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ORIGINAL STUDY

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# Investigation of Some Biochemical Parameters Changes Due to Coronavirus Infections

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**Abstract**

**Background: Coronavirus infection has been the severest pandemic in recent years. Several biomarkers for direct assessment and rapid diagnosis have been used, such as IgM and PCR.**

**Objectives: The aim of this study was to investigate the critical biomarkers, either a mineral or an enzymatic inhibition or activation.**

**Materials and Methods: This study was conducted on COVID-19 patients who were suspected of being infected with the coronavirus, using serum of 25–80 years of age, males. The following biochemical tests (LDH, CK-MB, Ferritin, Mg, Zn, Cu and Ceruloplasmin) were measured at a private laboratory in Baghdad.**

**Results: The results showed that three trace elements significantly changed, positively or negatively, in 50 male patients who had a severe coronavirus infection. The study explored the correlation between the above parameters and the immune system which impaired the function of some organs in the body.**

**Conclusion: We can conclude that all the biomarkers, including Mg, Zn, Cu, CP, CKD, LDH and ferritin, significantly changed during coronaviruses infections which are involved in the main cellular functions and play a vital role against viral infection. Our results highly recommend following these parameters clinically as biomarkers for coronavirus infection instead of performing several other viral tests.**

*Keywords:* Coronavirus, Biomarkers, Viral infections, Statistical analysis, Trace elements

## 1. Introduction

Coronavirus Disease 19 (COVID-19) is a complex multi-systemic disease whose pathogenesis is not fully understood. The virus can mutate quickly and therefore there are many variants. Due to the viral infections, an inflammatory response develops in most patients. The inflammatory process due to infection with SARS-CoV2 has been suspected to play a crucial role in the pathogenicity of multiple organ failure and is responsible for dramatic outcomes in patients. Several inflammatory biomarkers including white blood count have been routinely used to follow

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and diagnose anyinflammatory process of infections [1–3].

Cost-effective biomarkers, such as those that are routinely requested by medics enable risk stratification to allow prudent resource allocation [4]. Multiple biochemical biomarkers such as lactate dehydrogenase (LDH), C-reactive protein, fibrinogen, and D-Dimer, which are commonly used in clinical practice to monitor the process of sepsis are also followed by several studies to assess the development of coronavirus infection [5]. Most of these biomarkers have been found to be remarkably changed due to viral infection. However, the correlation between these biomarkers with the infection has not been well investigated. For instance, LDH catalyzes the last step of aerobic glycolysis in the pyruvate to lactate conversion [6] LDH has been shown to be a potential predictive biomarker in patients with COVID-19. The elevated level of LDH signifies tissue hypoperfusion, indicating the extent of the disease; hence, it may affect prognosis [7, 8].

However, studies have shown that LDH is not associated with poor prognosis. Iron deficiency is another biomarker that was found to be remarkably changed due to viral infection. It is established that the metabolism of iron is involved in several pathogenetic disease mechanisms, including infections and various hematological and immunological disorders [9]. Recent studies have shown that iron metabolism can undergo significant modifications which can be employed in predicting mortality even in patients admitted to intensive care units. Furthermore, serum ferritin has been recently cited as one of the indicators of mortality in COVID-19 patients [10].

Moreover, deficiencies in serum biomarkers of Cu, Se and Zn were suspected to be involved in inflammation, oxidative stress, and viral entry into the cells by decreasing ACE-2 expression. Other factors that are proposed to be involved in COVID-19 pathogenesis are Mg, Cu, Fe and Zn have also been found significantly changed due to the infection [11, 12]. Magnesium (Mg) was previously studied with immune deficiency during COVID 19 infection [13]. As it has a strong relationship with the immune system, and immunological functions are disturbed in cases of Mg deficiency [14, 15]. Since the immune response is involved in COVID-19 progression, serological assays were developed in many countries [16]. However, there are still many challenges and knowledge gaps in the clinical applications of antibodies and other biochemical markers to diagnose and correlate these biomarkers in such infections [17].

The purpose of this study was to investigate the correlation between biochemical parameters clinically for COVID-19 infection in Iraqi male patients. We used our private lab to investigate various stages of infection. The study was designed using parameters that routinely appear in our lab for similar patients. Several routine tests were excluded, such as complete blood count, IgM (checked but excluded) and CT scan [18].

## 2. Materials and methods

### *2.1. Study design and patiens*

This study was conducted on COVID-19 patients who were suspected of being infected with the coronavirus, using serum of 25–80 years of age, males. The following biochemical tests (LDH, CK-MB, Ferritin, Mg, Zn, Cu and Ceruloplasmin) were measured by Dimension ®EXL™ 200 – SIEMENS in a private Laboratory, Baghdad, Iraq, using commercial kits that provided with the mentioned instrument. 100 cases were divided into two groups, the first group of control patients n = 50(Healthy), and the second group of patients n = 50. All the rules for collecting and storing the samples in this study had ethical approval signed by the patients in the study or by their relatives in severe cases. Only patients who were diagnosed with coronavirus by the clinic were included in this study.

### *2.2. Statistical analysis*

Software Prism GraphPad 8.0.1 was used for statistical analysis. T-test was performed to find significance between the average values of patients and healthy control. All the compared values were shown to be significant. P value was considered $P < 0.05$.

## 3. Results and discussion

The biochemical analysis of the serum samples taken from COVID-19 patients 25–80 years of age/males) compared with the healthy controls has shown a highly significant increase in (LDH, CK-MB, IgM, Ferritin, Ceruloplasmin, Mg, and Cu) as shown in (Table 1) mean; (620.8–329.3) $P < 0.0001$, (43.26–13.40) $P < 0.0001$, (481.3–141.2) $P < 0.0001$, (89.5–37.71) $P < 0.0001$, (3.76–2.10) $P < 0.0001$ and (177.8–96.98) $P < 0.0001$ respectively. However, a clear decrease was seen for the Zn parameter, mean; (50.38–91.84) $P < 0.0001$. Most of these results were confirmed by previous studies. However, here, we try to interpret the correlation among these parameters by following through their pathways. The sub-figures are shown all in one figure as in (Fig. 1). All the statistical results are shown in Table 1.

It is well established that infection with coronavirus SARS COV-2 affects the immune system in the body.

*Table 1. The measurement of biochemical parameters of two groups (control & patients).*

| Parameters | Groups | Mean | t-value | SD of Discrepancy | 95% Confidence Interval | P-value | P-value summary |
|---|---|---|---|---|---|---|---|
| LDH | Control | 329.3 | 42.00 | 55.44 | 313.5 to 345.0 | <0.0001 | **** |
| | Patients | 620.8 | 70.48 | 62.28 | 603.1 to 638.5 | <0.0001 | **** |
| CK-MB | Control | 13.40 | 29.10 | 3.255 | 12.47 to 14.32 | <0.0001 | **** |
| | Patients | 43.26 | 52.37 | 5.841 | 41.60 to 44.92 | <0.0001 | **** |
| Ferritin | Control | 141.2 | 38.74 | 25.76 | 133.8 to 148.5 | <0.0001 | **** |
| | Patients | 481.3 | 88.24 | 38.57 | 470.4 to 492.3 | <0.0001 | **** |
| Mg | Control | 2.10 | 75.55 | 0.1966 | 2.045 to 2.157 | <0.0001 | **** |
| | Patients | 3.76 | 44.35 | 0.6004 | 3.596 to 3.937 | <0.0001 | **** |
| Zinc | Control | 91.84 | 61.45 | 10.57 | 88.84 to 94.84 | <0.0001 | **** |
| | Patients | 50.38 | 73.79 | 4.828 | 49.01 to 51.75 | <0.0001 | **** |
| CP | Control | 37.71 | 25.22 | 10.57 | 34.70 to 40.71 | <0.0001 | **** |
| | Patients | 89.50 | 56.67 | 11.17 | 86.33 to 92.68 | <0.0001 | **** |
| Cu | Control | 96.98 | 69.46 | 9.872 | 94.17 to 99.78 | <0.0001 | **** |
| | Patients | 177.8 | 66.54 | 18.90 | 172.4 to 183.2 | <0.0001 | **** |

This was emphasized using the sequencing approach methodology [19]. However, multiple biochemical parameters could be changed due to this infection which consequently leads to the worst pathological complications. Some of these biochemical parameters have been studied enormously such as LDH, CK, and ALT [20]. This paper investigates some of these biomarkers and electrolytes in serum blood but also discusses their functionality due to the changes.

The first important trace element found remarkably affected is that zinc. Our results showed that the levels of zinc in blood serum were substantially decreased by almost half than in the healthy control. Although the body uses this element in tiny amounts, zinc is still required by at least a hundred enzymes to perform essential chemical reactions. Zinc facilitates crucial interactions, for example, it is involved in generating DNA, the growth of cells, protein expression, recovering damaged tissues, and aiding the Immune system [20]. Recent studies mentioned that the human body is protected by zinc from viral attacks [21]. Research studies indicated that the presence of zinc in physiological concentrations increases the ciliary beat frequency in the lungs that are targeted by the coronavirus [22]. Coronavirus increases with the damage of ciliated epithelium and ciliary dyskinesia which consequently affects mucociliary clearance [23].

The enhancement of ciliary clearance would remove virus particles and also decrease the chance of secondary bacterial infections. Another essential role of zinc against viruses is that zinc could preserve the tissue barrier from damage. For example, zinc was found fundamentally involved in the expression of tight junction proteins such as Claudin-1 and ZO-1. Therefore, high levels of zinc could probably improve lung tolerance against mechanical ventilation damage [24].

It is worth mentioning that viral application was found to be directly inhibited by Zinc. Multiple studies showed that fusion with the host membrane can be prevented by zinc [25]. It was also shown that zinc weakens the protein translation and processing of viruses in various ways [26]. Moreover, zinc helps maintain muscle from hard exercise by improving aerobic capacity to provide oxygen to the muscles [27]. The pathway that describes the zinc deficiency due to the coronavirus is still unclear. However, the studies mentioned above show that the consumption of zinc by the body could be due to viral infection. Therefore, it can be clearly stated that zinc deficiency is a beneficial indicator and a biomarker for coronavirus infection and its replacement may be suitable for further trials of treatment. Consequently, the supplementation of zinc is probably a direct and quick treatment for coronavirus, which is the best, safest, and quickest approach to stimulate special immune cells and increase oxidative stress.

Copper is another important trace element that was found significantly reduced in the blood serum of coronavirus patients in comparison to the healthy control. Lower copper levels are associated with low responses in the immune system, which increases viral and bacterial infections [28]. Despite the fact that many necessary biochemical processes in the body are

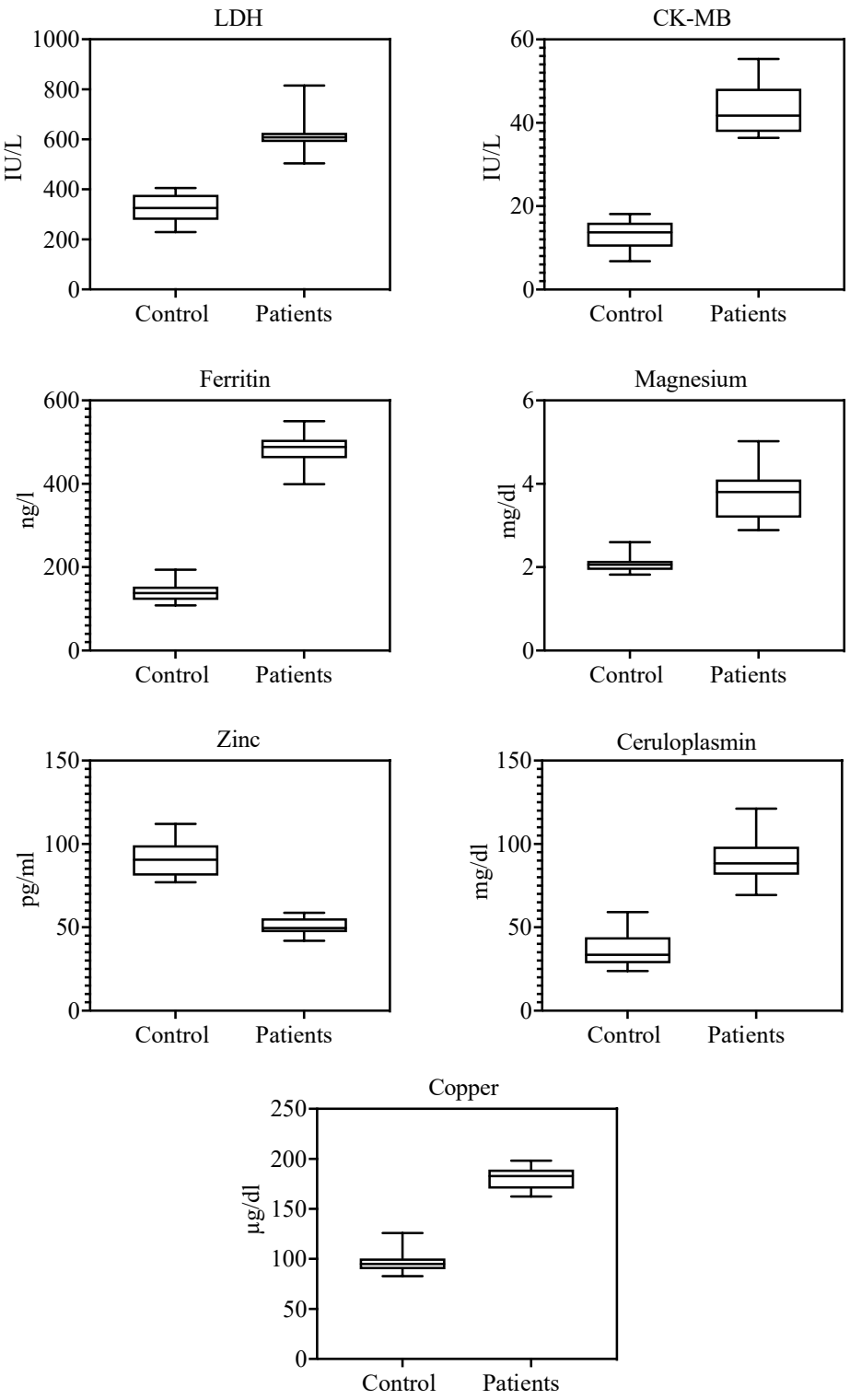


*Fig. 1. The concentrations' levels for all the examined biochemical parameters for both healthy control and coronavirus patients.*

mediated by copper elements [29, 30], it also blocks a crucial protein of SARS COV2 replication. Therefore, copper is considered an antiviral element which fights against infections within the immune system and also by direct contact with the virus [31]. A recent study found an increase in copper levels in patients surviving COVID-19 and it has been quantified as a biochemical marker for diagnosis [32].

Another study investigated the CP ceruloplasmin concentrations as a total protein concentration only without estimating its enzymatic activity. A significant positive correlation was found with mild COVID-19 linked to both CP and copper levels [33]. This reduction can be interpreted as follows: CP is made in the liver in the WBC when it can be coordinated with six copper atoms, which are released into the plasma [34]. The main reason for an increase in CP is inflammation. CP levels are reduced possibly due to irregularly high levels of copper. Thus, both CP and copper are consumed at the same time.

Magnesium is another crucial trace element that was found remarkably doubled in the blood serum of coronavirus patients in comparison to the healthy control. Magnesium concentrations in coronavirus patients were increased by about twofold. The results agreed with a previous study, which found that 35% of coronavirus patients who had hypermagnesemia suffered from respiratory failure and required mechanical ventilation. Another study suggested adding a test of magnesium in serum blood to the panel of examinations routinely ordered to diagnose severe SARS-CoV-2 infections [35]. Magnesium plays an essential role in various pathways such as protein synthesis, metabolism, glycolysis and cell growth [36]. It also controls muscle and nerve functions.

It relieves tight and cramped muscles by regulating muscle contraction and relaxation [37]. It works as a bronchodilator for the lungs' muscles and therefore expands the airways for better respiration [38]. Thus, it can relieve asthma symptoms. More importantly, to mention is that magnesium operates the activity of the innate and adaptive immune systems [39]. It also controls the activity of neutrophils, macrophages, and lymphocytes. Therefore, low levels of magnesium are also associated with increased amounts of inflammatory mediators [40]. However, hypermagnesemia was found significantly increased in severe ICU cases of coronaviruses [41]. These results confirm our findings, which showed hypermagnesemia in our selected patients with coronavirus infection. The mechanism by which magnesium increases in such cases is still unclear. However, magnesium can be released into the bloodstream during muscle contraction and relaxation. Since the cross-bridge cycle of muscle contraction and relaxation depends on the exchange of magnesium with calcium, when magnesium binds to troponin C in turn, triggers the relaxation.

It then consequently leads to cramped muscles and disables the respiratory system causing respiratory failure [42]. Since magnesium protects against viral infections, magnesium levels increase due to adequate intracellular magnesium concentrations needed to activate lymphocytes and natural killer cells in the immune system. Therefore, hypermagnesemia reduces muscle contraction-relaxation by an abnormal exchange of magnesium with calcium concentrations and results in impairment of respiration. Therefore, magnesium supplementation in such cases is inappropriate.

Another substantial change found in coronavirus patients is the LDH and CKP parameters. Both of these parameters were studied deeply in different countries and found to be doubled in coronavirus patients in comparison to the healthy control. However, most of these studies have not explained the change of these parameters pathologically but only statistically [43]. A recent review performed a metanalysis for 1159 Coronavirus patients collected from eight studies showed that CK concentrations were significantly elevated abnormally in comparison to the control. In the same review, a meta-analysis of six studies showed that the value of LDH was remarkably higher in coronavirus patients in comparison to the control. Regarding CK parameters, some studies showed that the highest values of CK were associated with severe coronavirus patients but both severe and non-severe patients were diagnosed with coronary heart disease, hypertension and stroke [44].

However, LDH values which are a cytoplasmic cellular enzyme were also shown to be higher in non-severe coronavirus cases. These two parameters have been studied broadly and pointed to as biomarkers for muscle tissue damage. LDH is also released in cases of anaemia, kidney disease, and liver disease. All of the above-mentioned were occasionally diagnosed occasionally as a result of coronavirus infection [45].

Human ferritin is another biochemical parameter that was found elevated significantly in coronavirus patients in comparison to the healthy control. It is well-established that serum ferritin is considered an acute phase reactant that reflects the degree of chronic and acute inflammatory reactions in the body [46, 47]. Also, each ferritin molecule is able to store up to 5000 iron atoms that protect the body from anemia [47]. Hyperferritinaemia could have probably resulted from a mediator of inflammation. A higher ferritin level is a sign of an activated monocyte-macrophage system [48].

Therefore, an increased level of ferritin is a symptom of a defect in the immune system. It could be raised in coronavirus and any inflammatory disease. Here, ferritin can be highlighted as one of the biomarkers that change during coronavirus infection, along with other above-mentioned parameters such as CK, LDH and the essential minerals in the blood. However, ferritin must be taken into consideration as it plays a vital role in the immune system due to

its composition that includes heavy chain (FTH) and ferritin light chain (FTL) which are involved in the oxidation process of converting Fe II to Fe III.

## 4. Conclusion

Although multiple tests could facilitate the diagnosis of the Coronavirus infection, important biochemical markers could be considered due to changes during coronavirus infection. Here, our findings include some of the factors that appeared to change during coronavirus infection.

The pathways of the deficiency of the most significant biochemical parameters correlate to the immune system and others could be due to functional impairment in the body. Therefore, our findings emphasized the pathways of these parameters, particularly the trace elements and the minerals that have shown a significant change during the coronavirus infection. All the measured parameters, such as Mg, Zn, Cu, CP, CKD, LDH and ferritin are significantly changed during coronavirus infections, which are all involved in cellular functions and play a vital role against viral infection. Finally, our results would highly recommend the monitoring of these parameters as biomarkers for coronavirus infection and trying to find a rapid treatment for each of them.

## Ethical approval

All patients were assessed following the ethical standards of the responsible committee on human subjects in the Ramadi City Institutions of Health, Ministry of Health. Informed consent was obtained from all patients for their participation in the study.

## Funding

## Conflicts of interest

No conflict of interest in this project.

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