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Disorders of Blood Gases, Electrolytes, Magnesium, Albumin and Calcium Metabolism in SARS-CoV-2-infected Patients

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Abstract

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)-infection is characterized by several malfunctions, including severe pulmonary disorders. Other metabolic consequences of SARS-CoV-2-infection have not been clearly defined. The present study assessed the status of blood gases, calcium metabolism, and electrolytes in SARS-CoV-2-infected individuals. One hundred and thirty-four newly diagnosed SARS-CoV-2-infected patients (age ranged 65-82years) attending Mullingar Regional Hospital, Republic of Ireland, participated in this study. They all had pulmonary disorders, pyrexia, body pains, etc. SARS-CoV-2 was confirmed in all patients using the RT-PCR molecular test method. The data of another 121 plasma samples of apparently normal, non-SARS-CoV-2-infected individuals taken before the emergence of Covid-19 served as controls. Levels of partial pressure of oxygen (pO_2), saturated oxygen ($SatO_2$), partial pressure of carbon dioxide (pCO_2), and ionized calcium (Ca^{2+}) were determined in all participants using the potentiometric method in RAPIDPOINT 500 Blood Gases System. Plasma vitamin-D was determined by immune enzymatically technique using DXi 800 Access Immunoassay System. Total calcium, phosphate, albumin, magnesium, and electrolytes were determined by the photometric method using Beckman Au680- Chemistry Analyzer. The results showed significantly ($p<0.05$) higher levels of pCO_2 and HCO_3^- in COVID-19-patients compared to controls. Significantly($p<0.05$) lower levels of pO_2, $SatO_2$, pH, K^+, albumin, total-calcium, Ca^{2+}, magnesium, and vitamin-D were observed in COVID-19 patients compared to controls. Corrected calcium, PO_4^-, Na+, and Cl^- levels did not show significant ($p>0.05$) changes in the COVID-19-patients compared to controls. Abnormal blood gases, acidosis, hypomagnesaemia, hypoalbuminemia, hypovitaminosis D and calcium metabolic disorders could be features of COVID-19-disease.

Keywords*: Blood gases, Calcium metabolism, Covid-19, Electrolytes.*

Introduction

Severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is a novel coronavirus that emerged in Wuhan, China, in late 2019. The virus has an affinity for the angiotensin-converting enzyme-2 (ACE2) receptor molecule that is highly expressed on the surface of alveolar epithelial cells, enterocytes, arterial and venous endothelial cells, as well as arterial smooth muscle cells within many organs, including lung, stomach, and intestines [1, 2]. It also binds via its spike protein to the ACE2 receptor in the kidney, bone marrow, brain, spleen, myocardial cells, oesophagus, and ileum [3].

The consequent endothelial injury, microvascular angiopathy and increased level of hypoxia wade with decrease in the density of ACE2 in the viral targets of the infected models [4, 5]. There is enhanced hypoxia on

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upregulation of ACE2 expression in human pulmonary artery smooth muscle cells [6]. The density of ACE2 in each tissue, therefore, correlates with the susceptibility of the tissue and severity of infection [7]. Severe acute respiratory syndrome coronavirus-2 is characterized predominantly by respiratory disease in the form of viral pneumonia. Most patients with SARS-CoV-2 only experience mild symptoms, but some develop life threatening complications.

SARS-CoV-2 can cause life-threatening acute respiratory distress syndrome (ARDS) that may lead to severe inflammation, fibrosis, and impaired diffusion of gases in the lungs [8]. Report shows that among those who develop noticeable symptoms, about 81% develop mild to moderate symptoms like mild pneumonia, 14% develop severe symptoms (dyspnea, hypoxia, or more), and 5% suffer critical symptoms like respiratory failure, shock, or multiorgan dysfunction [9]. Hospital records show that approximately 14.2% to 30% of in-patients are further admitted to the intensive care unit, primarily for mechanical ventilation to resolve hypoxia and other complications [10-12].

The mortality in hospitalized Covid-19 patients ranges from 13.2% to 28.3%, with the majority of reports coming from China and the United States of America [2, 13, 14]. Previous studies reported severe hypoxia in Covid-19 patients in New York City [15]. Hypoxemia has been confirmed to contribute significantly to mortality in patients with Covid-19 [16]. Covid-19 patients require an oxygen saturation of the recommended 92–96% range). It was also reported that all $SatO_2$ categories <90% on admission was associated with higher hazard mortality compared to $SatO_2$ >90% [17].

The metabolic consequences of hypoxemic respiratory failure may include acidosis, glucose metabolic disorder, lipid metabolic disorder, minerals, and electrolyte disorders with general metabolic dysfunctions. Hypoxia and inflammation are intertwined at the molecular, cellular, and clinical levels. Most of the clinical events that produce acute hypoxia would enhance various cytotoxic functions of neutrophils and could cause hyper inflammation [18]. Animal models exposed to low oxygen concentrations results in increased vascular permeability, accumulation of inflammatory cells, and elevated serum cytokine levels [18].

Like other viruses, SARS-CoV-2 has the potentials to hijack the host cell machinery. Several studies show that the coat proteins of many viruses are potential Ca^{2+}-binding proteins [19, 20]. So, the viruses can appropriate or interrupt both Ca^{2+} signaling pathways and other Ca^{2+}-dependent processes for its metabolic processes. Also, viruses have the potential to alter host calcium-permeable channels and pumps across the plasma membrane or subcellular organelles modulating intracellular free Ca^{2+} [21]. A lower level of calcium has been observed in the early stage of SARS-CoV-2 infection, but the severe/critical cases showed significantly lower calcium levels compared to mild/moderate cases [22]. The level of virulence of SARS-CoV-2, therefore, accounts for its classification as Hazard Group 3 [23]. Since Covid-19 pandemic is a universal threat with the potential to disrupt several organ functions and metabolic activities, the specific objective of this study was to determine the status of blood levels of pCO_2, pO_2, saturated O_2 ($SatO_2$), pH, plasma levels of HCO_3^-, K^+, albumin, total calcium, ionized calcium (Ca^{2+}), vitamin D, magnesium, PO_4^-, Na+ and Cl^- in SARS-CoV-2-infected patients.

Materials and Methods

Materials

One hundred and thirty-four newly diagnosed Covid-19 infected patients presenting directly to Mullingar Regional Hospital, Mullingar, the Republic of Ireland with the pulmonary disorder, pyrexia, vomiting, pains etc., volunteered to participate in this study. Another 121 plasma samples of apparently normal, non-Covid-19 infected individuals taken before the emergence

of Covid-19 served as controls. Informed consent was obtained from every participant before the commencement of this study. The Institutional Review Board approved this study, and ethical approval was obtained from the Texila American University Ethical Committee.

Study Type

This is a cross-sectional study.

Selection of the Area

This study was carried people living in the Mullingar metropolis and its environs, where Covid-19 prevalence was 2% at the time the study was conducted. Analyses of samples was carried out at Mullingar Regional Hospital, Mullingar, Republic of Ireland.

Sample Size Determination

The sample size was determined using the following formula.

$$N = \frac{Z \propto^2 pq}{d^2}$$

Where:

N = required sample size

Zα/2 = Standard deviation at 95% confidence interval = 1.96.

d = the degree of precision expected (3%).

p = prevalence is 2%.

$$Z = 1.96, p = 2\%, q = 1, d = 0.03$$

$$N = \frac{1.96 \times 1.96 \times 0.02 \times 0.98}{0.03^2}$$

$$Sample\ size = 83.7$$

Sampling Techniques

A simple random technique was employed to recruit the Covid-19 patients for this study.

Data Collection

Participants were asked to respond to a questionnaire for information about the clinical presentation such as *pulmonary disorder, pyrexia, vomiting, body pains* after confirmation of SARS-COV-2 status. Five milliliters (ml) of venous blood sample were taken and put into a lithium heparin bottle for the determination of PCO_2, PO_2, saturated O_2 ($SatO_2$), pH, plasma levels of HCO_3^-, K^+, albumin, total calcium, ionized calcium (Ca^{2+}), vitamin D, magnesium, PO_4^-, Na+ and Cl^-. 3ml of the blood was centrifuged, and the plasma separated and stored at -20^0C for the determination of pH, plasma levels of HCO_3^-, K^+, albumin, total calcium, ionized calcium (Ca^{2+}), vitamin D, magnesium, PO_4^-, Na+ and Cl.

Study Location

This study was carried out at Mullingar Regional Hospital, Mullingar, Republic of Ireland.

Methods

Testing for SARS-CoV2

For confirmation of Covid-19, RT-PCR Molecular Test was carried out using Cepheid Genexpert System. The principle is based on the fact that RNA is first transcribed into complementary DNA (cDNA) by reverse transcriptase from total RNA or messenger RNA (mRNA). The cDNA is then used as the template for the qPCR reaction.

Determination of Blood Gases and Ionized Calcium

Levels of blood gases and ionized calcium were determined in all participants using RAPIDPOINT 500 Blood Gases System. The operation is based on the potentiometric Principle. An electrochemical interaction between the analyte of interest and the sensor generates an electrochemical signal that is proportional to the amount of analyte in the sample.

Determination of Plasma Vitamin D

Plasma vitamin D was determined using UNICEL DXi 800 Access Immunoassay System. The principle is based on the use of paramagnetic particle solid phase and chemiluminescent detection for the determination of the analytes. Two-site Immunoenzymatically (Sandwich) method.

Determination of Plasma Total Calcium, Phosphate, Albumin, Magnesium, and Electrolytes

Total calcium, phosphate, albumin, magnesium, and electrolytes were determined using Beckman Au680- Chemistry Analyser. The principle is based on the reaction of analytes with assay-specific reagents through a biochemical reaction leading to a colour formation directly proportional to the activity of the analyte in the serum. The ISE module of AU680 used to determine the Electrolytes (NA, K, and Cl), mixture aspiration roller-pump pulls ion-selective electrode reference solution to the reference electrode where measurements are taken, and the solution is sent to waste.

Statistical Analysis

Statistical analyses were performed using Statistical Package for Social Sciences (SPSS) for Windows, version 21.0 (SPSS Inc. Chicago, USA). Data were expressed as Mean ± SD. Student (T) test was used for comparison of Covid-19 patients and controls. The changes were considered significant when p-values were less than 0.05.

Results

As shown in Table 1, plasma levels of albumin, magnesium, vitamin D, total calcium, and ionized calcium (Ca^{2+}) decreased significantly ($p<0.05$) in Covid-19 patients compared with controls. The corrected calcium, PO_4, and Cl^- did not show significant ($p>0.05$) changes in the Covid-19 patients compared with controls. As demonstrated in Table 2, Covid-19 patients showed significantly ($p<0.05$) higher levels of pCO_2 with significantly ($p<0.05$) lower levels of pO_2, $SatO_2$, and pH compared with controls. Plasma electrolytes in Covid-19 patients (Table 3) showed a significantly ($p<0.05$) higher level of HCO_3^- and significantly ($p<0.05$) lower level of K^+ compared with controls. Plasma levels of Na^+ and Cl^- did not show significant ($p>0.05$) differences in Covid-19 patients compared with controls.

Table 1. Levels of Plasma Calcium, Magnesium, Phosphate, Albumin and Vitamin D in Covid-19 Patients and Controls

Levels	**Controls**	**Covid-19 Patients**	**p-values**
	(N=121)	(N=134)	
Age	62.4±15.9	65.8±17.1	>0.05
Total calcium (mmol/l)	2.4±0.1	2.2±0.19	<0.0001*
Corrected calcium(mmol/l)	2.34±0.09	2.34±0.14	=0.86
Ionized calcium (mmol/l)	1.19±0.04	1.09±0.03	<0.0001*
Phosphate (mmol/l)	1.06±0.16	1.01±0.27	=0.06
Magnesium (mmol/l)	0.85±0.12	0.82±0.13	=0.048*
Vitamin D (nmol/l)	60.4±12.5	33.8±16.3	<0.0001*
Albumin (g/l)	42.4 ±2.8	36.1±2.62	=0.008*
*=Significantly different from controls; N= Number of participants			

Table 2. Levels of Blood Gases and pH in Covid-19 Patients and Controls

Levels	**Controls (N=121)**	**Covid-19 Patients (N=134)**	**p-values**
PO_2 (kPa)	11.0±0.83	6.70±0.58	<0.0001*
PCO_2 (kPa)	5.50±0.38	7.4±0.99	<0.0001*
pH	7.40±0.023	7.27±0.07	<0.0001*
$SatO_2$ (%)	92.0±4.05	72.2±9.60	<0.0001*
*=Significantly different from controls; N= Number of participants			

Table 3. Levels of Electrolytes in Covid-19 Patients and Controls

Levels	Controls (N=121)	Covid-19 Patients (N=134)	p-values
Na^+ (mmol/l)	137.7±2.4	137.3±5.72	0.49
K^+ (mmol/l)	4.75±0.4	4.05±0.51	0.02*
Cl^- (mmol/l)	102.6 ±2.8	102.3±5.7	0.69
HCO_3^- (mmol/L)	23.40±1.63	25.8±1.97	<0.0001*
*=Significantly different from controls; N= Number of participants			

Discussion

Pulmonary and extra-pulmonary dysfunctions have been reported in patients with SARS-CoV-2 infection. Available data show that inflammation of the lungs leads to alveolar architectural destruction and abnormal diffusion of gases in the affected patients. Diffuse alveolar damage similar to that of influenza virus infection has been reported in SARS-CoV-2 infected patients [24]. During inflammation, the lung tends to collapse and may become clogged with mucus. The resultant obstruction, therefore, reduces the airflow through the bronchial tubes. This and other factors might contribute to the significantly lower levels of pH, pO_2 and $SatO_2$ in the Covid-19 patients recruited for this study. This study could hypothesize that Covid-19 is characterized by respiratory acidosis. The acidosis could be explained by the significantly higher level of pCO_2, and significantly lower level of pH observed in Covid-19 patients recruited for this study. The significantly higher level of HCO_3^- in the Covid-19 patients could be due to the accumulation of pCO_2. Our findings seem to confirm the reports of other workers who reported that hypoxemia is a critical feature of Covid-19 requiring admission [25, 26]. Other studies show that the resultant hypoxia has the potential to enhance the overexpression of ACE2 receptors and the risk of tissue damage in Covid-19 patients [27]. The hypoxia has been reported to further increase levels of proinflammatory cytokines [28], complement activation [29], and destruction of endothelial cells lining the pulmonary arteries and capillaries of the Covid-19 patients [30, 31]. A significantly higher level of pCO_2 observed in this study could also be a consequence of pulmonary dysfunction in Covid-19 patients recruited for this study. The hypercapnia suggests emphysema and pulmonary odema in Covid-19 patients. Disruption of intercellular junctions, inflammatory, pro-coagulant responses, loss of alveolar functions, and cell swelling commonly found in Covid-19 patients could account for these abberations in gaseous homeostasis. Our study contradicts a report showing a higher level of blood pH (alkalaemia) in Covid-19 patients [32].

The blood electrolytes, including Na^+, K^+, Cl^- and HCO_3^- help in the regulation of nerve, muscle function, acid-base, and water balances. Deregulation of electrolytes contributes to several metabolic disorders. The plasma levels of Na^+ and Cl^- did not show significant changes in the COVID-19 patients. Meanwhile, the plasma level of K^+ decreased significantly in SARS-CoV-2 infected patients compared to controls. To the knowledge of the authors, this study is the first to report hypokalemia in SARS-CoV-2 infected patients. Since the SARS-COV-2 has the potential to alter the functions of the kidney, the relative hypokalemia observed in this study could be due to renal loss. This study tends to corroborate the report of a previous study that electrolyte imbalance is a feature of Covid-19 disease [33].

The physiological role of vitamin D is to form a Ca-binding protein for effective absorption of Ca^{++} in the intestine and reabsorption of filtered Ca^+ in the renal tubule. The significantly lower level of vitamin D observed in our Covid-19

patients is in agreement with an existing report showing a significantly lower level of vitamin D in Covid-19 patients [7]. Vitamin D deficiency could contribute to a significantly lower level of total calcium and ionized calcium in these patients. Several reports show that a virus has the potential to divert Ca^{2+} for its own metabolic activities. The alteration of host cells Ca^{2+} homeostasis is one of the strategies that viruses use to modulate host cells signal transduction mechanisms in their favor. Also, viruses like Polioviruses, Coxsakie virus, Herpes simplex virus etc., can trigger cytosolic Ca^{2+} influx. It has been reported that Ca^{2+} is essential for virus entry, viral gene replication, virion maturation, and release [21]. In another study, it was reported that the viral proteins directly or indirectly disturb Ca^{2+} homeostasis by (1) altering membrane permeability and/or manipulating vital components of the Ca^{2+}-signaling apparatus; (2) binding of viral proteins directly to Ca^{2+} for structural integrity or functionality; and (3) critical virus-host interactions depend on cellular Ca^{2+}-regulated proteins or pathways [34]. Other studies show that Ca^{2+} plays an important role in the replication of rotaviruses and the pathogenesis of rotavirus infection [35]. Host calcium-permeable channels and pumps mediate transportation of Ca^{2+} across the plasma membrane and modulating intracellular free Ca^{2+}. Therefore, Ca^{2+} pumps play important roles in viral pathogenesis and virus-host interaction. These and other factors like renal disorders could also contribute to the significantly lower levels of total calcium and Ca^{2+} observed in the Covid-19 patients recruited for this study. This study corroborates a finding where consistent hypocalcemia was reported in all Covid-19 patients [36]. Usurpation of Ca^{2+} during coagulation processes in SARS-CoV-2 infected patients is another possible pathway that could contribute to a significantly lower level of Ca^{2+} in the patients [37]. This study corroborates the report of [34], who stated that both mild/moderate and severe cases of Covid-19 showed low calcium levels in the early stage of infection and decreased steadily with the severity of infection. A significantly lower level of albumin observed in this study could also contribute to hypocalcaemia in Covid-19 patients. Possible consequences of hypocalcemia could account for the enzyme, neurological, mental, metabolic, cardiovascular, and musculoskeletal disorders commonly reported in the Covid-19 patients. The corrected calcium level didn't show any significant change in the Covid-19 patients for reasons yet to be known.

Magnesium is the second most abundant intracellular cation and the fourth most abundant cation, which plays an important physiological role in the system. Activities of over 300 enzymes are dependent on magnesium [38]. Magnesium balance is maintained by the regulation of renal reabsorption [39]. It is essential for the synthesis of nucleic acids and proteins, for intermediary metabolism, and for specific actions in neuromuscular and cardiovascular systems. Renal insufficiency, malnutrition due to anorexia, and malabsorption could account for a significantly lower level of magnesium in Covid-19 patients recruited for this study. This study agrees with a report showing a significantly lower level of magnesium and proposed the possibility of magnesium supplementation for supportive treatment in Covid-19 patients [40]. This study may contradict a study reporting a higher level of magnesium in patients with Covid-19 [41].

Albumin is one of the major transport proteins that is synthesized in the liver. During chronic infection, protein synthesis is switched to protective molecules (e.g., immunoglobulins) at the expense of transport proteins like albumin [42]. Several studies have reported abnormal liver functions in Covid-19 patients [43]. This liver disorder is possible in Covid-19 patients since SARS CoV-2 also binds to ACE2 receptors in the liver [44, 45]. Other studies reported that the liver disorder resolves in the survivors of Covid-19 [45]. These and other

factors could account for impaired synthesis and the significantly lower level of albumin in the Covid-19 patients recruited for this study. Our finding, therefore, corroborates the report of other researchers who stressed that hypoalbuminemia is common in Covid-19 patients and linked the degree of hypoalbuminemia to disease severity [44, 45]. The serum albumin levels were found to gradually decrease both in severe and non-severe Covid-19 patients [44]. In another study, albumin level was hypothesized to be an independent predictor of the risk of nonsurvivors in critically ill patients with Covid-19 [46].

Conclusion

Abnormal blood gases, acidosis, hypomagnesemia, hypoalbuminaemia, *hypovitaminosis D,* and calcium metabolic disorders are possible features of COVID-19 disease.

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Declaration of Conflicts of Interest

The authors of this research did not receive any grant for the project and declare that there is no conflict of interest.

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