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Evaluation of Zinc, Magnesium and Copper Levels and the Relation with Severity and Mortality of COVID-19 in Females Childbearing Age Iraqi patients

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Abstract

Trace minerals are important elements for the growth and sustainability of the functions of the body's systems, including the Females Reproductive Tract (FRT). The importance these elements, such as Zinc (Zn), Magnesium (Mg), and Copper (Cu), have structural, protective, and immune roles. Most of them participate in many enzymatic reactions, so they are of crucial importance. During the COVID-19 pandemic. Coronavirus invades the body by binding to the angiotensin-converting enzyme 2 (ACE2) receptors which are expressed in many tissues and organs, such as the FRT. The importance of these minerals was demonstrated through the clear impact of their concentrations within the body in inhibiting or progressing the severity of infection. It also clearly shows their role in supporting the immune system to resist the virulence of the virus through supplements that support the therapeutic courses for COVID-19. In the present study, we evaluate Zn, Mg, and Cu concentrations in three stages of Females Childbearing Age COVID-19 patients (FCA-COVID-19) admitted to a Samarra hospital in comparison to control non-COVID-19 patients. This study was performed in Samarra hospital for the period of September 2021 to August 2022. Blood samples of 105 females divided into groups included: the Comparator group (healthy control group) included 30 apparently healthy subjects (according to age with a range of 20 and 38 years), and the other three groups included 25 patients each group(according to age groups between 20and 38 years) The diagnosis was made real-time reverse transcription polymerase chain reaction (PCR-RT) by the consultant medical staff, where the patients were categorized according to the severity of the disease.The results of this study showed significant differences in Zn, Mg, and Cu concentrations detected in FCA-COVID-19, in which the Zn, Mg, and Cu concentrations were decreased in patient groups compared with control at p= 0.0001. According to current study results and other studies examining the effect of COVID-19 on Zn, Mg, and Cu concentrations, it is suggested that COVID-19 does significantly influence the concentrations of these minerals in Females of Childbearing Age. Also, maintaining the normal levels of these minerals has a great effect in preventing the symptoms of infection from turning from moderate to severe. As well as its role in shortening the period of stay in the hospital.

Keywords: COVID-19, Zn, Mg, Severity and Mortality

Introduction

The Covid-19 pandemic, which spread globally very quickly and included millions of victims between the infected or the dead, caused a large number of symptoms that affected the organs of the body and significantly affected many clinical markers. Trace minerals within the body and in their natural range have critical effects on various biological processes and have been one of the clinical classes that influence and are severely affected by COVID-19. In this

study, the concentrations of Zn, Mg, and Cu were estimated and the effect of changing their concentrations on the general health of females of childbearing age was investigated. The intense respiratory disease coronavirus disease 2019 (COVID-19) surfaced in China in December 2019 and discovered that a brand-new member of the coronavirus family (SARS-CoV and SARS-CoV-2) was the cause, where it belongs to RNA viruses [1-3]. COVID-19 enters the lungs and leads to respiratory difficulties such as bronchitis and pneumonia which can be developed a decreased ability for oxygenation and may develop multiple organ failures and hypoxic brain damage [4]. Coronaviruses identify the human cell receptor; ACE2. The ACE2 receptor and transmembrane serine protease 2 (TMPRSS2) are expressed in many tissues and organs. [2,5]. In addition to the lungs, Coronaviruses attack other organs with high ACE2 expression, including cardiac, renal, intestinal, endothelial cells, testis, ovary, vagina, uterus, and placenta [6]. Trace elements like Zn, Mg and Cu are essential for health, and play an essential role in females' reproduction and fetal development. Correspondingly, both excess and deficiency of essential trace elements were shown to be associated with females' infertility and adverse pregnancy outcome [7]. Zinc is an important microelement in all body tissues and fluids, especially intra-cellularly. Total Zn in the human body is evaluated at 2–3 g and less than 0.2% is found in plasma, where about 0.1% of the Zn range of the body (i.e., 2–3 mg) needs to be supplied daily [8,9]. Zinc is essential for the normal functioning of the RT because its cells develop and proliferate rapidly [9]. It's an important trace element that has a big impact on health, notably in terms of preserving immunological physiology, growth, and development. Additionally, zinc is regarded as a promoter of both innate and acquired immunity and an agent of antiviral immunity [10]. Zinc is distributed especially in muscle, bone, and secondarily in skin and liver [11]. Many clinical disorders are linked to zinc deficiency such as slowed growth, delayed wound healing, Immune system dysfunction, disturbance of smell and taste, hypogonadism, and delayed tissue repair [10,12]. Magnesium is the fourth most prevalent mineral in the human body [13]. The normal human body contains about 20-28 g of Magnesium mostly in bone and muscle. Both sites are easily mobilized during deficiency. Magnesium is an essential component in many enzyme reactions (600 enzymes are activated) either as a metalloenzyme or an intermediary activator. It is most important in those reactions involving phosphate transfer, protein synthesis, and activates a variety of transporters [14,15]. The total Mg in the body is 60% in bone and teeth, 40% intracellular, and less than 1% in extracellular fluids. The balance between daily intake and renal loss determines how much of the nutrients are stored by the body [15]. Magnesium hinders nerve-muscle conduction, slows the release of acetylcholine from motor nerve ends, and relaxes the skeletal muscle. As a result, it successfully regulates and avoids preterm labor, gestational hypertension, preeclampsia, and eclampsia with minimal fetal side effects [16]. Severe magnesium deficiency can result in impairment of neuromuscular function [14].

Copper is an essential trace element; it plays an important role in our metabolism because it allows most critical enzymes to function properly [17]. The normal Cu concentration in the blood is between 74 and 131 µg/dL associated with sex and age [18]. It's maintaining the strength of the blood vessels, also there are some essential roles Cu plays in the body e.g., ATP synthesis, synthesis of the antioxidant superoxide dismutase which fights free radicals, keeps functioning normally thyroid gland, contributes to the formation of certain hormones. The imbalances between Zn and Cu levels play role in human health [19]. Dietary Cu is absorbed in the small intestine rapidly and enters the circulation. Cu is distributed in the blood and associated with larger proteins in a plasma pool. Copper is essential for the proper functioning and maintenance of the human immune system, where it helps T helper cells, B cells, neutrophils, natural killer cells, and macrophage's function. These cells play a role in the generation of antibodies, cell-mediated immunity, and the eradication of pathogenic

microorganisms [20]. Copper deficiency can result in bone and connective tissue abnormalities, neutropenia, and immunosuppression via reduced T-cell proliferation [20,21].

Materials and Methods

During the period September 2021 to August 2022, 75 females of childbearing age have been diagnosed with COVID-19 visited Samara General Hospital, aged 20 - 38 years, and donated blood samples, which were stored at -20ºC until they were assayed. All clinic-pathological data were obtained from patients directly through oral interviews with patients and from the patients' folders in cooperation with the supervising physicians. The sample that might interfere were excluded. Patients were divided into three groups and were categorized according to the clinical stages each including twenty-five patients: Stage I, Stage II, and Stage III. Also, the healthy control group consisted of 30 healthy females childbearing Age subjects under the supervision of a physician sub-specialist within the same age range as the patients.

Methods

The determination of serum Zn, and Cu concentration was done by the Colorimetric Kit for LTA S.r.l. company/ Milano • Italy (https://www.ltaonline.it/), and the determination of serum Mg concentration was done by the Colorimetric Humazym Kit for Human company/ Wiesbaden • Germany (https://www.human.de).

Statistical Analysis

Statistical Analysis System- SAS (2021) program was used to detect the effect of different factors in this study. The least significant difference –LSD test (Analysis of Variation-ANOVA) was used to significantly compare between means in this study.

Results and Discussions

The results in the below Table, Figures 1, 2, and 3 showed the Zn, Mg, and Cu concentrations in patients and control groups. The results in below Table showed a significant decrease in Zn concentration in patients' group **[**(87.9600 ± 4.86895), (67.4800 ± 4.42644), and (63.7600±5.30943)] µg/dL, respectively, compared with control (110.8667 ± 5.35456) µg/dL, (*p*=0.0001). Also, results showed that there was a significant decreases concentration for three groups of patients for significant decreases in the concentrations of Mg in three groups of patients **[(**2.2384 ± 0.04661), (2.0376±0.10445), and **(**1.7876 ± 0.06463)] mg/dL, respectively, compared with the control) 2.4307± 0.03787) mg/dL, (*p*=0.0001). And a significant decreases in the concentration of Cu for three groups of patients [**(**101.280±6.81004), (80.840±3.26190), and (70.280±4.02616)] µg/dL, respectively, compared with control (140.8667 ±5.50068) µg/dL,(*p*=0.0001).

TABLE 1: *Zn, Mg, and Cu Concentrations in studied groups*

Groups	Mean ± SD		
	Zn (µg/dL)	Mg (mg/dL)	Cu (µg/dL)
Control	110.8667 ± 5.3545a	2.4307 ± 0.03787 a	140.8667 ± 5.50068 a
Stage I	87.9600 ± 4.86895 b	2.2384 ± 0.04661 b	101.280 ± 6.81004 b
Stage II	67.4800 ± 4.42644 c	2.0376 ±0.10445 c	80.840 ± 3.26190 c
Stage III	63.7600 ± 5.30943 d	1.7876 ± 0.06463 d	70.280 ± 4.02616 d
p-value	0.0001	0.0001	0.0001

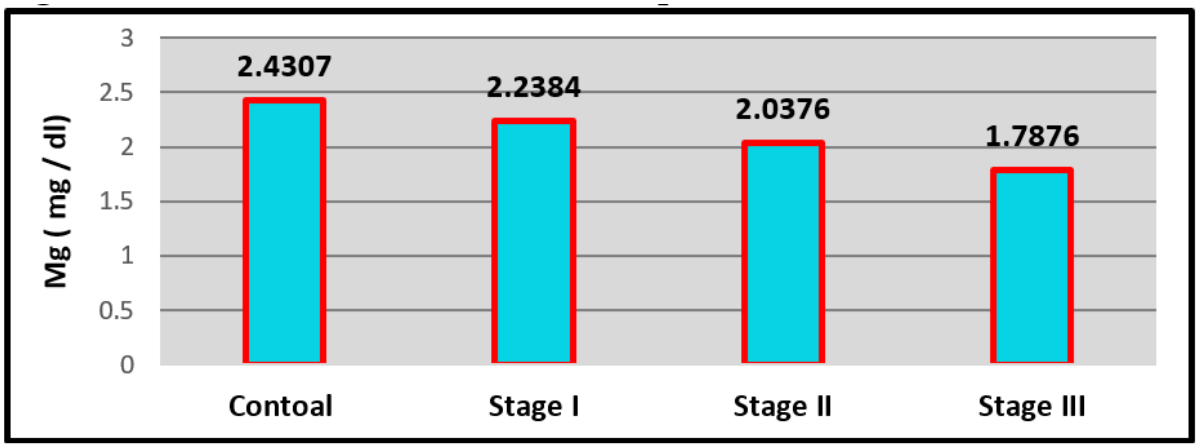

Figure 1: *Zn Concentrations in Covid-19 patients and control*

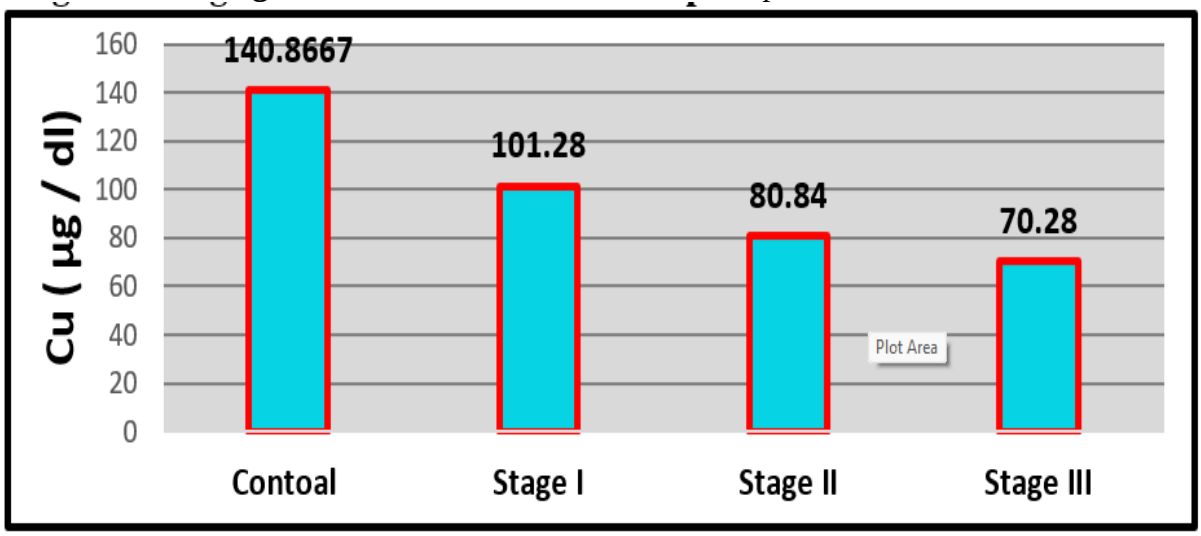

Figure 2: *Mg Concentrations in Covid-19 patients and control*

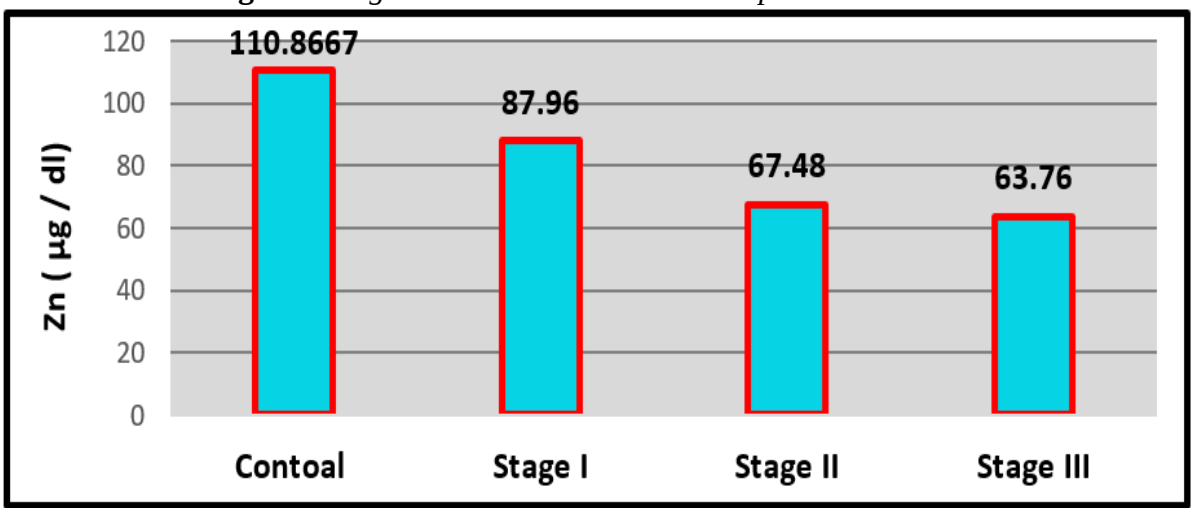

Figure 3: *Cu Concentrations in Covid-19 patients and control*

Results showed that decreased Zn, Mg, and Cu levels were associated with the severity of the injury. Results of Zn study were in agreement with Skalny, A. V., et al [22], Maares, M., et al [23], Ivanova, I. D., et al [24], Shakeri, H., et al [25], and Zeng, H. L., et al [26]. Results of Mg study agreed with Zeng, H. L., et al [26], and Muhammad, Y., et al [27], Results of Cu study were agreement with Muhammad, Y., et al [27] and Pvsn, K. K., et al [28].

The study of trace minerals needs high interest because of their decisive effect in a distinctive role in human health in general, and increase the chance for survival of Covid-19 patients in particular [29], this has led many studies to suggest that these minerals approved the treatment courses [30-32], thus other studies have suggest molecular mechanisms of work and effect of these minerals in curbing the capabilities of the SARS virus[33,34]. The proven and potential functional roles of minerals make them of paramount biological importance, as optimal concentrations of minerals are necessary to make them a key player in various roles such as their role in the metabolism process as a cofactor in enzymatic reactions [35], in the work of the immune system [28], and as an essential part of the treatment courses for the Corona pandemic [30,31,33,36]. the light was shed on the great role of these elements in resisting the infection and decline that could be caused by the Coronavirus, in addition to their previously known roles such as the effect of the concentrations of these elements in pathogenesis and prevention of chronic hepatitis B, C and E, and type-2 diabetes mellitus [22,29]. Evaluating serum metal levels in COVID-19 patients displayed the effect of these metals with different disease severity and has been verified to investigate the independent association between serum metal concentrations and heart rate, respiratory rate, body temperature, C-reactive protein levels, oxygen saturation (SpO2), and lung damage. where the Zn serum is associated positively with SpO2, and inversely with fever, lung damage, and C-reactive protein concentrations [22]. Clinical results show that Zn status affects the susceptibility and severity of the infection, and COVID-19 is defined by a considerable drop in total serum zinc. Additionally, Zn was significantly lower in male patients than in females' patients. Overall, results indicate that decreased zinc level was associated with increased mortality and prolonged hospital stays and suggesting that may act as a new prognostic indicator for the severity and progression of COVID-19 [23,37]. Studies have also demonstrated that zinc may reduce viral replication and increase immune responses [32]. The Zinc also supports modulation of inflammatory response and cytokine production using immunonutrition which was a novel concept that has been applied to other diseases as well [36] and administering a high dosage of intravenous zinc (HDIVZn) guards against hypoxia injury to a number of body organs, including the heart, liver, and kidneys [29]. Even after vaccination, low zinc status may affect the vaccination responses [32], Therefore, taking zinc supplements (within the recommended upper safety limits) supports the treatment or prevents COVID-19 [30], which may be at least partially mediated by the modulatory effect of Zn on SARS-CoV-2 spike protein interaction with angiotensin-converting enzyme 2 (ACE2) [22]. Lower Zn level was also observed in RT-PCR-positive pregnant females [38]. So, the administration of zinc sulfate along with hydroxychloroquine and azithromycin significantly improved clinical outcomes and reduced the risk of mechanical ventilation, and mortality when compared to the protocol lacking Zn supplementation [39]. Albumin is the major zinc loading and regulating protein in serum blood, and hypoalbuminemia is linked to severe COVID-19 infection [40]. Therefore, as albumin concentrations fall, the overall zinc binding capacity of serum decreases, which should result in an increase in free zinc. This wasn't seen in the serum of COVID-19 individuals, though. Instead, there was a similar fall in both serum zinc indicators, where it was found that serum zinc levels—both free and total—as well as serum zinc-binding capacity—were both declining [41]. Previous studies showed that ACE2 interacts with the SARS-CoV-2 spike protein in a way that is favored by low zinc levels, and vice versa. It also showed that ACE2 expression is inhibited by high zinc levels, which reduces the amount of viral contact [42]. Zinc supplements have been linked to decreased morbidity and mortality in children, as well as a reduction in the length and severity of disease symptoms [43]. Magnesium contributes to the heightened immunological and inflammatory responses seen in COVID-19 patients. It is the second most prevalent intracellular cation after potassium [44]. Magnesium deficit stimulates endothelial cells, boosts granulocyte oxidative burst, primes phagocytes, and raises cytokine levels, all of which contribute to inflammation [45]. COVID-19

mimics several metabolic processes seen in latent subclinical magnesium shortage, including a decrease in T cells, increased plasma concentrations of inflammatory cytokines, and endothelial dysfunction [44-46]. The magnesium levels in COVID-19 severe patients were found to be significantly lower than those in non-severe patients, according to the findings. that the change from COVID-19 clinical manifestations that are modest to those that are severe may be exacerbated by a low Mg concentration [44].

A trace element copper is crucial for human health. copper is rapidly absorbed in the small intestine and is rapidly appeared in the circulation. copper is dispersed in the blood into three aggregations: a plasma pool associated with bigger proteins, copper has been demonstrated to have anti-inflammatory, antiviral, and antioxidant actions that are protective. Therefore, it is hypothesized that supplementing with Cu and Zn alone or as an adjuvant may be advantageous with promising efficacy and a favorable safety profile to reduce symptoms and stop the spread of the severe form of SARS-CoV2 infection by inducing their veridical effects through several fundamental molecular cascades, such as modulation of immune responses, redox signaling, autophagy, and obstruction of viral entry and genome replication during SARS-CoV2 [33]. Low Cu concentration individuals are extremely susceptible to infections due to a decrease in the number and activity of these blood cells. The human immunodeficiency virus type 1 (HIV-1) and other enclosed or nonenveloped, single- or double-stranded DNA and RNA viruses are only a few of the contagious viruses that Cu can destroy. Additionally, Cu is highly effective at killing a number of viruses on contact, including SARS-CoV2 [31]. Cu concentrations decreased following ICU admission. Cu supplementation thus has a significant role in controlling IL-2 and in treating immunological dysregulation in severely ill COVID-19 patients [29]. reported that persistent TNF-α- induced lung inflammation can lead to Cu lack. The condition COVID-19 is linked to an increase in inflammatory cytokines, which can produce Cu deficiency and cause lung inflammation [27].

Conclusion

This study concluded that the Zn, Mg, and Cu concentrations in females of reproductive age are significantly and proportionally affected by the severity of Covid-19 infection. results of this study showed that Zn, Mg, and Cu concentrations decreased in clearly the severe stage of COVID-19 disease in females of reproductive age. Also, the current study showed the importance kept the Zn, Mg, and Cu concentrations in the normal range in resistance in Females of Childbearing Age COVID-19 **PATIENTS AND** preventing the symptoms of infection from turning from moderate to severe. As well as it has a role in shortening the period of stay in the hospital.

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