23]. However, despite these limitations, many studies have reported and emphasized the impact of hypertension on COVID-19, and many researchers are still interested in the relationship between hypertension and COVID-19 because blood pressure could be changed after the modulation of ACE2 by SARS-CoV-2.

ACE2 and the RAS pathway

The RAS has a crucial role in maintaining blood pressure and electrolyte balance. There are 2 RAS pathways that counteract each other. In the classical RAS pathway, Ang I is converted to Ang II by ACE, which is expressed on the endothelial cells in the lung, kidney, heart, and brain[16]. Ang II activates Ang II type 1 receptor (AT1R), and AT1R induces several detrimental effects to the body, including vasoconstriction, inflammation, and fibrosis[16]. On the other hand, in the non-classical RAS pathway, ACE2 converts Ang I to Ang-(1-9) and Ang II to Ang-(1-7). Ang-(1-7) activates G pro-

tein-coupled receptor Mas and Mas receptor counteracts the detrimental effects of classical RAS pathway by induction of vasorelaxation, cardioprotection, anti-inflammation, and anti-oxidative action, especially in pathological conditions[24-27]. ACE and ACE2 have principal roles in the RAS pathway by balancing both RAS pathways. In the experimental model, ACE2-deficient mice developed acute lung injury and acute respiratory distress syndrome (ARDS), and recombinant ACE2 protected mice from severe acute lung injury[28]. It has also been reported that Ang II level is elevated in patients with acute lung injury[29], and that the elevated level of Ang II is associated with the severity of infection[30].

ACE2 acts as a receptor for the entry of SARS-CoV-2 into host cells through the process of endocytosis[16]. If SARS-CoV-2 invades the host cells and the immune system fails to defeat it, the virus reproduces rapidly and occupies ACE2 downregulating the production of functional ACE[28]. This induces upregulation of the classical RAS pathway and accelerates lung injury, inflammatory cytokine release, and systemic inflammation[8].

Relationship between RAS blockade and COVID-19

There has been an emerging concern regarding the effect of ACE-Is and ARBs on the severity of COVID-19. ACE-Is and ARBs cannot directly affect the activity of ACE2, but they are known to increase the expression and activity of ACE2 by blocking the classical RAS pathway[31,32]. If a patient with increased ACE2 expression by RAS blockade therapy is infected with SARS-CoV2, there are 2 possibilities in terms of the progression of the infection. First, increased ACE2 expression at the baseline would increase virus entry and infectivity, causing harmful effects. Second, activation of the non-classical RAS pathway and reduced action of the classical RAS pathway by increased ACE2 can cause beneficial effects on acute lung injury and systemic inflammation[33]. Several retrospective studies have analyzed which of these 2 effects of RAS blockade would be dominant in patients with COVID-19.

Despite a number of studies, there are still no consistent conclusions regarding the effects of RAS blockade therapy. In an early Chinese single-center, retrospective study, the authors reported a positive impact of RAS blockade therapy in COVID-19[34]. The study allocated patients with hypertension and COVID-19 into 2 groups according to the use of ACE-I or ARB and compared the disease severity and mortality between the groups. There were 43 patients in the ACE-I or ARB group and 83 patients in the non-ACE-I or ARB group. RAS blockade users showed significantly lower baseline high sensitivity C-reactive protein and procalcitonin levels (p=0.049 and p=0.038, respectively). Furthermore, the proportion of critically ill patients was lower in tendency (9.3% vs 22.9%; p=0.061).

However, most studies could not find any association between RAS blockade therapy and severe outcomes of COVID-19. A case-control study in Italy compared 6,272 COVID-19 patients with an age- and sex-matched general population[35]. After adjusting for medications and comorbid diseases, ACE-I or ARB therapy had a neutral impact on disease severity and mortality (all p>0.05). In a study from New York, propensity-score matched groups were compared, and none of the antihypertensive medications, including ACE-Is and ARBs, were found to be associated with COVID-19 severity[36]. Guo et al. performed a meta-analysis to evaluate the association between ACE-I or ARB therapy and mortality in COVID-19[37]. A total of 3,936 hypertensive patients with COVID-19 were included from 9 studies. In this study, ACE-I or ARB therapy was not associated with disease severity compared with nonmedication of ACE-I or ARB (OR, 0.71; 95% CI, 0.46-1.08). In another meta-analysis, 10,014 patients with COVID-19 were included from 13 studies. ACE-I or ARB therapy was not associated with disease severity (OR, 0.88; 95% CI, 0.60-1.31) or all-cause mortality (OR, 0.95; 95% CI, 0.57-1.58)[38].

On the other hand, other studies have reported a negative impact of RAS blockade therapy. In a retrospective cohort study from France, 116 hospitalized COVID-19 patients who were admitted to the intensive care unit (ICU) or died in the hospital were analyzed[39]. After adjustment for age, sex, comorbid heart disease, and other antihypertensive medications, the risk of ICU admission or death was higher in the ACE-I or ARB therapy group than in the non-use group (OR, 1.73; 95% CI, 1.02-2.93). Another study in France also reported a negative impact of ACE-I or ARB use in patients with severe COVID-19[40]. In this study, 149 patients hos-

pitalized with COVID-19 were divided into an ACE-I or ARB group (n=44) and a no ACE-I or ARB group (n=105). ACE-I or ARB use independently increased the risk of acute kidney injury (OR, 3.28; 95% CI, 2.17-4.94), which is an independent risk factor for increased mortality in COVID-19[41,42].

A nationwide Korean population-based cohort study analyzed 1,954 hospitalized patients with COVID-19[43]. Among them, 377 patients used ACE-I or ARB, and those patients demonstrated a 3-fold higher in-hospital mortality rate (9% vs 3%; p<0.001). In addition, acute cardiac events such as cardiac arrest and acute heart failure were more frequent compared with nonusers (cardiac arrest: 2% vs 1%; p=0.01; acute heart failure: 10% vs 6%; p=0.02). We also analyzed 130 patients with severe COVID-19 in a retrospective cohort study[44]. The patients who received ACE-I or ARB showed an increased risk of both in-hospital mortality and severe complications such as ARDS and acute kidney injury. In particular, among the patients with ACE-I or ARB therapy, high equivalent doses of ACE-I or ARB was associated with higher in-hospital mortality.

In summary, it is still difficult to reach a definite conclusion regarding the effect of RAS blockade therapy in patients with COVID-19. All published data are from retrospective studies and have a limitation associated with the study design. The results may vary depending on whether the data were surveyed from epidemiological studies or extracted from the medical records. The different effects of RAS blockade among the various studies might also be attributable to ethnic differences in ACE2 expression. East Asian populations express higher ACE2 in tissues than other populations[45]. RAS blockade might induce ACE2 upregulation more prominently, affecting the prognosis of COVID-19 in Asian patients. There are several ongoing randomized controlled trials to identify the effects of ACE-I or ARB in patients with COVID-19 (NCT04338009, NCT04312009, and NCT04311177). The results from these prospective studies will help to conclude the effects of RAS blockade therapy.

Relationship between Electrolyte and COVID-19

Many studies have reported that electrolyte disorders accompany COVID-19[9,10]. Lippi et al. conducted a meta-analysis to identify the association between electrolyte imbalances and the severity of COVID-19. They reported that hypokalemia, hyponatremia, and hypocalcemia were associated with severe COVID-19[46]. There are several causes of electrolyte disorders in patients with COVID-19. The first is altered RAS activation by downregulated ACE2. In the process of virus entry and replication, ACE2 is depleted and downregulated[8]. This causes a loss of antagonizing function of ACE2 against the classical RAS pathway and shifts the RAS balance toward the ACE/Ang II pathway[33]. Ang II activates AT1R, and AT1R induces renal sodium and water reabsorption. In addition, increased aldosterone causes increased urinary potassium excretion[16,47]. Second, SARS-CoV-2 can invade renal tubular cells directly, thus causing tubular dysfunction. Proximal convoluted tubular epithelial cells and podocytes are known to coexpress ACE2 and TMPRSS2. Therefore, these cells are susceptible to virus invasion[48]. Virus particles were also identified in proximal tubules and podocytes of kidney by transmission electron microscope[49]. Third, gastrointestinal infection also contributes electrolyte imbalance. In early epidemiological studies, only 3% of COVID-19 patients had gastrointestinal symptoms[50]. However, recent studies have reported more common gastrointestinal manifestations among infected patients (9-11%)[51,52]. As gastrointestinal tract cells have a high expression of ACE2 and mutation of the virus occurred during the replication process, these may increase gastrointestinal infection and cause electrolyte disorders[52]. These mechanisms act in combination, resulting in various electrolyte disorders.

Hypokalemia

Hypokalemia in COVID-19 is mainly caused by increased aldosterone concentration, which consequently induces an increased loss of potassium from urine[46,53]. In an early epidemiology study from China, hypokalemia ($\leq$3.5 mmol/L) was present in 54% (95 of 175) of COVID-19 patients on admission[11]. In particular, 18% (31 of 175) of patients had severe hypokalemia (<3 mmol/L) and had worse inflammatory indexes such as increased lactate dehydrogenase, C-reactive protein, and creatine kinase. The proportion of severe hypokalemia was higher in severely or critically ill patients than in mildly or moderately ill patients. Of interest,

mildly ill COVID-19 patients with hypokalemia achieved normokalemia within 5 to 8 days of potassium replacement, whereas correcting the potassium level in severely ill patients with hypokalemia was more difficult and required 10 to 14 days to achieve steady normokalemia[11]. This suggests that in severe COVID-19, activation of the classical RAS pathway increases the aldosterone level and that disease severity would be related to the degree of response to potassium replacement in hypokalemia.

The heart is also an organ vulnerable to SARS-CoV-2 invasion because of its high expression of ACE2[18]. Hypokalemia can trigger ventricular arrhythmia, which is a potentially life-threatening condition[11,54]. The incidence of ventricular fibrillation is known to be 5-fold higher in patients with hypokalemia than those with hyperkalemia[55]. In hospitalized patients with COVID-19, it has been reported that ventricular fibrillation or ventricular tachycardia occurred in 8 out of 761 patients (1.1%)[56]. Taking these risks into account, potassium levels should be maintained above 4 mmol/L in COVID-19 patients with hypokalemia[11,57].

Hyponatremia

Hyponatremia is the most common electrolyte disorder among patients with COVID-19 and is mainly caused by syndrome of inappropriate secretion of antidiuretic hormone (SIADH)[58,59]. Several lung pathologies such as ARDS, pneumonia, and pulmonary malignancy are well-known disorders that can cause SIADH[60]. Increased proinflammatory cytokine release such as interleukin (IL)-6 induces antidiuretic hormone (ADH) production by direct stimulation (non-osmotic ADH release). Indirect stimulation of IL-6 is mediated by an injury to the alveolar basement membrane, resulting in activation of hypoxic pulmonary vasoconstriction pathway that lead ADH release[61]. Hyponatremia caused by diarrhea in COVID-19 patients without respiratory symptoms has also been reported, and therefore gastrointestinal sodium loss should also be considered[62]. An Italian study evaluated the clinical impact of hyponatremia in COVID-19[12]. Hyponatremia was associated with more severe outcomes such as ICU admission or death, and serum sodium concentration demonstrated an inverse correlation with IL-6. In addition, when tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, was administered in patients with hyponatremia, the serum sodium concentration was increased after 48 hours. This also supports the correlation between hyponatremia and IL-6 in patients with severe COVID-19.

Hypocalcemia

Calcium ions (Ca^{2+}) play a crucial role in membrane fusion and the entrance of virus[63-67]. Several studies have reported that hypocalcemia is an independent risk factor for severe disease and long-term hospitalization in patients with COVID-19[13,65,68]. Previous studies have presented several explanations about the correlation between hypocalcemia and disease severity. First, a lower calcium concentration might reflect a higher viral load and lead to a prolonged period of virus shedding[65]. Second, serum calcium concentration is related to lung function and defense capacity against pathogenic microorganisms. Therefore, hypocalcemia may cause delayed recovery from pulmonary infection[65,69,70]. Third, hypocalcemia may be related to malnutrition. Chronic malnutrition causes vitamin D deficiency, which can lead to hypocalcemia, and therefore hypocalcemia patients would be vulnerable to infection[71].

Interestingly, dihydropyridine calcium channel blockers (CCBs) (nifedipine and amlodipine) improved mortality and also decreased risks for intubation and mechanical ventilation in a small retrospective study of 65 patients with COVID-19[72]. Similarly, in an experimental study, amlodipine, felodipine, and nifedipine also limited the growth of SARS-CoV-2 in the epithelial cells of the kidney (Vero E6) and lung (Calu-3)[73]. Future research is needed on the potential of CCBs to mitigate COVID-19.

CONCLUSION

Comorbid hypertension may be a risk factor for severe COVID-19, but the relationship cannot be clearly confirmed owing to limitations of the retrospective study design and various confounders. Although ACE2 plays an important role in COVID-19, the effects of RAS blockade therapy on COVID-19 remain uncertain. Patients who have been taking ACE-I or ARB are recommended to continue medication un-

less there is a definite reason for withdrawal. Electrolyte disorders such as hypokalemia, hyponatremia, and hypocalcemia are frequent in patients with COVID-19, particularly in patients with severe COVID-19. Electrolyte imbalances occur as a result of the alteration of the RAS pathway, gastrointestinal loss, effects of proinflammatory cytokines, and renal tubular dysfunction caused by direct renal invasion.

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