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Potassium Levels in COVID Subjects: Current Observations and New Possibilities for its use in COVID Diagnosis

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Abstract- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causing covid infection in humans is a major global threat to healthcare and economy. According to the recent statistics of the World Health Organization (WHO), the disease has already involved all continents, with almost 117,498,522 cases with more than 2,606,626 deaths all over the globe until March 2021. It is thus, imperative to study and develop pharmacological treatments suitable for the prevention and treatment of COVID-19. The COVID causing virus is mainly transmitted through cough or sneeze droplets generated by an infected person. Hence its early and accurate diagnosis appears essential for minimizing spread, prevention and eventually containment of the pandemic. Also, since the clinical presentation of the COVID infection is varied starting from asymptomatic to severe cases, it reinforces the need for detection methods that are simple, early and with good sensitivity and specificity. This article reviews impact of potassium ions in functioning of various organs in humans and its possible role in COVID disease progression.

Keywords: *potassium, ivermectin, favipiravir, remdisivir, coronavirus, SARS-CoV-2, COVID-19.*

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Potassium Levels in COVID Subjects: Current Observations and New Possibilities for its use in COVID Diagnosis

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Abstract- Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) causing covid infection in humans is a major global threat to healthcare and economy. According to the recent statistics of the World Health Organization (WHO), the disease has already involved all continents, with almost 117,498,522 cases with more than 2,606,626 deaths all over the globe until March 2021. It is thus, imperative to study and develop pharmacological treatments suitable for the prevention and treatment of COVID-19. The COVID causing virus is mainly transmitted through cough or sneeze droplets generated by an infected person. Hence its early and accurate diagnosis appears essential for minimizing spread, prevention and eventually containment of the pandemic. Also, since the clinical presentation of the COVID infection is varied starting from asymptomatic to severe cases, it reinforces the need for detection methods that are simple, early and with good sensitivity and specificity. This article reviews impact of potassium ions in functioning of various organs in humans and its possible role in COVID disease progression. Looking at the critical role of potassium ions in human body, it is speculated that estimation of potassium ions in the urine of covid patients could be beneficial and may enable early treatment options and arrest disease progression considerably. This article hypothesizes the possible role of active constituents of herbal medicines, known for their anti-covid properties, through balancing the level of potassium ions in the human body.

Keywords: potassium, ivermectin, favipiravir, remdisivir, coronavirus, SARS-CoV-2, COVID-19.

I. INTRODUCTION

Coronavirus disease 2019 (COVID-19), also known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is caused by a strain of coronavirus belonging to the Coronaviridae family continues to spread around the world affecting the lives of billions of people worldwide. The International Committee on Taxonomy of Viruses (ICTV) has named the virus causing COVID infection as SARS-CoV-2 [1, 2]. Many findings regarding COVID-19 etiology, epidemiology, diagnosis, and treatment strategies have been reported and it is evident that COVID affects almost all organs like heart, lungs, liver, kidney, brain, [3] causing loss of sense of taste and rashes in the skin.

It has been suggested by Moreno-Pérez et al. [4] that serum potassium levels is a sensitive biomarker of severe progression of COVID-19, although the clinical significance of lower levels of potassium ions in serum of COVID patients is not clear. Lippi et al. [5] establish that COVID-19 severity is associated with lower serum concentrations of sodium, potassium and calcium.

A study conducted at Wenzhou Central Hospital and Sixth People's Hospital of Wenzhou, Wenzhou, China, observed various levels of plasma potassium in covid affected patients. Nearly 18% patients were classified as having severe hypokalemia (plasma potassium 3.5 mmol/L), 37% hypokalemia (plasma potassium 3-3.5 mmol/L), and 46% normokalemia (plasma potassium >3.5 mmol/L). From the above reports, it appears potassium levels could be potential indicators of covid progression. Patients with severe hypokalemia had higher body temperature, higher creatine kinase levels, higher lactate dehydrogenase levels and higher C-reactive protein levels. Patients with severe hypokalemia were given potassium at a dose of 40 mEq per day and they responded well to potassium supplements as they recovered. Distribution of potassium across the cell membrane appears to be critical for normal cellular function [6].

To understand the impact of potassium level in covid subjects, I looked at all possible roles that potassium plays in human body and extrapolated these reports in covid scenario and a hypothesis in this regard is described in this paper.

II. PLASMA POTASSIUM LEVELS AND ITS ASSOCIATION WITH ANGIOTENSIN-CONVERTING ENZYME 2 (ACE2)

ACE2, is the principal counter-regulatory mechanism for the main axis of the rennin-angiotensin system (RAS), which is critical in the control of blood pressure and electrolyte balance by balancing potassium and sodium [7]. The invasion of the human cells by the covid-2 virus is through binding of the virus to the ACE2 receptors present on the surface of the cell membrane of human vital organs, such as heart, liver, kidney, and lungs. The low levels of potassium observed in COVID-19 patients possibly reflects a disordered rennin-angiotensin system activity, which increases as a

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result of reduced counter activity of angiotensin-converting enzyme 2.

SARS-CoV-2 virus binds to ACE2 and enhances the degradation of ACE2 and, thus, decreases the counteraction of ACE2 on RAS. This leads to increased reabsorption of sodium and water, thereby increasing blood pressure and excretion of potassium [8]. In addition, patients with COVID-19 often have gastrointestinal symptoms, such as diarrhea and vomiting, leading to disruptions of homeostasis of electrolytes and pH [9].

a) *Role of potassium in multiplication of other viruses*

K⁺ deficiency affects host-virus interactions by affecting the accessibility of virus attached to tissue and by affecting the intracellular synthesis of new virus. Since supplementation of potassium reverses such affects, it was concluded that such in-vitro effects of virus suppression was achieved by potassium depletion [10].

Choi et al. [11] showed 50% decrease in HIV-1 production when the host cells of CD4⁺ lymphoblastoid cells infected by HIV-1 (strain LAI) was incubated in low K⁺ medium in comparison to a normal K⁺ concentration (5 mM). The decrease in HIV-1 production by low K⁺ medium and increase by high K⁺ media has been attributed to its effects on HIV-1 reverse transcription. Potassium is required for efficient viral replication and to induce cells for disease and infection.

K ions are reported to promote viral infection [12] since negative-stranded (SNS) 2 RNA viruses exposed to high K⁺ also displayed enhanced infectivity.

b) *Potassium levels in other viral infections*

Viral infections, such as Dengue and Chikungunya, have also been reported to precipitate hypokalemic paralysis [13]. This is attributed to redistribution of potassium in cells or increased urinary potassium wasting as a result of transient renal tubular abnormalities.

c) *Role of anti-covid drugs and potassium levels*

i. *Ivermectin (IVM) and potassium*

Ivermectin, a highly active broad-spectrum, anti-parasitic agent used to treat scabies [14], is a non-selective inhibitor of three important mammalian P-type ATPases. When used at high doses, IVM causes adverse effects [15]. With respect to the inhibition of the Na(+), K(+)-ATPase, IVM acts by a mechanism different from the classical cardiac glycosides, based on selectivity towards the isoforms, sensibility to the antagonistic effect of K(+) and to ionic conditions favoring different conformations of the enzyme. Administration of IVM with or without albendazole to rats showed significant increase (P<0.05) in serum potassium, urea, creatinine, glucose and cholesterol concentrations while serum albumin was significantly reduced (P<0.05) [16].

Apart from its uses to address parasitic infections, IVM has been reported to inhibit the replication of COVID-2 virus [17] and identified as an inhibitor of interactions between the human HIV integrase protein and the importin α/β 1 heterodimer. In COVID context, IVM is known to affect the nuclear transport of viral proteins that is essential for the replication cycle and inhibition of the host's antiviral response.

ii. *Potassium and Favipiravir*

Favipiravir, released in 2002 in Japan, as an inhibitor of influenza virus replication was subsequently proved to have inhibitory activity against several classes of viruses, including EBOV [18], and used as a prophylaxis and also for therapy during the recent EBOV epidemic in West Africa is an inhibitor of the RNA-dependent RNA polymerase of many RNA viruses, including influenza viruses, arenaviruses, phleboviruses, hantaviruses, flaviviruses, enteroviruses, and noroviruses. QT interval, indicative of rate of heart beats is slower when QTc is prolonged and this has already been described in other EBOV-infected patients treated outside Africa and electrolyte disturbances, particularly hypokalaemia, may induce QTc interval prolongation [19].

Potassium levels <3.0 mmol/l can be arrhythmogenic and specifically can cause QTc interval prolongation, hence the regulation and control of potassium levels in such patients is high. The cardiac involvement in SARS-CoV-2 is high (44.4% of infected patients admitted to ICU experienced an arrhythmia) and hence the significance to maintaining normokalaemia in these patients is emphasized to reduce morbidity and mortality [20].

iii. *Remdesivir and potassium*

Remdesivir, an adenosine analogue, is a broad antiviral agent for filovirus, Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), Marburg virus, respiratory syncytial virus (RSV), HCV, pneumoviruses, coronaviruses and several paramyxoviruses. A potent inhibitor of SARS-CoV-2 replication, Remdesivir affects such viruses is in human nasal and bronchial airway epithelial cells [21]. A recent paper by Wang et al. [22] have shown increased levels of plasma potassium in patients treated with Remdesivir.

d) *Hypokalemia and cardiovascular disease*

Yadav et al. [23] report that in China, 27.8% of admitted COVID-19 patients had myocardial injury mortality with higher elevated troponin levels causing death of 59.6% patient vs 8.9% death of patients with normal troponin levels [24]. Since nearly 7% to 17% of patients with cardiovascular disease have lower levels of plasma potassium levels, drugs, such as angiotensin-converting (ACE2) enzyme inhibitors, have a positive effect on mortality and morbidity rates in heart failure

patients since they increase plasma potassium concentration.

e) *Herbal medications and potassium levels*

There are ample numbers of herbal drugs that can offer as a source of potassium [25]. Active phytoconstituents of medicinal plants such as *Withania somnifera*, *Tinosporacordifolia* and *Ocimum sanctum* have been found to affect the activity of the protease of SARS-CoV-2, affecting its multiplication [26]. Shimmi et al. [27] demonstrate that *Withania somnifera* treatment increases the level of potassium in serum of rats that were challenged with gentamycin. Similarly *T. cordifolia* dose-dependently has been shown to increase potassium levels [28]. It is tempting to speculate that the anti-covid activity of such plant extracts could also be through the route of balancing the levels of potassium ions in the human body which needs to be experimentally proven in COVID patients. There are some conflicting reports on inability of *Glycyrrhiza glabra* (licorice) extract to influence the potassium levels in humans [29] and the potassium levels were normal in 98.3% patients with a dose of 8.7 g per day for 18 days. Also, some herbal drugs which are used as laxatives like *Cassia senna* L may lead to hypokalemia, since *senna* can cause excessive water and potassium loss. [30]. Hence, choice of herbal medicines to be taken for addressing potassium levels must be practiced with caution.

f) *Lung diseases and potassium levels*

Chronic Obstructive Pulmonary Disease (COPD) is a disease of increasing public health importance and COPD patients display typical features of acute respiratory infections like productive cough and dyspnoea along other metabolic derangements such as hyponatremia, hypokalemia, hyperbilirubinemia, elevated transaminases, elevated blood urea and elevated serum creatinine etc.[31]. Patients with COPD also show a slower rate of potassium exchange than the control subjects [32]. Levels of serum electrolytes e.g sodium, potassium, magnesium, and chloride are abnormal in patients with acute exacerbation of COPD and in particular the levels of potassium is 3.19 ± 0.96 mEq/l in such patients in comparison to healthy controls (potassium = 4.50 ± 0.02 mEq/l [33, 34].

It is also consistent with reported associations between increased urinary potassium and increased airway hyper responsiveness [35] and also lower lung function in girls [36] and lower levels of serum potassium were associated with a greater risk of asthma [37]. However, there are studies that report no association of serum potassium and asthma. [38, 39].

g) *Potassium level in other diseases*

A recent study linked potassium with irritable bowel syndrome and showed that dietary potassium, was inversely correlated with risk of Crohn's disease in

two large prospective cohorts of US women [40]. The levels of potassium had an inverse association with the disease activity in state of inflammation [41]. Hypokalemia is reported in several rheumatoid arthritis (RA) patients [42], which are reported to alleviate pain due to RA through diets rich in potassium.

In hyperaldosteronism (PHA), a disorder that is increasingly recognized as one of the most prevalent forms of secondary hypertension [43], there is hypokalemia due to an increased urinary potassium excretion. Similarly, a case of severe hypokalemia in a dementia patient [44] exists. Hypokalemic paralysis with low plasma potassium (<3.5 mEq/L) is caused either by an enhanced shift of potassium ion into the cells or following a significant renal or gastrointestinal loss of potassium[45].

h) *Potassium level in urine as markers for disease progression*

A study by Afridi et al. [46] show lower levels of calcium, potassium, magnesium and sodium in blood, serum and scalp hair of Acquired Immune Deficiency Syndrome (AIDS) suffering subjects in comparison to healthy controls, and the levels of these elements were higher in urine samples of the AIDS patients than in those of the control group, opening up a new possibility of examining levels of potassium as a measure of covid patients.

Khandelwal et al. [47] report low values of serum sodium (Hyponatremia) and potassium (hypokalemia) in dengue patients. The mean value of serum sodium was 133.92 mEq/L and of serum potassium was 3.62 mEq/L in such patients with more lower values in severely affected dengue patients in comparison to mildly affected dengue patients.

As SARS-CoVirus, Corona-2 virus also uses angiotensin converting enzyme 2 (ACE2) as a cell entry receptor [48]. Recent human tissue RNA-sequencing data demonstrated that ACE2 expression in kidney was nearly 100-fold higher than in lungs. Li et al. [49], hence the kidney disease may be caused by coronavirus entering kidney cells through an ACE2-dependent pathway. Hence, the possibility of having potassium in the urine of covid affected patients with acute kidney injury/necrosis appears high.

i) *Potassium and mental health*

70 percent of the ions that play a significant role electrical and cellular function in human cells is through potassium ions. Lower levels of potassium ions (between 2.7 mEq/L–3.3 mEq/L) is known to cause mental tiredness, depression, mood swings, psychosis, muscular weakness, disorientation, nervousness and confusions [50].

The COVID-19 pandemic has implications in the emotional and social functioning of the affected patients. A recent publication report development of mental health issues such as depression, anxiety,

insomnia within 3 months of diagnosis in ~ 18% of COVID-19 patients [51]. It is tempting to speculate that potassium supplementation in covid affected patients could improve such mental issues and such supplementations could be along with the regular anti-viral regime that is prescribed to the affected patients. In normal health, serum potassium levels is between 3.5 to 5.2 mmol/L and disturbances in potassium levels have adverse effects on skeletal and cardiac muscle function [52] and lower potassium levels in urine samples indicates cardiac dysfunction [53]. It is possible that potassium supplementation can better the cardiac function and reduce the mortality due to cardiac failure in covid patients.

j) Potassium estimation methods

Potassium levels from spot urine specimens collected at any time has been successfully developed by Tanaka et al. [54] using emission flame photometry. The most commonly used methods are methods as described by Kawasaki et al.[55], Brown et al. [56] and Tanaka et al. [54].

III. CONCLUSIONS AND FUTURE DIRECTIONS

Potassium plays an important role (Normal serum potassium level = 3.5-5.0 mEq/L) in regulation of the heart beat and function of muscles. Along with sodium, potassium is also involved in regulation of water and acid-base balance in blood and tissue [57]. In mammals, the osmotic pressure and water distribution maintenance is the primary function of electrolytes such as sodium and potassium and these ions play a role in maintenance of pH, in oxidation reduction reactions, in heart muscle functioning and as cofactors for enzymes [58] and the body restores potassium balance by shifting the plasma potassium into cells or by renal elimination.

The new coronavirus is reported to cause low potassium levels because it blocks an enzyme called ACE2 that regulates blood pressure by balancing potassium and sodium. Mg^{+2} and K^+ participate in several biochemical processes and its deficiency affects lung function and also influence respiratory symptoms. Increased airway sensitiveness is reported to be associated with a higher urinary potassium excretion [59].

Presence of covid virus in the body fluid such as urine is contradictory. While Wang et al. [60] report the presence of SARS-CoV-2 in sputum (72%), fibrobronchoscope brush biopsy (46%), pharyngeal swabs (32%), feces (29%), and blood (1%) and no detection of virus in urine samples suggesting that the transmission of the SARS-CoV-2 is by the fecal route [61]. However, a recent study by Peng et al. [62] could detect the covid virus in 1 sample of urine of the 9 patients tested (11%). Ling and colleagues [63] reported 66 patients with COVID-19 from Shanghai, China. Urine

samples of 4 patients (6.9%) were positive for COVID-19. In 3 patients, urinary samples were positive even after clearance of virus in oropharyngeal samples.

Tinospora cordifolia is reported for covid use. It has high potassium (0.845%) and could be playing a role in improving the hypokalemia status in covid patients [64]. Use of drugs that promote potassium loss like hydrochlorothiazide must be avoided. Further, the decreased potassium levels in conditions such as chronic renal failure, were restored to normal by day 30 in *Boerhaavia diffusa* root extract treatment, which can be attributed to the potassium nitrate content (6%) in the *B. diffusa* root extract [65]. *Withania somnifera* root extract may have some role in maintaining some of the serum electrolyte levels especially potassium within normal limit [27].

In addition to respiratory organs, up-regulation of ACE2 expression was also identified in urogenital system including kidney proximal tubule cells, bladder urothelial cells and genital organs including testis. Since the hypokalemia effect has been monitored and found to last more than 5 months in subjects with COVID-19 pulmonary infection and continued to have hypokalemia and even after the disappearance of the common COVID-19 symptoms [66], the suggestion of examining the estimation of potassium in urine of covid patients assumes critical importance. Since COVID-19 is detected in urine of infected individuals, infection transmission through urine remains possible, hence medical interventions like endoscopy and urethral catheterization for covid patients' needs to be done with care and caution [67].

Acute kidney injury (AKI) represents reduced glomerular filtration rate and/or reduced urine flow associated with mortality which is a regular feature in COVID-19 disease. Biomarkers of tissue damage e.g. creatinine may identify patients of particular risk [68]. Burns and Ho [69] report the higher levels of potassium in the urine of acute kidney injury patients, supporting our hypotheses in diagnosis of covid patients by measuring urine potassium levels. AKI has been found to be an independent risk factor for death in hospitalized COVID-19 patients [70], hence detection of covid virus in the urine might indicate possible kidney injury as described by de Souza et al. [71]. Also, in COVID patients, due to gastrointestinal disturbances, there is loss of water and electrolytes in the body, which is associated with diarrhea. Treatment of such patients with adequate water and electrolyte helps [72].

For the suggestion of testing urine of covid patients for the detection of virus genetic material requires no additional requirements than what is carried out presently with the nasopharyngeal (NP) swab and/or an oropharyngeal (OP) swab of the suspected/affected patient and then the isolation of RNA of the covid virus is carried out in a biosafety level III lab. The viral RNA is then subjected to RT-PCR that requires trained and

skilled personnel and also facilities for handling PCR products in air-controlled laboratories. Hence, the recommendation of Goudoris et al. [73] that the diagnosis of COVID-19 should be based on clinical data, epidemiological history and new diagnostic methods with higher sensitivity and specificity, as well as faster results, appears relevant and essential.

Rapid antigen lateral flow assays, although is rapid and low-cost for detection of SARS-CoV-2, it suffers from poor sensitivity early in infection [74]. Infectious SARS-CoV-2 was successfully isolated from urine of a COVID-19 patient and since the isolated virus isolated could infect new susceptible cells, it was emphasized that urine samples must be handled with care [75], however damage to kidney is ruled out [76].

Since the early diagnosis of covid would reduce spread of the disease, I believe the present hypothesis of using potassium estimation in urine of covid patients as results of diagnostic tests will have significant and beneficial implications for minimizing risks for health professionals and humans in general. Although Liu et al. [77] found that COVID disease severity could be predicted by lower counts of lymphocytes, neutrophils, albumin and increased values of LDH and CRP, the present observations of novel associations of potassium ions in viral diseases in general, tempts me to suggest examination of potassium levels in the urine of COVID patients' although, this merits further investigation.

Genetic variation in covid virus have been reported to be restricted to the gene coding for the spike protein [78, 79] and such mutations have been suggested to play a prominent role in viral transmission and overall stability of the virus. In the recent past, the United Kingdom has faced a rapid surge in COVID-19 cases and genome mapping has indicated multiple mutations in the spike protein gene and mutations in other genomic regions of the viral genome. Studies have shown that these variants are more transmissible than previously circulating variants [80]. Nearly 14% of SARS-CoV-2 variants were not detectable by RT-PCR using commercialized primers [81], hence one cannot ascertain that the employed methods of covid virus detection like RT-PCR might not yield false negative results. The currently described hypothesis of estimation of potassium ions in urine of covid patients will not be affected by such mutations and hence in all probabilities might serve as a fool-proof method for detection of covid-19 infection.

A recent study with 290 non-ICU admitted patients with COVID-19 in a hospital of Modena, Italy has revealed an increase of urinary potassium excretion in almost 95.5% cases [82] while another study with 175 patients where patients were classified based on serum potassium levels were found to improve by potassium supplementation through the use of potassium chloride at a daily dose of 40 mEq per day [83]. These recent reports do support the significance of monitoring

potassium levels in covid-19 patients and hence the current proposal of estimation of urinary potassium levels in covid-19 patients will benefit clinicians for faster diagnosis and initiation of treatment.

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Declaration of Competing Interest

The author declares that there are no known competing financial interests or personal relationships that could have appeared to influence the work reported this paper.

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