Biochemical Changes Of Electrolytes And Trace Elements Among Patient With Coronavirus Disease -19 (COVID -19) In Khartoum State

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Abstract

Background: coronavirus disease 2019 COVID-19 is a pandemic caused by severe acute syndrome coronavirus 2 (SARS-CoV-2) is respiratory and can be involved in multiorgan failure causes many biochemical changes in the human body, our study was designed to examine the serum level electrolytes and trace elements in COVID-19 patients and associated with severity of the disease.

Materials and methods: Cross-sectional study includes 50 COVID-19 patients conducted during the period from December 2020 to April 2021 and 50 healthy as control group. Blood samples were collected from the study group and measured electrolytes sodium and potassium by easy lite, calcium, phosphate, zinc, and copper by using calorimeter methods, statistical analysis was conducted using the SPSS version.

Results: The study showed that in COVID-19 patients there was a significantly low level of sodium (132 ± 4.3), potassium (3.2 ± 0.4), and calcium (7.8 ± .98) in comparison to control, insignificant in level of phosphorus and magnesium when compared with control group respectively (P.value = 0.15 , 0.8 .) . There is significant decrease in the mean level of zinc and increase in the mean level of copper in COVID-19 patients when were compared to control group (p value = 0.000) ,. However there was strong correlation between sodium (r=-.753, p= .000) , potassium (r= -.736, p=.000) , Zinc (r= -.819, p= .000) and Copper (r= .700, p= .000) with severity of disease.

Conclusions: COVID-19 infection cause hypernatremia, hypokalemia, and hypocalcaemia. Low zinc and high copper levels, the level of parameters is correlated with the severity of the disease.

Keywords: COVID -19, Sodium, Potassium, Calcium, Phosphate, Magnesium, Copper Zinc

A. Introduction:

The term "coronavirus" means "halo" or "crown." Coronaviruses are enveloped, positive-sense single-stranded RNA viruses with a genome size range of 26 and 32 kbs (1,2). Coronaviruses are zoonotic infections that originate in animals and can be transmitted directly from one person to another. The seafood market in Wuhan, China, where COVID-19 is said to have first appeared, was later closed down by Chinese authorities (3). Infection is primarily spread from person to person through respiratory droplets, close personal contact, like touching or shaking hands, and fecaloral routes are rarely used. Therefore, it has been advised to place persons who have been exposed to infection under quarantine for 14 days (4,5). Electrolytes are compounds that dissolve in body fluids and can conduct an electrical current. The extracellular fluid and intracellular fluid include these substances, therefore electrolytes are essential for regulating homeostasis (6). Neurological symptoms of hyponatremia, one of the electrolyte diseases, are present. Headaches, disorientation, confusion, and nausea are common patient complaints. When the serum sodium levels are higher than 145 mmol/L, hypernatremia manifests. Tachypnea, trouble falling asleep, and agitation are all signs of hypernatremia (7). The virus's entry reduces ACE2 and stops angiotensin II from degrading, which leads to an increase in the production of aldosterone and potassium loss from urine (8,9).

Despite the rarity of reports of hypocalcemia during COVID-19 infection, we should therefore pay greater attention to changes in calcium/phosphorus metabolism in COVID-19 patients and closely monitor calcium levels, especially in those with a history of hypocalcemia, to prevent the condition from getting worse and to start the right treatment as soon as possible. (6,8,9). In the pathophysiology of COVID-19, trace elements play a significant role. Recent assessments have noted that amounts of zinc are necessary for both the innate and adaptive immune systems (10).

For instance, low levels of zinc impair the activity of natural killer (NK)cells, which are essential for maintaining the immune response against viruses and tumors (11). Zinc must be in balance with copper in order to neutralize any negative impacts that copper may have. Additionally, copper is an essential trace element for both humans and pathogens (12). No matter the causative agent (virus, bacterium, or fungus), a steady rise in serum copper is a characteristic of infection (13–15). However, there is no data on copper levels in people who have COVID-19 infection. One of the significant ions needed as a cofactor for the ATP enzyme, which is involved in numerous crucial enzymatic activities, is magnesium. By controlling the active sites of particular kinases, Mg^{2+} has also been shown to play a crucial immunological function in CD8+ T cell activation in infection [16]. Understanding the potential connection between magnesium and pulmonary outcomes of COVID-19 disease depends on the finding from a recent study that serum magnesium levels may have a protective impact against lung function loss in asthma-chronic obstructive pulmonary disease [17].

2-Material and Methods

2- 1 Study Group

A cross-sectional study was conducted during the period from December 2020 to April 2021 in Khartoum State. Sudanese patients with COVID-19 and patients who were diagnosed with COVID-19 during the study period were enrolled to participate in this study. The confirmation of COVID-19 will be based on a CT scan and/or RT-PCR. The total study group was 100, 50 patients with COVID-19 as a case study, and 50 healthy individuals were enrolled as a control group.

2-2 Criteria for Inclusion and Exclusion

Patients with any chronic disease that may have an impact on serum electrolytes calcium phosphate magnesium zinc and copper levels will be excluded.

2-3. Ethical considerations:

The study was revised and ethically approved by the ethical and scientific committee of the Faculty of Medical Laboratory Sciences, University of Alzaiem Alazhari. Samples were taken with verbal consent from patients or their relatives.

2.4. Data collection:

A direct interview questionnaire was used to collect data. Medical information was collected from the patient's file with the help of the treating physician.

2.5. Collection of specimens:

Venous blood samples were collected by using sterile, dry, plastic syringes and a tourniquet to make the veins more prominent. The puncture sites are cleaned with 70% ethanol and 5 mL of blood is collected in lithium heparin containers. The lithium heparin blood sample was centrifuged at 4000 rpm to obtain the plasma and then stored at (-4 c) until the analysis.

2.6. Measurement of biochemical parameters:

The serum electrolytes Sodium potassium is measured by EasyLyte analyzer ion selective electrode technology, the flow-through sodium electrode uses a selective membrane that is specially formulated to be sensitive to sodium ions, and the potassium electrode employs a similar design with the appropriate selective membrane material. Each electrode's potential is measured in relation to a fixed and stable voltage set by the double-junction silver silver chloride reference electrode.An ion-selective electrode develops a voltage that varies with the concentration of the ion to which it responds. (18)

The colorimetric method is used for measuring zinc and copper.

copper by a single reagent colorimetric test with dibromo-PAESA). The assay principle consists of dissociating copper from ceruloplasmin and other copper-containing proteins, by a denaturalizing agent in acidic conditions. free and the portion associated with copper will form the copper-3-5DiBr-PAESA complex. which is detected by absorbance at 580nm. (19). Zinc forms a red chelate complex with 2-(5-Bromo-2pyridylase)-5-(N-propyl-N-sulfopropylamino)-phenol in a single reagent calorimetric test with 5-Bromo-PAPS. (20) Calcium, phosphate, and magnesium blood levels were measured by the Cobas 6000 fully automated analyzer (Roche-Germany).

2.7. Data examination

The statistical analysis of the results was performed by using the Statistical Package for Social Sciences (SPSS) version 15.0 for Windows version 10 using a T-test for testing difference significance and a Pearson correlation test (r-value as the coefficient). A P value of 0.05 was considered statistically significant.

Results

This study described 50 adult patients (21–81 years old) who were hospitalized with COVID-19 in an isolation center in Sudan. The study aimed to determine the serum levels of sodium, potassium, calcium, phosphate, magnesium, copper, and zinc in COVID-19 patients and compare the results with a control group. The COVID-19 patients are classified into mild (n = 19), moderate (n = 9) and severe (n = 22) according to disease severity in figure (1).

In the present study, the majority of COVID-19 cases were males (52%), which demonstrated that the incidence of COVID-19 is higher in males than in females. Abnormal laboratory parameters were more frequently observed in confirmed COVID19 patients, particularly in mild, moderate and severe or critical patients, as shown in Tables (1,2) and figures (2,3,4,5).

Table (1) showed hyponatremia and hypokalemia that there was a significant decrease in the mean level of sodium, potassium, and calcium in COVID-19 patients when compared with the control group (p-value = 0.000). Insignificant differences were found in the levels of phosphorus and magnesium among COVID-19 patients. There was no significant difference in the levels of phosphorus and magnesium when compared with the control group. This study showed that there was a significant decrease in the mean level of zinc and an increase in the mean level of copper in COVID-19 patients when compared to the control group (p-value = 0.000), table 1.

Pearson correlation investigates the relationship between COVID-19 disease stages and biochemical changes in plasma parameters in table (2) and figures (2, 3, 4,) and (5) .

Negative correlation between sodium levels and disease severity stages, R = -0.75, P =.000; negative correlation between serum potassium levels and disease stages, R = -0.74 , P =0.000.

Negative correlation between Plasma Zinc level and stages of the disease, R= -0.8

P. value =0.000, Positive correlation between Plasma copper and stages of COVID-19 disease, R= 0.7, P. value =0.000,.

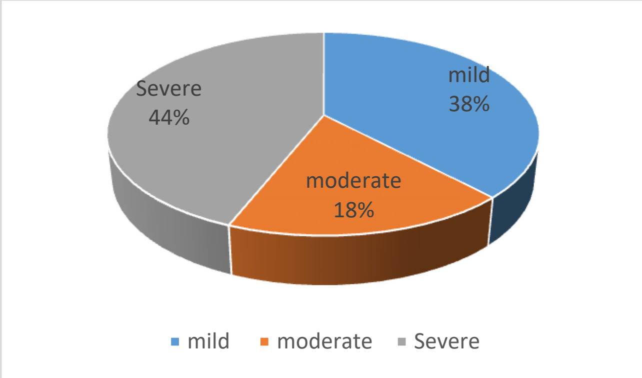

Figure (1) Distribution of stages of the disease in the case study

Table (1) Comparison of biochemical parameters means and Sd. among of the study groups

Test	**Cases (Covid19 patients)**	**Control (Healthy)**	**P value**
Sodium (Na mmol\L)	132 ±4.3	139±2.9	0.000
Potassium (K mmol\L)	3.2±.40	4.3±.46	0.000
Calcium (Ca mg\dL)	7.8±.98	9.2±.60	0.000
Phosphate (Ph mg\dL)	4.5±2.2	3. 9±.024	0.15
Magnesium (Mg mg/dL)	2.2 ±0.5	2.2±0.2	0.8
Zinc (Zn µg/dL)	60±26.8	85±23.4	0.000
Copper (Cu µg/dL)	219 ±89	93 ±23	0.000

Table (2) Correlation between the stages of the disease and biochemical changes in the plasma parameters

Test	Correlation(R-+)	P.value
Na mmol\L	-.753**	.000
K mmol\L	-.736**	.000
Zn µg \dL	-.819**	.000
Cu µg \dL	+.700*	.000

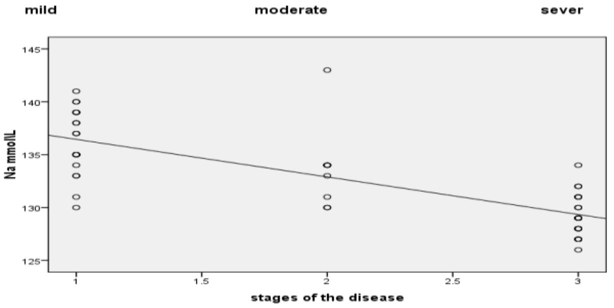

Figure (2) Correlation between Plasma Sodium (Na) level and stages of COVID 19 disease, R= -0.75 , P.value =.000

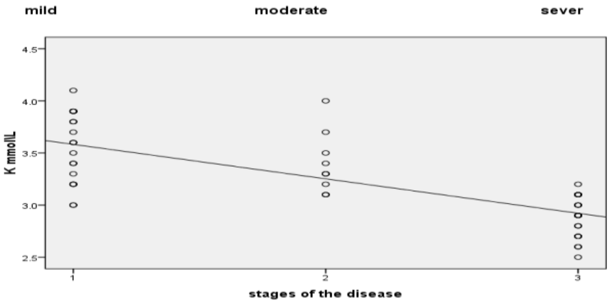

Figure (3) Correlation between Plasma level of Potassium (K) and stages of COVID 19 disease, R= -0.74P.value =0.000

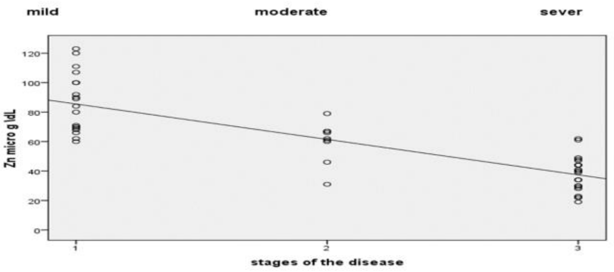

Figure (4) Correlation between Plasma Zinc (Zn) level and stages of COVID 19 disease, R= -0.8 P.value =0.000

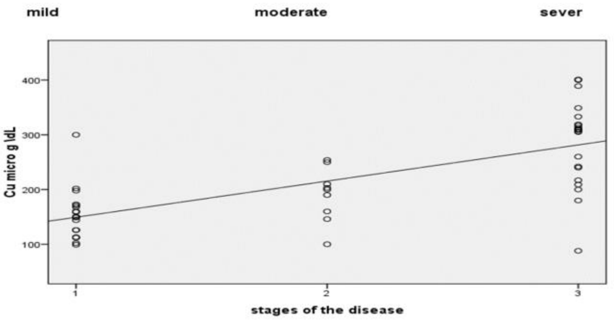

Figure (5) Correlation between Plasma Copper (Cu) and stages of COVID 19 disease, R= 0.7 , P.value =0.000

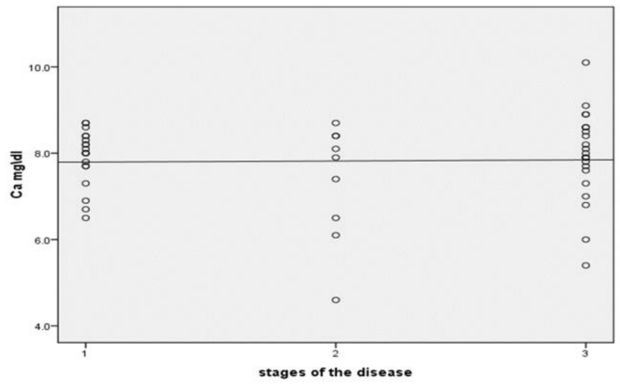

Figure (6) Correlation between serum Calcium (Ca) level and stages of COVID 19 disease R= 0.02 and P.value = 0.8.

Discussion

A new coronavirus known as COVID-19 was discovered in Wuhan, China, at the end of 2019. It caused havoc there, with an overall case-fatality rate (CFR) of 2.3% (4512 deaths among 68151 confirmed cases (21) found to spread from person to person like droplet infections (22) and was highly contagious, leading to a city lockdown to stop the spread of the illness (23) It began to spread over the world, and in March 2020 it reached Sudan (24).

COVID-19 is a huge global health problem due to its high rate of transmission and its high morbidity and mortality rates. Among the numerous pathophysiological effects associated with the virus, endocrine and metabolic disorders stand out. However, the particular consequences on the electrolytes, Calcium, Phosphorus, and trace elements metabolism system are still not fully understood., electrolyte and trace elements disturbances are commonly observed in patients with coronavirus disease 2019 (COVID-19) and associated with outcomes in these patients. Our study was designed to examine whether abnormal levels of electrolyte and trace elements are associated with mortality in COVID-19 patients.

Serum levels of electrolytes essential and trace elements are necessary for the well-functioning and maintenance of the immune system during any infection. In this present study, we measured serum levels of electrolytes and trace elements and their association with the severity of COVID-19 patients. The results indicate that these metal levels are altered in a severity-dependent manner.

This study described adult patients who were hospitalized with COVID-19 in an isolation center in Sudan. In the present study, the majority of COVID-19 cases were males (52%), which agrees with the study of Team TNCPERE (25) which demonstrated that the incidence of COVID-19 is higher in males than in females. This is due to dissimilar innate immunity, steroid hormones, and factors related to sex chromosomes.

The findings of this study, there was a significantly lower mean sodium and potassium levels in COVID-19 patients when compared to the control group , these results corroborated those of Carvalho et al. (26) who found that hyponatremia and hypokalemia were different associations with COVID-19 in comparison to controls. The enhanced production of antidiuretic hormone (ADH) in response to volume depletion after gastrointestinal fluid losses is thought to be responsible for these outcomes , severe illnesses have been linked to hyponatremia, hypokalemia, and hypocalcemia [27].

Some theories have developed, despite the fact that the pathophysiological mechanisms behind such alterations are still not completely known. SARS-interaction of Cov-2's with the ACE2 receptor may result in decreased ACE2 expression and increased angiotensin II, which stimulates potassium excretion and causes hypokalemia [28]. Additionally, diarrhea brought on by gastrointestinal dysfunction may be a cause in electrolyte imbalance (28). The kidneys and GI tract are key players in various processes that regulate fluid and electrolyte balance. Because of this, damage to them usually throws off the balance of fluid and electrolytes [29]. Electrolyte changes in patients, including sodium, potassium, chlorine, and calcium imbalances, are confirmed by similar studies of COVID-19 [30, 31].

Hyponatremia is one of the most frequent electrolyte abnormalities and is associated with a higher mortality risk in hospitalized patients [32].

Patients with COVID-19 who take RAS-inhibiting medications experience decreased aldosterone production, which can result in fluid and electrolyte imbalances. The central nervous system (CNS), the heart, the kidneys, and other GI tracts like the colon all express the mineralocorticoid receptor (MR), also known as the aldosterone receptor. Changes in ion concentration occur as a result of MR activation (such as sodium and potassium). These adjustments are required to keep the body's fluid and electrolyte equilibrium. In spite of this, MR is present in the large intestine [33–35]. Fluid and electrolyte imbalances result from a disruption of the aldosterone pathway, which also affects the absorption and secretion of ions in the colon. Electrolyte abnormalities, such as hyponatremia, hypokalemia, and hypochloremia, were more prevalent in COVID-19 patients than in controls, according to a case study [36]. A COVID-19 consequence called hypokalemia can increase acute respiratory distress syndrome (ARDS) and put patients at risk for cardiac damage [37]. In patients with acute COVID-19, hypernatremia is rather prevalent. Patients with hypernatremia have spent more time in intensive care and are at greater risk of passing away. As a result, in COVID-19 patients, the level of ions, especially sodium and potassium, is an important signal [38].

According to this study, there was a significantly lower mean calcium level in COVID-19 patients than in the control group , these findings supported by Yang's (39) finding that COVID-19 was independently related with hypocalcemia more so than the control group. Increased neuromuscular irritability, which is characterized by muscle spasms, tingling in the limbs, and perioral numbness, was found to be the most frequent side effect of hypocalcemia in a prior study. A rare complication of hypocalcemia is reversible cardiomyopathy [40]. The findings of the current study are similar with those of Ramesh (41) who found that COVID-19 was significantly associated with hypocalcemia more so than among controls.

When compared to the control group in this investigation, COVID-19 patients had normal levels of phosphate see table (1). Disagree with previous studies findings that hypophosphatemia was more significantly linked with COVID-19 than the control group (39, 41). Nutritional phosphate intake, intracellular to extracellular phosphate transfer, renal glomerular function, and tubular phosphate reabsorption all affect serum phosphate levels. Diets and environmental changes are likely to be to responsible for the discrepancy. Other earlier studies discovered that the link between hypophosphatemia and poor outcomes was likely mediated by the risk factors for hypophosphatemia, which are excessive energy consumption and catabolism as well as inadequate nutritional intake. Individuals with COVID-19 frequently suffered from malnutrition, which has been linked to a poor outcome for these patients. (42-47).

Additionally, the regular operation of immune cells may be impacted by cellular ATP depletion, which may be indicated by the low serum phosphorus level, which could affect the immune system's capacity to defend against viral infection. (42-47).

The current study shows the case study's normal serum magnesium level. Low of magnesium makes endothelium cells more susceptible to oxidative stress and encourages endothelial dysfunction. Low intracellular magnesium increases platelet-dependent thrombosis, and low serum magnesium is linked to increased thrombotic risk and slower fibrinolysis (48,49,50 ,51). Additionally, magnesium decreases mortality in vivo trials of induced pulmonary thrombosis and has antithrombotic properties (52). All of these shows that diffuse intravascular coagulopathy is more likely in COVID-19 individuals who are magnesium deficiency. Rare clinical data available on the serum Cu status of COVID-19 patients. The severity of the condition was positively correlated with higher serum copper levels among COVID-19 patients in this study table (1). Similar findings from previous studies have also shown that copper increased concentrations, with small deviations only in comparison to the healthy control group [53].

Additionally, a study conducted in Wuhan, China, found that patients with more severe diseases had generally higher Cu statuses, without finding a difference in full blood Cu between survivors and non-survivors [54].

Zinc is transiently transferred from the serum to the organs during infection and inflammation, resulting in momentarily low serum zinc levels, which return to normal as the inflammatory response decreases (55,56). When fighting infections, a normal zinc level is essential, by controlling the pro-inflammatory response, zinc signals have an anti-inflammatory effect during infection. (57)

Higher IL-6 responses have been linked to zinc deficiency. When COVID-19 causes severe lung injury, IL-6 is essential. When compared to mild, moderate, and controls in this study, it was found that the severe stage had significantly lower serum zinc levels see figure (4).

Similar findings were reported by Jothimani et al., who found that patients with decreased zinc levels had more serious problems and required longer hospitalizations in hospitals [29]. Numerous other studies [58, 59] reported reduced zinc levels in COVID-19-infected women, including pregnant women. Muhammad et al. [60] reported similar outcomes in the Nigerian population. In several studies, zinc supplements were also initiated as part of the standard treatment to confirm the role of zinc in the progression of the disease; the groups who were not given any supplements had higher mortality than the population taking zinc supplements [61]. Other findings for zinc and trace elements evaluated in severe COVID-19 patients are similar with those from earlier studies. When compared to mild-to-moderate COVID-19 infection, serum Zn levels have been reported to be reduced [62]. Skalny and others, 2021 (63) . Additionally, it was found that as compared to controls, increasing COVID-19 severity is linked to a large, steady decline in serum zinc levels as well as declines in serum calcium, iron, and selenium levels. However, there are higher levels of serum Cu and, in particularly, the Cu Zn ratio [63]. Additionally, according to the study, there is no obvious gender difference in the mean levels of sodium and potassium in COVID-19 patients (p-value 0.05). This result is in contrast a study by Vahidy et al. (64) who found that male patients hospitalized for COVID-19 had a larger proportion of abnormal laboratory values than female patients. The short sample size and environmental changes can be used as an explanation for this difference. Potassium and sodium have a high negative significant link ($r = -.736$, $p = .000$) according to the correlation study. This is similar to Zhou et al . (65), which discovered a high correlation between the severity of the disease and decreasing blood levels of sodium and potassium. The correlation study revealed a weak relationship between calcium and phosphate ($r = 0.02$, $p = 0.8$ and $r = -0.02$, $p=0.9$, respectively). This is in contrast to Yang's study, which found a significantly positive link between the severity of the disease and reduced blood levels of phosphate and calcium. Acute complications caused on by the virus can include acute kidney damage (AKI) and digestive issues for the patient. Fluid and electrolyte abnormalities are one of the side effects of kidney and GI involvement in COVID-19. The most prevalent of these conditions are hyponatremia, hypernatremia, hypokalemia, hypocalcemia, hypochloremia, hypervolemia, and hypovolemia. If untreated, these conditions can lead to a variety of complications for patients and even increase mortality (66). Additionally, changes in fluid, electrolyte, and trace element levels can be a good indicator of disease progression , this is due to the risk of fluid, electrolyte, and trace element disturbance complications requires special attention from clinicians in order to manage patients' fluid and electrolyte status, in addition to trace element supplements.

Conclusion: -

In conclusion, based on our results there was a significant decrease in serum levels of Sodium, Potassium, and Calcium in covid-19 patients when compared with the control group. In addition, there was a significantly strong negative correlation between serum levels of Sodium, Potassium, Calcium, and severity of patients of COVID-19. No biochemical change in Serum level of phosphate and magnesium among patients of COVID-19. Serum level of zinc decrease and serum copper levels increase when compared to mild, moderate and sever ill patients of COVID-19.According to our findings, serum levels of calcium were slightly lower in COVID-19 patients.

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