Review

A Review on the Possible Pathophysiology of Potassium Abnormalities in COVID-19

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Coronavirus disease 2019 (COVID-19) is a catastrophic contagious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Electrolyte disturbances are common complications of COVID-19. The present article examined the potential mechanisms of hypokalemia and hyperkalemia in patients suffering from COVID-19, in order to raise awareness of potassium disorders in SARS-CoV-2 infections. PubMed, Scopus, and Google Scholar were searched with keywords, such as "COVID-19", "SARS-CoV-2", "2019-nCoV", "Hypokalemia", "Hyperkalemia", "Serum potassium", and "Etiology", "Pathophysiology" up to April 20, 2021 without any search filters. We included articles that proposed potential mechanisms for potassium abnormalities in COVID-19 patients. Furthermore, we used backward and forward citation searching. Potassium abnormalities are considered to be important electrolyte disturbances, with reported incidences ranging from < 5% to > 50% in patients affected by SARS-CoV-2. Therefore, understanding the etiologies of potassium abnormalities could help to improve disease outcome. Utilization of ACE2 by SARS-CoV-2 in the renal cells, viral-induced tubular injury, and gastrointestinal abnormalities, such as anorexia, diarrhea, and vomiting may predispose COVID-19 patients to developing hypokalemia. Furthermore, depleted magnesium levels make hypokalemia refractory to treatments. In addition, hyperkalemia may occur because of reduced urinary output, as a consequence of renal failure. Changes in blood pH and medication-induced side-effects are other possible reasons for the deviation of potassium levels from the normal range. The etiology of potassium abnormalities in COVID-19 patients is multifactorial. Therefore, the early detection and management of potassium disorders is vital and would improve the outcome of patients with COVID-19.

Keywords. hypokalemia, hyperkalemia, physiopathology, etiology, COVID-19, SARS-CoV-2

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INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is responsible for the coronavirus disease 2019 (COVID-19) pandemic, was first detected via its substantial pulmonary symptoms in Wuhan (China) in late December 2019.[1] The infection continued to spread rapidly and remains a serious threat to global health.[2] In addition to respiratory symptoms, such as cough and dyspnea, other clinical manifestations involving

multiple organs have also been reported.[3] Since the start of the pandemic, it has been shown that individuals with underlying health conditions, such as diabetes, cancers, cardiovascular diseases, and kidney disorders are at higher risk of being infected or having severe outcomes.[4] The deviation of laboratory parameters from the normal range is among the factors which could predispose COVID-19 patients to having a poor prognosis.[5] Potassium disorders in COVID-19 patients are common. The incidence of hypokalemia and hyperkalemia have been reported in 20.9 to 55% and 2.3 to 10.3% of patients with COVID-19, respectively.[6-12] In addition, both low and high potassium levels can influence the prognosis of COVID-19 patients and make them more susceptible to developing unfavorable outcomes, including death.[6, 7, 9, 13] Therefore, special attention must be paid to understanding the possible etiologies of potassium abnormalities, which could help clinicians to manage this disease more effectively. In this review, we aimed to explain the pathophysiology of hypokalemia and hyperkalemia in patients affected by SARS-CoV-2.

MATERIALS AND METHODS

Electronic databases, including PubMed and Scopus, as well as the Google Scholar search engine, were searched using the keywords "COVID-19", "SARS-CoV-2", "2019-nCoV", "Coronavirus disease 2019", "Severe acute respiratory syndrome coronavirus 2", "2019 novel coronavirus", "Hypokalemia", "Hyperkalemia", "Potassium disorders", "Serum potassium", "Etiology", "Pathophysiology", "Kidney", "Gastrointestinal", "Acid-base", and "Drugs" up to April 20, 2021. No search filters were used for language, time period, or article type. All articles that proposed potential mechanisms for potassium abnormalities in patients with COVID-19 were included. Backward and forward citation searching was also performed, in order to include all relevant articles.

KIDNEY DISORDERS

Serum potassium homeostasis is mostly regulated by the renal system.[14] Nearly all of the potassium filtered by the glomerulus is reabsorbed through the proximal tubule and the ascending limb of the loop of Henle.[14] In order to maintain a steady serum potassium level, approximately 90% of the daily potassium intake is excreted in the urine, mainly along the distal tubules and cortical collecting duct (CCT).[14] The remaining 10% is lost in the stool and a very small amount in sweat.[14] Therefore, any conditions which impair kidney function will also disrupt the potassium balance.

In the case of COVID-19, patients may undergo varying degrees of renal functional impairment, mainly because of interstitial and tubular involvement, which is characterized by hematuria, proteinuria, as well as elevated serum creatinine and blood urea nitrogen.[15, 16] Angiotensin-converting enzyme 2 (ACE2), which serves as a receptor for SARS-CoV-2, is expressed much more in the kidneys than in the lungs, with about four-times the number in the renal proximal tubule cells as are found in the type II pneumocytes.[17] Moreover, viral nucleic acid has been detected in the urine of infected patients, reflecting the high vulnerability of the renal system to the SARS-CoV-2 infection.[18]

Hypokalemia and ACE2 Utilization

As discussed earlier, hypokalemia is a common disorder in patients infected with SARS-CoV-2. Elevated urinary potassium excretion has been reported as the most common cause of hypokalemia among COVID-19 patients.[6, 9, 11, 19] The renin-angiotensin-aldosterone system (RAAS) is a hormone system responsible for regulating blood pressure, fluid maintenance, and electrolyte homeostasis.[20] In this system, angiotensin-converting enzyme (ACE) transforms angiotensin I into angiotensin II, which is then capable of stimulating aldosterone release.[20] Aldosterone enhances urinary potassium excretion. In an opposite axis, the ACE2 inhibits ACE functioning. [21] In the case of coronavirus binding with ACE2, for cell entry, it has been shown that ACE2 would be downregulated.[22] Once the activity of ACE2 has been reduced, ACE becomes over-activated which leads to the generation of more Angiotensin II.[23, 24] Therefore, following SARS-CoV-2 cell entry, aldosterone is produced in high quantities, which promotes potassium wasting via the urine.[25] The majority of studies have considered the downregulation of ACE2 following SARS-CoV-2 cell entry and the subsequent increase in aldosterone release as the most likely reason for urinary potassium loss.[6, 9, 19, 26]

Hypokalemia and Tubular Damage

A number of studies have reported an increased

loss of potassium via the urine, without any evidence of hyperaldosteronism in patients with COVID-19.[27, 28] Mabillard *et al.* reported the case of a COVID-19 patient developing hypokalemia during hospitalization.[27] Particularly interesting was the fact that the patient had not received any medication to interfere with her potassium hemostasis and had shown no evidence of renal potassium wasting due to an underlying disease.[27] Furthermore, her hypokalemia could not have been due to hyperactivity of the RAAS, because her serum aldosterone levels were not elevated.[27] Therefore, the most likely cause of hypokalemia would be a virus-mediated injury of the tubular epithelium, although that could not be proven in this case.[27] Moreover, renal proximal tubular injury, also known as Fanconi syndrome, is common in COVID-19 cases.[29] Fanconi syndrome is characterized by inadequate reabsorption in the proximal renal tubules, resulting in the wasting of phosphate, amino acids, glucose, and bicarbonate in the urine.[30] Hypokalemia is usually mild to moderate in Fanconi syndrome and it may be caused by bicarbonaturia, which would increase potassium loss in the urine.[30] Kormann *et al.* reported that 30 of their 40 COVID-19 patients developed Fanconi syndrome during their study.[29] Finally, obvious proximal tubular injuries have also been observed during the autopsies of infected patients, which support the hypothesized increase in the urinary excretion of potassium due to tubular damage in hypokalemic patients.[31, 32]

Hyperkalemia and Renal Failure

Recent reports have found acute kidney injury (AKI) to be prevalent among patients suffering from COVID-19 and to also be associated with adverse outcomes.[33, 34] A pooled analysis of 22 studies estimated the incidence of AKI to be 11% (95% CI: 7.4 to 15.1%).[33] It is important to note that one of the most concerning manifestation of AKI is hyperkalemia.[35] In line with this, a case study reported the mean serum potassium levels of nine COVID-19 patients with AKI to be 5.6 ± 0.7 mmol/L, which was much higher than the reference value (3.5 to 5 mmol/L).[36] Furthermore, AKI is defined by rising serum creatinine concentrations or a reduction in urine output.[30] Most recent studies have shown that COVID-19 patients who had higher serum creatinine also tended to have significantly greater serum potassium levels.[15, 37] In addition, decreased urine output could also increase potassium levels in the context of AKI, since it diminishes sodium and water delivery to the ENaC in the distal tubules.[30] In a study of 3,993 SARS-CoV-2 patients, potassium levels were significantly higher in patients who developed AKI, compared with those who did not ($P < .001$).[38] Mohamed *et al.* estimated the incidence of hyperkalemia to be up to 23% in COVID-19 patents with AKI.[39] Moreover, the catabolic state and rhabdomyolysis, which results in tissue breakdown and subsequent cellular potassium release, may occur in 7 to 20% of COVID-19 patients with AKI.[39, 40]

Patients with a history of chronic kidney disease (CKD) are among those most susceptible to SARS-CoV-2.[41] Developing hyperkalemia in these patients, as a consequence of an impaired glomerular filtration rate, has been a constant concern for clinicians.[42] Moreover, the risk of elevated potassium levels in patients requiring maintenance hemodialysis must also be considered during the pandemic, due to a reduction in hemodialysis times, because of concern about viral exposure in clinical settings. A study conducted at the hemodialysis center of Wuhan found that the main reasons of death among patients with confirmed COVID-19 were cardiovascular and cerebrovascular complications, rather than pneumonia.[43] These deaths were thought to be a result of complications associated with hyperkalemia, due to decreased hemodialysis.[43]

Considering renal impairment is the most common reason for hyperkalemia in patients affected by SARS-CoV-2, special care should be taken in monitoring and managing this critical threat.

GASTROINTESTINAL SYSTEM IMPAIRMENT

Gastrointestinal manifestations, such as diarrhea, vomiting, and anorexia have been reported in some patients with COVID-19.[44] The small intestine enterocytes express ACE2 at substantially higher levels than any other organs, including the lungs and kidneys.[45] Visualization of the SARS-CoV-2 nucleocapsid protein in gastric, duodenal, rectal epithelial cells and even isolation of its RNA from stool samples confirms involvement of the gastrointestinal system in around 50% of infected patients.[46, 47] Therefore, considering the important role that the gastrointestinal system plays in dietary potassium absorption, the intestinal manifestations caused by SARS-CoV-2 may also be responsible for the disruption in potassium homeostasis.

Hypokalemia and Diarrhea

Diarrhea is a relatively common symptom in COVID-19 patients.[48] A recent meta-analysis of 43 studies reported the pooled prevalence of diarrhea to be 7.7% (95% CI: 7.2 to 8.2%).[48] Gastrointestinal losses of potassium, owing to excess stool passing, would be another possible cause of hypokalemia in patients affected by SARS-CoV-2. In a study conducted by Kang *et al.*, aimed at understanding the characteristics of COVID-19 patients with diarrhea, the serum potassium levels were found to be significantly lower in patients who developed diarrhea than among those who did not ($P < .05$).[49] Furthermore, in a study investigating the serum potassium status of 175 COVID-19 patients, diarrhea was found to occur in 29% of cases with severe hypokalemia, but the diarrhea was generally mild, with a mean of six onsets per day.[6] Furthermore, the BK channel on the cell surface of the enterocytes is sensitive to aldosterone.[50] Considering the hyperaldosteronism status in the case of SARS-CoV-2 pathogenesis, these channels would be over expressed, subsequently leading to potassium excretion into the lumen of the gastrointestinal tract.

Hypokalemia and Vomiting

Vomiting is another common hallmark of gastrointestinal symptoms, having a similar prevalence to diarrhea in COVID-19 patients.[48] It is important to note that hypokalemia from vomiting may be the result of direct potassium wasting, but the main mechanism is urinary potassium lost due to the ensuing metabolic alkalosis and volume depletion induced hyperaldosteronism.[30]

Hypokalemia and Anorexia

Another common gastrointestinal manifestation is anorexia, which may be as a consequence of prolonged face mask or ventilation helmet use, or may simply be as a result of severe illness.[19] Clearly, a loss of appetite and inadequate potassium intake may result in hypokalemia in patients with COVID-19.

In summary, although the involvement of the gastrointestinal system is one possible reason for the reduced serum potassium levels, the role of gastrointestinal symptoms in the development of hypokalemia has not been supported in several studies.[6, 9, 12] For example, in a study investigating the incidence of hypokalemia in COVID-19 patients, they reported that lower serum potassium levels might primarily result from losses in urine, rather than from the gastrointestinal tract.[6] The researchers provide the following reasons for this assertion: 1) a small proportion of hypokalemic patients had diarrhea or vomiting; 2) the prevalence of diarrhea was not significantly different between patients with severe and mild hypokalemia ($P > 0.05$); and 3) the majority of patients presented with mild diarrhea, which had a short duration.[6] Similarly, in an investigation by Tsiberkin *et al.*, hypokalemia was found in 37.2% of patients affected by SARS-CoV-2, although patients with symptoms of gastrointestinal potassium loss had been excluded at the beginning of the study.[11] Nonetheless, given the important role of potassium disorders in the prognosis of the COVID-19 disease, any possible etiology must be carefully considered and substantial efforts made to correct it.

ACID-BASE STATUS

Acid-base abnormalities are often accompanied by the transcellular exchange of potassium.[14] These changes mostly occur along with metabolic acid-base disorders and are less related to respiratory acidosis and alkalosis.[35] In the case of low blood pH, some excess extracellular hydrogen ions would be buffered in cells. In order to maintain electroneutrality, hydrogen enters the cells causing potassium to enter the extracellular fluid, thereby inducing elevated potassium levels. Using the same mechanism, alkalotic status is attributed to lower potassium levels and hypokalemia.[35]

Hypokalemia and Alkalosis

Patients with COVID-19 may experience various degrees of acid-base disorders.[51-53] Laboratory data from 169 SARS-CoV-2 positive participants showed that the prevalence of alkalosis was much higher than acidosis (68.6 vs. 0.6%).[52] Moreover, in another study evaluating the clinical characteristics of COVID-19 patients, 29.41% had alkalosis and there were none with acidosis.[53] The most obvious explanation for the high blood pH in infected patients would appear to be an over activation of the RAAS and ensuing aldosterone secretion, which leads to metabolic alkalosis.[54] Respiratory alkalosis could also occur, due to hypoxia-driven hyperventilation in severe cases of COVID-19,

which may also lead to hypokalemia.[19] Chen *et al.* demonstrated that the prevalence of blood pH levels over 7.45, in patients with confirmed COVID-19, was statistically higher in severe hypokalemic patients, compared to those with normal potassium levels (29 vs. 6%, $P < .05$).[6] Furthermore, in a study conducted by Tsiberkin *et al.*, patients with hypokalemia had higher blood pH levels than those in the control group (7.46 vs. 7.35, $P = .001$).[11]

Hyperkalemia and Acidosis

Metabolic acidosis in patients with COVID-19 could be due to lactic acid generation, which is secondary to hypoxia or even septic shock.[51] In agreement with this hypothesis, research has reported higher levels of lactic acid in those who died of COVID-19, when compared to those who survived, both before and after intubation.[51] In addition, considering the high vulnerability of diabetic patients to SARS-CoV-2 infection, the incidence of diabetic ketoacidosis (DKA), arising from insulin deficiency, would be a lethal complication of the disease.[55] Once infected with SARS-CoV-1, the virus could attack the pancreatic islands by binding to the ACE2 receptors, causing insulin depletion.[56] Consequently, it has been postulated that the risk of developing DKA would be higher in diabetic patients with COVID-19.[55] However, it is important to note that high anion gap metabolic acidosis (i.e. lactic acidosis and ketoacidosis) cannot stimulate potassium release into the extracellular fluid to cause hyperkalemia.[35] The commonly observed onset of hyperkalemia in DKA patients may be due to reasons other than metabolic acidosis, including glycemic hyperosmolality and insulin deficiency. Glycemic hyperosmolality can be attributed to osmotic water transfer from the cells to the extracellular fluid, which is accompanied by the movement of potassium out of the cells. Insulin promotes potassium movement into the cells by increasing the activity of the Na/K ATPase pump. Therefore, in the case of DKA, insufficient insulin will likely lead to hyperkalemia.[35, 57]

INTERRELATIONSHIP BETWEEN HYPOKALEMIA AND HYPOMAGNESEMIA

Magnesium is the second most abundant intracellular cation, after potassium.[58] Magnesium deficiency, defined as serum magnesium below 0.65 mmol/L, is relatively common, but is often underdiagnosed since its measurement and monitoring is not routinely undertaken in clinical settings.[59, 60] Potassium depletion occurs frequently in patients with hypomagnesemia, and almost half of hypokalemic patients have a concomitant magnesium deficiency.[61] The concurrent depleted magnesium levels may also aggravate hypokalemia, by impairing the Na-K ATPase pump functioning and thereby exacerbating urinary potassium loss through the ROMK channels.[62] Furthermore, it is important to note that magnesium deficiency causes hypokalemia to become refractory to potassium treatment.[61] Alnafiey *et al.* reported the case of a 34-year-old patient who had recovered from COVID-19.[63] He presented with hypokalemia, due to renal potassium wasting, as well as hypomagnesemia during hospitalization, which was not a side effect of medication, acid-base disorders, or congenital syndromes and he had no prior history of hypokalemia before becoming infected with SARS-CoV-2.[63] Five months after recovery from the infection, the patient still had persistent hypokalemia and hypomagnesemia, even though all COVID-19 symptoms had disappeared.[63] While the exact mechanism for the development of persistent hypokalemia and hypomagnesemia is not clear, widespread tubule-interstitial renal involvement could be a possible explanation, and clinicians must be aware about these potential long term complications of COVID-19.

MEDICATION-INDUCED POTASSIUM ABNORMALITIES

A wide range of pharmacologic agents have been reported to alter the potassium balance via a variety of mechanisms.[64,65] There are a number of medications that may be involved in the development of potassium disorders in SARS-CoV-2 positive patients, below we cover some of the most likely.

Hypokalemia and Thiazide and Loop Diuretics

The development of acute respiratory distress syndrome (ARDS), which is associated with pulmonary edema in patients with COVID-19, requires conservative fluid management with the aim of reducing intravascular volume and thereby improving lung function and oxygenation.

However, this restricted fluid resuscitation should be considered with caution, due to the hypovolemic condition of some patients.[66, 67] In the COVID-19 setting, diuretics are promising medications that can not only help relieve pulmonary edema, but are also widely administrated to patients with high blood pressure or heart failure.[68]

Thiazide and loop diuretics (e.g. furosemide) are two common diuretics which compromise the potassium content through inhibiting Na-Cl and Na-K-2Cl cotransporters in the distal tubules and the thick ascending limb of the loop of Henle, respectively, thereby augmenting the sodium and water delivery to the ENaC and further inducing potassium excretion.[30] The renal potassium wasting that occurs as a result of diuretic therapy is a typical contributing factor for hypokalemia, particularly through the use of thiazides, which increase the risk five-fold.[69] In a comparison between COVID-19 patients with hypokalemia vs. the normokalemic group, diuretic therapy was found to be a significant risk factor for developing hypokalemia (OR = 1.94, 95% CI: 1.08 to 3.48; $P < .05$).[19] Among patients with hypokalemia, 37.5% were on furosemide and 1.6% on thiazide, at the time of diagnosis.[19] In contrast, another study found that the amount of thiazide diuretics used in confirmed COVID-19 patients with low potassium levels was not significantly higher than among those with normal potassium levels ($P > .05$).[11] A similar conclusion was also drawn by Moreno-Pérez *et al.*, in that the use of diuretics during the first 72 hour of hospital admission did not influence the onset of mild hypokalemia ($P > .05$) or severe hypokalemia ($P > .05$) in SARS-CoV-2 patients, irrespective of whether they were administered as a group of thiazides, loop and other diuretics or only loop diuretics.[9]

Hypokalemia and Corticosteroids

Corticosteroids are useful agents in suppressing immune responses and inflammatory processes, which may also induce irreversible damage to a number of tissues. Since the outbreak of the COVID-19 pandemic, there has been extensive debate on the effectiveness of corticosteroids in these patients. Recent meta-analyses, on both observational studies and randomized clinical trials, have reported a significant reduction in mortality and the need for mechanical ventilation in patients receiving corticosteroids.[70-72]

In high doses, some corticosteroids, like cortisone and hydrocortisone, have mineralocorticoid effects, in addition to intrinsic glucocorticoids effects, resulting in sodium and water retention and the loss of potassium in urine.[73] Furthermore, using univariate logistic regression, Alfano *et al.* showed that corticosteroids were significantly associated with hypokalemia in their cohort of COVID-19 patients (Hazard ratio (HR) = 1.66, 95% CI: 1.01 to 2.74; $P = .05$).[19] In addition, another study found that receiving glucocorticoids was significantly higher in severe hypokalemic patients, compared to mild hypokalemic patients (23 vs. 8%, $P = .05$).[6] Finally, a recent systematic review and meta-analysis reported that corticosteroid treatment was associated with the development of hypokalemia, with a risk ratio of 2.28 (95% CI: 1.07 to 4.55, $P < .05$) in SARS-CoV-2 patients.[74]

Hypokalemia and Chloroquine/Hydroxychloroquine

Chloroquine and hydroxychloroquine are commonly prescribed drugs for the treatment of malaria, rheumatoid arthritis, and systemic lupus erythematosus, and both have been repurposed as potential medications for COVID-19.[75, 76] Chloroquine impairs the terminal glycosylation of ACE2, reducing spike protein affinity and thereby SARS-CoV-2 entry.[77] Moreover, rapidly elevating endosomal pH, by adding chloroquine to cells, has been reported to disrupt ongoing fusion events between the virus and endosomes, thus impeding the infection.[77] Hypokalemia is a common complication from overdosing with chloroquine or hydroxychloroquine and is thought to be secondary to an intracellular shift and the retention of potassium ions in cells, rather than total body potassium depletion.[35, 78] In relation to the high prevalence of QTc prolongation in chloroquine/hydroxychloroquine toxicity, treating with sodium bicarbonate to narrow the QRS widening or giving epinephrine to maintain adequate systolic blood pressure might help to move potassium into the cells, subsequently exacerbating hypokalemia.[79] In the context of COVID-19, Fteiha *et al.* conducted a study with 90 patients who were treated with hydroxychloroquine.[80] QTc prolongation occurred in 16% of the patients and was significantly related to hypokalemia (OR = 5, 95% CI: 1.3 to 20; $P < .05$) and furosemide therapy (OR = 3.7, 95% CI: 1.01 to 13.7; $P < .05$), while the presence of hypokalemia

did not correlate with receiving furosemide.[80]

Hypokalemia and Antiviral Drugs

Remdesivir and lopinovir are two of the most promising drugs for the treatment of COVID-19.[81] In a recent randomized clinical trial on COVID-19 patients who were given a 10-day course of remdesivir (n = 197), a 5-day course of remdesivir (n = 199), or standard care (n = 200), hypokalemia was recorded in 7, 5, and 2% of the patients in each group; respectively.[82] Furthermore, in a study of 10 hospitalized COVID-19 patients receiving lopinovir, hypokalemia was diagnosed in seven patients, about four days after beginning the treatment.[83] The mechanism by which low potassium occurred in these patients is not fully understood, however clinicians must monitor their patients for hypokalemia after beginning treatment with these drugs.

Hypokalemia and Beta-2 Adrenergic Agonists, Hyperkalemia and Beta-2 Adrenergic Antagonists

Beta-2 adrenergic activity promotes potassium movement into the cells by enhancing the activity of the Na/K ATPase pump.[35] Cardiovascular complications, such as myocardial infarction, stress induced inflammation and pulmonary edema among COVID-19 patients, could stimulate beta-2 adrenergic activity.[26] Apart from these situations, which increase the production of endogenous catecholamines in COVID-19 patients, giving beta-2 agonist nebulizers for the treatment of dyspnea, or even the intravenous administration of norepinephrine for those who have septic shock, may further increase beta-2 adrenergic activity, thereby provoking hypokalemia.[84]

Conversely, elevated serum potassium levels are primarily seen after the administration of non-selective beta blockers, such as propranolol and labetalol.[64] Consequently, the risk of hyperkalemia must be considered in COVID-19 patients who receive such medications, due to their high blood pressure, angina pectoralis, tachycardia, and other cardiovascular complications.

Hyperkalemia and Angiotensin-converting Enzyme Inhibitors (ACEi) or Angiotensinogen II Receptor Blockers (ARB)

The results of several studies have found that hypertension, cardiovascular diseases and diabetes are very common among COVID-19 patients.[41] These conditions typically require treatment with RAAS inhibitors, including ACEi and ARBs.[85] Since the emergence of this new coronavirus, controversy has existed over the administration of RAAS inhibitors in infected patients, since it is suspected that RAAS inhibitors induce the overexpression of ACE2, thereby increasing SARS-CoV-2-mediated receptor utilization, which may also increase disease severity.[86] However, a number of studies have reported that RAAS inhibitors appear to be safe and without significant side effects in patients suffering from COVID-19.[85, 87, 88]

Decreased angiotensin II production or the inhibition of its receptor through the administration of ACEi and ARB, respectively, may reduce aldosterone secretion, impairing urinary potassium excretion.[35] Whether or not RAAS inhibitors are safe and beneficial for patients with COVID-19, the potential risk of elevated potassium levels must be taken into consideration, particularly in patients with kidney diseases, heart failure, diabetes, and the concurrent use of drugs promoting potassium retention, such as potassium-sparing diuretics.[89, 90] However, a retrospective study of 469 hospital admissions for COVID-19, of whom 91 patients received ACEi/ARB during their hospital stay, found no significant differences in the incidences of hyperkalemia between those who used ACEi/ARB and those who did not ($P > .05$).[87] Similarly, a prospective study on 338 SARS-CoV-2 affected patients who received ACEi/ARB, found that hyperkalemia was not significantly associated with ACEi (OR = 1.15; 95% CI: 0.39 to 3.38), ARB (OR = 0.46, 95% CI: 0.16 to 1.36), or a combination of ACEi and ARB (OR = 1.09, 95% CI: 0.44 to 2.67).[85] The downregulation of ACE2, in the case of SARS-CoV-2 cell entry, is thought to counter the potassium retaining activity of ACEi/ARB.[85]

Hyperkalemia and Succinylcholine

The depolarizing neuromuscular blocking agent, succinylcholine, remains the first choice for rapid sequence induction, due to its short onset of action and rapid recovery time. Depolarization of the postsynaptic neuromuscular junction promotes potassium to move out of the cell and results in a sudden elevation of the serum potassium level.[91] The administration of succinylcholine during the

intubation of a 66-year-old SARS-CoV-2 patient was associated with cardiac arrest, as a consequence of hyperkalemia.[92] Given that renal failure is common in COVID-19 patients, serum potassium elevation may put them at higher risk of developing severe hyperkalemia after receiving succinylcholine.[92]

CONCLUSION

The etiology of potassium abnormalities in COVID-19 patients is multifactorial (Table 1). In the case of hypokalemia, urinary potassium loss is the most likely cause of lowered serum potassium levels, which could be linked to ACE2 utilization by SARS-CoV-2 and the resultant hyperaldosteronism state, or viral-induced tubular injury. As common gastrointestinal symptoms of COVID-19, such as a loss of appetite, diarrhea, or vomiting could also trigger hypokalemia. Given that depleted serum magnesium levels could make hypokalemia refractory to treatment, special attention must be paid to its correction. The most common cause of hyperkalemia is reduced urinary output due to renal failure. In addition, potassium abnormalities may also result from acid/base imbalance or as a side-effect of medications the patients are treated with. Irrespective of the cause, the early detection and rapid management of potassium disorders is vital and greatly improves the prognosis for patients with COVID-19.

Probable Etiology of Potassium Abnormalities in COVID-19 Patients

Hypokalemia
Lack of Appetite
Renal Loss
Elevated aldosterone levels due to ACE2 utilization in the case of SARS-CoV-2 cell entry
Tubulopathy
Medications
Thiazide and loop diuretics
Corticosteroids
Penicillins
Aminoglycosides
Gastrointestinal Loss
Vomiting
Diarrhea
Magnesium Deficiency
Transcellular Shift
Medications
Insulin overdose
Beta-2 agonist
Chloroquine/hydroxychloroquine
Alkalosis
Miscellaneous
Remdesivir
Lopinovir
Impaired Excretion
Chronic kidney disease
Acute kidney injury
Congestive heart failure
Medications
ACEi/ARB
Beta-2 antagonist
NSAID
Heparin
Potassium sparing diuretics
Trimethoprim
Trans Cellular Shift
Tissue breakdown
Insulin deficiency
Acidosis
Medications
Beta-2 antagonist
Succinylcholine

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme inhibitor; ENaC, epithelial sodium channel; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensinogen II receptor blocker; NSAID, Nonsteroidal anti-inflammatory drug.

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ETHICS APPROVAL

The present study was approved by ethic committee of Shahid Beheshti University of Medical Sciences, Tehran, Iran (IR.SBMU.RETECH.REC.1400.271).

CONFLICT OF INTEREST

The authors have declared that no conflict of interest exists.

REFERENCES

1. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. New England Journal of Medicine. 2020;382(8):727-33.
2. Zheng J. SARS-CoV-2: an emerging coronavirus that causes a global threat. International journal of biological sciences. 2020;16(10):1678.
3. Gupta A, Madhavan MV, Sehgal K, et al. Extrapulmonary manifestations of COVID-19. Nature medicine. 2020;26(7):1017-32.

4. Emami A, Javanmardi F, Pirbonyeh N, Akbari A. Prevalence of Underlying Diseases in Hospitalized Patients with COVID-19: a Systematic Review and Meta-Analysis. Archives of academic emergency medicine. 2020;8(1):e35.
5. Soraya GV, Ulhaq ZS. Crucial laboratory parameters in COVID-19 diagnosis and prognosis: An updated meta-analysis. Medicina Clínica. 2020;155(4):143-51.
6. Ma X, Zou F, Yu F, et al. Nanoparticle Vaccines Based on the Receptor Binding Domain (RBD) and Heptad Repeat (HR) of SARS-CoV-2 Elicit Robust Protective Immune Responses. Immunity. 2020;53(6):1315-30.e9.
7. Liu S, Zhang L, Weng H, et al. Association Between Average Plasma Potassium Levels and 30-day Mortality During Hospitalization in Patients with COVID-19 in Wuhan, China. International Journal of Medical Sciences. 2021;18:736-43.
8. Greco A, Rabito G, Pironi M, et al. Hypokalaemia in hospitalised patients. Swiss medical weekly. 2016;146:w14320.
9. Moreno-P O, Leon-Ramirez J-M, Fuertes-Kenneally L, et al. Hypokalemia as a sensitive biomarker of disease severity and the requirement for invasive mechanical ventilation requirement in COVID-19 pneumonia: A case series of 306 Mediterranean patients. International Journal of Infectious Diseases. 2020;100:449-54.
10. Szoke D, Caruso S, Aloisio E, et al. Serum potassium concentrations in COVID-19. Clinica Chimica Acta. 2021;512:26-7.
11. Tsiberkin AI, Klyaus NA, V. SY, P. SA. Hypokalemia in hospitalized patients with pneumonia associated with COVID-19. “Arterial’naya Gipertenziya” (“Arterial Hypertension”). 2020;26:462-7.
12. Nasomsong W, Ungthammakhun C, Phiboonbanakit D, et al. Low serum potassium among patients with COVID-19 in Bangkok, Thailand: Coincidence or clinically relevant? Tropical Doctor. 2020:0049475520978174.
13. Noori M, Nejadghaderi SA, Sullman MJ, et al. Epidemiology, prognosis and management of potassium disorders in Covid-19. Reviews in medical virology. 2021:e2262.
14. Clase CM, Carrero J-J, Ellison DH, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. Kidney International. 2020;97(1):42-61.
15. Cheng Y, Luo R, Wang K, et al. Kidney disease is associated with in-hospital death of patients with COVID-19. Kidney International. 2020;97(5):829-38.
16. Goel N, Jain D, Haddad DB. COVID-19 and the Kidneys, Implications and Outcomes. Iran J Kidney Dis. 2021;1(1):1-9.
17. Zou X, Chen K, Zou J, et al. Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019-nCoV infection. Frontiers of medicine. 2020;14(2):185-92.
18. Kim J-M, Kim HM, Lee EJ, et al. Detection and isolation of SARS-CoV-2 in serum, urine, and stool specimens of COVID-19 patients from the Republic of Korea. Osong public health and research perspectives. 2020;11(3):112.
19. Alfano G, Ferrari A, Fontana F, et al. Hypokalemia in Patients with COVID-19. Clinical and experimental nephrology. 2021:1-9.
20. Simões e Silva AC, Lanza K, Palmeira VA, Costa LB, Flynn JT. 2020 update on the renin–angiotensin–aldosterone system in pediatric kidney disease and its interactions with coronavirus. Pediatric Nephrology. 2020.
21. Chenna A, Konala VM, Bose S, et al. Acute Kidney Injury in a Case Series of Patients with Confirmed COVID-19 (Coronavirus Disease 2019): Role of Angiotensin-Converting Enzyme 2 and Renin-Angiotensin System Blockade. Case Reports in Nephrology. 2020;2020:8811931.
22. Kuba K, Imai Y, Rao S, et al. A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. Nat Med. 2005;11(8):875-9.
23. Silhol F, Sarlon G, Deharo J-C, Vaïsse B. Downregulation of ACE2 induces overstimulation of the renin–angiotensin system in COVID-19: should we block the renin–angiotensin system? Hypertension Research. 2020;43(8):854-6.
24. Noori M, Nejadghaderi SA, Sullman MJM, et al. How SARS-CoV-2 might affect potassium balance via impairing epithelial sodium channels? Molecular biology reports. 2021:1-7.
25. Muhanna D, Arnipalli SR, Kumar SB, Ziouzenkova O. Osmotic Adaptation by Na(+)-Dependent Transporters and ACE2: Correlation with Hemostatic Crisis in COVID-19. Biomedicines. 2020;8(11).
26. Barkas F, Filippas-Ntekouan S, Liontos A, et al. Multifaceted persistent hypokalaemia in a patient with coronavirus disease 2019. Internal medicine journal. 2020;50(10):1289-91.
27. Mabillard H, Tedd H, Speight A, et al. Case Report: Renal potassium wasting in SARS-CoV-2 infection. F1000Research. 2020;9:659.
28. Mandal AKJ, Kho J, Metaxa S, Missouris CG. COVID-19 and late-onset hypertension with hyporeninaemic hypoaldosteronism. International journal of clinical practice. 2021;75(1):e13773.
29. Kormann R, Jacquot A, Alla A, et al. Coronavirus disease 2019: acute Fanconi syndrome precedes acute kidney injury. Clinical Kidney Journal. 2020;13(3):362-70.
30. Rennke HG, Denker BM. Renal pathophysiology the essentials2020.
31. Su H, Yang M, Wan C, et al. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. Kidney International. 2020;98(1):219-27.
32. Werion A, Belkhir L, Perrot M, et al. SARS-CoV-2 causes a specific dysfunction of the kidney proximal tubule. Kidney International. 2020;98(5):1296-307.
33. Kunutsor SK, Laukkanen JA. Renal complications in COVID-19: a systematic review and meta-analysis. Annals of medicine. 2020;52(7):345-53.
34. Vakhshoori M, Emami SA, Heidarpour M, Mortazavi M, Shafie D. Corona Virus Disease 2019 (COVID-19) and Its Effect on Renal System, A Systematic Review and Meta-analysis. Iranian Journal of Kidney Diseases. 2020;14:419-57.

35. Palmer BF, Clegg DJ. Physiology and Pathophysiology of Potassium Homeostasis: Core Curriculum 2019. American Journal of Kidney Diseases. 2019;74(5):682-95.
36. Patel N, Rein JL, Sanchez-Russo L, Winston J, Uribarri J. COVID-19-Associated Acute Kidney Injury: A Case Series. Kidney medicine. 2020;2(5):668-9.
37. Portolés J, Marques M, López-Sánchez P, et al. Chronic kidney disease and acute kidney injury in the COVID-19 Spanish outbreak. Nephrology Dialysis Transplantation. 2020;35(8):1353-61.
38. Chan L, Chaudhary K, Saha A, et al. AKI in Hospitalized Patients with COVID-19. Journal of the American Society of Nephrology: JASN. 2021;32(1):151-60.
39. Mohamed MMB, Lukitsch I, Torres-Ortiz AE, et al. Acute Kidney Injury Associated with Coronavirus Disease 2019 in Urban New Orleans. Kidney360. 2020;1(7):614-22.
40. Pei G, Zhang Z, Peng J, et al. Renal Involvement and Early Prognosis in Patients with COVID-19 Pneumonia. Journal of the American Society of Nephrology. 2020;31(6):1157-65.
41. Ssentongo P, Ssentongo AE, Heilbrunn ES, Ba DM, Chinchilli VM. Association of cardiovascular disease and 10 other pre-existing comorbidities with COVID-19 mortality: A systematic review and meta-analysis. PLOS ONE. 2020;15(8):e0238215.
42. Einhorn LM, Zhan M, Walker LD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. Archives of internal medicine. 2009;169(12):1156-62.
43. Ma Y, Diao B, Lv X, et al. Epidemiological, Clinical, and Immunological Features of a Cluster of COVID-19–Contracted Hemodialysis Patients. Kidney International Reports. 2020;5(8):1333-41.
44. Zhong P, Xu J, Yang D, et al. COVID-19-associated gastrointestinal and liver injury: clinical features and potential mechanisms. Signal transduction and targeted therapy. 2020;5(1):256.
45. Zang R, Gomez Castro MF, McCune BT, et al. TMPRSS2 and TMPRSS4 promote SARS-CoV-2 infection of human small intestinal enterocytes. Science immunology. 2020;5(47).
46. Xiao F, Tang M, Zheng X, et al. Evidence for Gastrointestinal Infection of SARS-CoV-2. Gastroenterology. 2020;158(6):1831-3.e3.
47. Wu Y, Guo C, Tang L, et al. Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. The lancet Gastroenterology & hepatology. 2020;5(5):434-5.
48. Sultan S, Altayar O, Siddique SM, et al. AGA Institute Rapid Review of the Gastrointestinal and Liver Manifestations of COVID-19, Meta-Analysis of International Data, and Recommendations for the Consultative Management of Patients with COVID-19. Gastroenterology. 2020;159(1):320-34.e27.
49. Kang MK, Kim KO, Kim MC, et al. Clinical characteristics of coronavirus disease 2019 patients with diarrhea in Daegu. The Korean journal of internal medicine. 2020;35(6):1261-9.
50. Sørensen MV, Matos JE, Sausbier M, et al. Aldosterone increases KCa1.1 (BK) channel-mediated colonic K+ secretion. The Journal of physiology. 2008;586(17):4251-64.
51. Zhang L, Li J, Zhou M, Chen Z. Summary of 20 tracheal intubation by anesthesiologists for patients with severe COVID-19 pneumonia: retrospective case series. Journal of anesthesia. 2020;34(4):599-606.
52. Wang C, Zhou L, Chen J, et al. The differences of clinical characteristics and outcomes between imported and local patients of COVID-19 in Hunan: a two-center retrospective study. Respiratory Research. 2020;21(1):313.
53. Qian G-Q, Yang N-B, Ding F, et al. Epidemiologic and clinical characteristics of 91 hospitalized patients with COVID-19 in Zhejiang, China: a retrospective, multi-centre case series. QJM: An International Journal of Medicine. 2020;113(7):474-81.
54. Rennke HG, Denker BM. RENAL PATHOPHYSIOLOGY. 4th ed2014.
55. Palermo NE, Sadhu AR, McDonnell ME. Diabetic Ketoacidosis in COVID-19: Unique Concerns and Considerations. The Journal of Clinical Endocrinology & Metabolism. 2020;105(8):2819-29.
56. Yang JK, Lin SS, Ji XJ, Guo LM. Binding of SARS coronavirus to its receptor damages islets and causes acute diabetes. Acta diabetologica. 2010;47(3):193-9.
57. Adrogué HJ, Lederer ED, Suki WN, Eknoyan G. Determinants of plasma potassium levels in diabetic ketoacidosis. Medicine. 1986;65(3):163-72.
58. Moe SM, Daoud JR. 11 - Disorders of Mineral Metabolism: Calcium, Phosphorus, and Magnesium. In: Gilbert SJ, Weiner DE, editors. National Kidney Foundation Primer on Kidney Diseases (Sixth Edition). Philadelphia: W.B. Saunders; 2014. p. 100-12.
59. Wallace TC. Combating COVID-19 and Building Immune Resilience: A Potential Role for Magnesium Nutrition? Journal of the American College of Nutrition. 2020;39(8):685-93.
60. Pagana K, Pagana T, Pagana T. Mosby's Diagnostic & Laboratory Test Reference. 14th ed: Elsevier; 2019.
61. Kardalas E, Paschou SA, Anagnostis P, et al. Hypokalemia: a clinical update. Endocrine connections. 2018;7(4):R135-r46.
62. Huang C-L, Kuo E. Mechanism of Hypokalemia in Magnesium Deficiency. Journal of the American Society of Nephrology. 2007;18(10):2649-52.
63. Alnafiey MO, Alangari AM, Alarifi AM, Abushara A. Persistent Hypokalemia post SARS-coV-2 infection, is it a life-long complication? Case report. Annals of medicine and surgery (2012). 2021;62:358-61.
64. Ben Salem C, Badreddine A, Fathallah N, Slim R, Hmouda H. Drug-induced hyperkalemia. Drug safety. 2014;37(9):677-92.
65. Veltri KT, Mason C. Medication-induced hypokalemia. P T. 2015;40(3):185-90.
66. Kevorkian JP, Riveline JP, Vandiedonck C, et al. Early short-course corticosteroids and furosemide combination to treat non-critically ill COVID-19 patients: An observational cohort study. The Journal of infection. 2021;82(1):e22-e4.
67. Casey JD, Semler MW, Rice TW. Fluid Management in Acute Respiratory Distress Syndrome. Seminars in

Respiratory and Critical Care Medicine. 2019;40(1):57-65.

68. Wile D. Diuretics: a review. Annals of clinical biochemistry. 2012;49(Pt 5):419-31.
69. Rodenburg EM, Visser LE, Hoorn EJ, et al. Thiazides and the risk of hypokalemia in the general population. Journal of Hypertension. 2014;32(10):2092-7.
70. Group TWREAfC-TW. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis. JAMA. 2020;324(13):1330-41.
71. Ye Z, Wang Y, Colunga-Lozano LE, et al. Efficacy and safety of corticosteroids in COVID-19 based on evidence for COVID-19, other coronavirus infections, influenza, community-acquired pneumonia and acute respiratory distress syndrome: a systematic review and meta-analysis. CMAJ: Canadian Medical Association journal = journal de l'Association medicale canadienne. 2020;192(27):E756-e67.
72. van Paassen J, Vos JS, Hoekstra EM, et al. Corticosteroid use in COVID-19 patients: a systematic review and meta-analysis on clinical outcomes. Critical Care. 2020;24(1):696.
73. Katzung BG. Basic and Clinical Pharmacology 14E: McGraw-Hill Education; 2017.
74. Yang Z, Liu J, Zhou Y, et al. The effect of corticosteroid treatment on patients with coronavirus infection: a systematic review and meta-analysis. Journal of Infection. 2020;81(1):e13-e20.
75. Wong A. COVID-19 and toxicity from potential treatments: Panacea or poison. Emergency Medicine Australasia. 2020;32(4):697-9.
76. Bakhsh H. Hydroxychloroquine toxicity management: A literature review in COVID-19 era. Journal of Microscopy and Ultrastructure. 2020;8(4):136-40.
77. Vincent MJ, Bergeron E, Benjannet S, et al. Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. Virology journal. 2005;2:69.
78. Clemessy JL, Borron SW, Baud FJ, et al. Hypokalaemia related to acute chloroquine ingestion. The Lancet. 1995;346(8979):877-80.
79. Chai P, Ferro E, Kirshenbaum J, et al. Intentional Hydroxychloroquine Overdose Treated with High-Dose Diazepam: an Increasing Concern in the COVID-19 Pandemic. Journal of Medical Toxicology. 2020;16.
80. Fteiha B, Karameh H, Kurd R, et al. QTc prolongation among hydroxychloroquine sulphate-treated COVID-19 patients: An observational study. International journal of clinical practice.n/a(n/a):e13767.
81. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for Coronavirus Disease 2019 (COVID-19): A Review. Jama. 2020;323(18):1824-36.
82. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients With Moderate COVID-19: A Randomized Clinical Trial. Jama. 2020;324(11):1048-57.
83. Liu F, Xu A, Zhang Y, et al. Patients of COVID-19 may benefit from sustained Lopinavir-combined regimen and the increase of Eosinophil may predict the outcome of COVID-19 progression. International journal of infectious diseases: IJID: official publication of the International Society for Infectious Diseases. 2020;95:183-91.
84. Natesan V. Beta-adrenergic blocker treatment for COVID-192020.
85. Hakeam HA, Alsemari M, Al Duhailib Z, et al. Association of Angiotensin-Converting Enzyme Inhibitors and Angiotensin II Blockers With Severity of COVID-19: A Multicenter, Prospective Study. Journal of Cardiovascular Pharmacology and Therapeutics. 2020:1074248420976279.
86. Soria Arcos F, Romero Puche A, Vicente Vera T. Controversy regarding ACE inhibitors / ARBs in COVID-19. Rev Esp Cardiol (Engl Ed). 2020;73(6):516-.
87. Adrish M, Chilimuri S, Sun H, et al. The Association of Renin-Angiotensin-Aldosterone System Inhibitors With Outcomes Among a Predominantly Ethnic Minority Patient Population Hospitalized With COVID-19: The Bronx Experience. Cureus. 2020;12(9):e10217-e.
88. Rico-Mesa JS, White A, Anderson AS. Outcomes in Patients with COVID-19 Infection Taking ACEI/ARB. Curr Cardiol Rep. 2020;22(5):31-.
89. Cruz CS, Cruz AA, Marcílio de Souza CA. Hyperkalaemia in congestive heart failure patients using ACE inhibitors and spironolactone. Nephrology, dialysis, transplantation: official publication of the European Dialysis and Transplant Association - European Renal Association. 2003;18(9):1814-9.
90. Textor SC, Bravo EL, Fouad FM, Tarazi RC. Hyperkalemia in azotemic patients during angiotensin-converting enzyme inhibition and aldosterone reduction with captopril. The American journal of medicine. 1982;73(5):719-25.
91. Martyn J AJ, Richtsfeld M, Warner David O. Succinylcholine-induced Hyperkalemia in Acquired Pathologic States: Etiologic Factors and Molecular Mechanisms. Anesthesiology. 2006;104(1):158-69.
92. Sigurdsson TS, Þorvaldsson AP, Asgeirsdottir S, Sigvaldason K. Cardiac arrest in a COVID-19 patient after receiving succinylcholine for tracheal reintubation. Br J Anaesth. 2020;125(2):e255-e7.

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