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Zinc level in COVID-19 infection: Truth or myth?

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ABSTRACT

Background: COVID-19 is accompanied by a systemic hyperinflammatory reaction and thromboembolic consequences. Zinc has antiviral, anti-inflammatory, and antioxidant properties. Moreover, zinc deficiency adversely affects immune cells' survival and function. Although it is uncertain if COVID-19 individuals lack zinc, zinc administration is used in treatment. We aimed to determine if there is a change in zinc levels in COVID-19 individuals and the relationship between zinc levels and illness severity and outcome. **Methods:** Sixty individuals with COVID-19 infection verified by PCR were recruited. Patients' demographics, degree of illness at the time of blood specimen, and prognosis were gathered. The zinc level in serum was measured in the first 72 hours of admission, using a cutoff for normal zinc levels between 70.6 and 114 g/dl for women and 72.6 and 127 g/dl for men. **Results:** Sixty individuals with an average age of 50.7 + 14.41 years were enrolled in the study; 51.7% were males, 60% were diabetics, 73% had hypertension, and 35% had obesity, where BMI was above 30 kg/m^2. Regarding the COVID-19 severity, the percentage was 28.3%, 50%, and 21.7% for mild, moderate, and severe cases, respectively. There was a high prevalence of zinc deficiency; about 87% (n=52) of the patients had below-normal zinc values. The median zinc level was 39.5 (20.5-58) µg/dl. No statistically significant association was observed between blood zinc levels and illness severity or prognosis. **Conclusion:** Zinc insufficiency might be a risk component for the incidence of COVID-19 infection. Nevertheless, it seems unrelated to the disease course or outcome.

Introduction

In December 2019, the novel coronavirus infection COVID-19, induced by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus, has swiftly progressed, and remains to pose a danger to people, society, and medical organizations around the globe [1,2]. Multiple organs may be affected by COVID-19, which manifests largely as an acute respiratory disease [3]. The vast majority of

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patients present minor indications. However, certain instances develop into pneumonia, ARDS, and even multi-organ failure and shock [4].

In extreme situations, the pathophysiology of COVID-19 is likely complex, culminating in a systemic hyperinflammatory reaction and concomitant thromboembolic consequences. Similar to numerous other illnesses, the human body's immune response affects the progression and mortality of COVID-19 [2, 5]. Diet has a crucial role in the care of body systems and the homeostasis of several organs, including immune function [6, 7].

The trace metal zinc has a significant immunoregulatory effect, throughout adaptive and innate immunological responses. It plays a crucial function in cell survival, proliferation, and initiation. It contributes to the function of epithelial barriers necessary for a strong protective system and infection protection [7, 8]. Zinc operates not just as an anti-inflammatory drug but as an antioxidant that stabilizes cell membranes [9]. The potency of zinc being antiviral includes viral replication, topoisomerase, and inhibition of RNA synthesis [10].

Zinc deficiency adversely affects the survival and function of immune cells, including phagocytosis, cytokine secretion, death of target cells, and antiviral properties [7,11]. Zinc administration is effectively conveyed for treating COVID-19 individuals, notwithstanding that it is uncertain if they lack zinc [2].

Few investigations established the impact of zinc insufficiency on COVID-19 individuals; however, **Jothimani et al.** found that a substantial proportion of COVID-19 patients were zinc-deficient. Most zinc-deficient individuals experienced greater problems, and the insufficiency was related to a lengthy hospital stay and higher fatality rates [2]. Nevertheless, future research, including 242 individuals, found no link between zinc administration and decreased COVID-19-related death [12]. Furthermore, zinc's efficacy as an adjuvant treatment for COVID-19 has not been demonstrated yet [7].

Rationale

The purpose of the present investigation is to determine if there is a change in zinc levels in COVID-19 patients and the relationship between zinc levels and symptom severity and outcome.

Study methods

Cairo University Medical School's Institutional Review Board and Ethics Committee authorized this prospective cross-sectional analytical research study. Recruitment of patients started in November 2021 at Kasr Al-Ainy hospitals, Cairo University. It included adult patients ($\geq$ 18 years), both genders, able and willing to give informed oral consent, suffering from COVID-19 infection by confirmed real-time reverse-transcriptase polymerase-chain-reaction (RT-PCR) assay. Patients who refused blood sample withdrawal or could not give oral informed consent were excluded.

For every participant, the basic information was collected:gender, age, and comorbidities, e.g., obesity, diabetes mellitus, hypertension, and assessment of COVID-19 severity during the blood collection. Severity was determined according to the WHO classification into **mild COVID-19:** infected patients showing no symptoms of hypoxia or pneumonia; **moderate COVID-19:**individuals with symptomatic indications of pneumonia and oxygen levels of more than 90% on ambient air;**severe COVID-19:** individuals exhibiting symptomatic indications of serious pneumonia, such as a respiration rate of more than 30 breaths per minute, significant breathing difficulties, or an oxygen levels of less than 90% on ambient air; and **critical COVID-19:**patients who fulfill the criteria for acute respiratory distress syndrome (ARDS), septic shock, or who need life-sustaining interventions such as vasopressor therapyor mechanical ventilation (non-invasive or invasive) [13].

Blood sampling during the patient hospital stay within 72 hours of admission provided that there was no history of prior zinc intake and serum level of zinc was obtained using a colorimetric method with a fully automated Indiko Plus analyzer. The zinc content reference level for females was 70.6 – 114 μg/dl and for males was 72.6 – 127 μg/dl [14].

The patient's outcome was mentioned, whether improvement or death.

Data obtained were tabulated and statistically analyzed. The Mann-Whitney U test is employed to evaluate continuous variables represented as median (Inter-Quartile Range, IQR). The Chi-square test is employed to evaluate categorical variables reported as numbers (%). $p <$

0.05 will be regarded as a statistically significant significance level.

Results

This study included 60 patients. Their mean age was 50.7 ± 14.41 years, ranging from 18 to 80 years, almost equally distributed among both genders, with males constituting around 51.7% (n= 31). All patients were hospitalized either in ordinary rooms 65% (n=39), intermediate or intensive care units 35% (n=21).

Sixty percent of this cohort were diabetics (n=36), 73% of them had hypertension (n=44), and 35% had obesity (n=21), where BMI was above 30 kg/m^2. Twenty percent had a combination of the three metabolic disorders (n= 12); diabetes mellitus, hypertension, and obesity, while 40% had two diseases (n=24), and 28.3% had one disease only (n=17), (**Table 1)**.

Regarding the COVID-19 severity according to the WHO classification, the percentages were 28.3% (n=17), 50% (n=30), and 21.7% (n=13) for mild, moderate, and severe cases, respectively. Critical cases were excluded due to the inability to give informed consent.

Patients' outcomes revealed final improvement and discharge from the hospital in 68.3% (n=41) and deterioration and mortality in 31.7%(n=19).

None of the patients were on zinc supplements at that time, and there was a noticeable significant frequency of zinc insufficiency in the study population; about 87% (n=52) of the patients had below-normal zinc values. The median zinc level was 39.5 (20.5-58)µg/dl. The association between serum zinc and disease severity was assessed. Blood zinc levels did not vary significantly across patients with mild versus moderate or severe disease (**Table 2)**. Moreover, there was no statistically significant association between baseline blood zinc levels and disease outcome (**Table 3)**.

Table 1. Baseline characteristics of the study population (n=60).

Parameter	
Age (Years) Mean (SD)	50.7 (14.41)
Gender Male/Female	31 (51.7%)/ 29 (48.3%)
Diabetes mellitus	36 (60%)
Hypertension	44 (73%)
Hospitalization status	
Ordinary room	39 (65%)
Intermediate or intensive care	21 (35%)

Table 2. Serum zinc median level according to COVID-19 disease severity.

	Mild	**Moderate**	**Severe**	***P***
Serum zinc Median (IQR)	36 (16-52)	44.5 (29-61)	39 (20-57)	0.5

Table 3. Association between serum zinc levels and disease outcome

	Improved and discharged (n = 41)	**Progressed and died (n = 19)**	***P***
Serum zinc Median (IQR)	38 (20-53)	45 (36-64)	0.2

Discussion

The current study included 60 patients with COVID-19 confirmed by PCR, with no history of receiving zinc supplementation before hospitalization, aiming to detect the serum level of zinc to know whether there is an association between blood zinc levels and COVID-19 infection, including the course of the disease or the outcome.

It was found that there is a significant frequency of zinc insufficiency in this group; about 87% (n=52) of the patients had low zinc values. The median zinc level was 39.5 (20.5-58) µg/dl. There was no significant correlation between COVID-19

infection severity (**Table 1**) and the disease outcome regarding improvement or mortality (**Table 2**).

Zinc is an important mineral that has a function in the control of both adaptive and innate immune responses, where it regulates the functioning, differentiation, maturation, and proliferationof lymphocytes and leukocytes [15]. Its deficiency may be associated with an altered immune response resulting in a proinflammatory state that may put the tissues in danger of damage due to an overactive immune response in conjunction with decreased resistance towards pathogens [16]. Its role in combating or preventing viral infection in the era of the COVID-19 pandemic has been discussed in many articles. Different mechanisms were proposed as barrier function, antiviral, and antioxidant actions, hand in hand with modulation of the immune system [17].

Thus, many researchers questioned the hypothesis that altered zinc status is associated with an increased risk of COVID-19 infection, which encouraged using zinc supplementation as potentially protective against the pandemic [17,18]. **Keles et al.**, 2022, had found a significant increase in the incidence of hospitalization and mortality in children with COVID- 19 and low levels of serum zinc [19].

Razeghi et al., 2021 revealed a significant association between Zn level and COVID-19 severity (p-value = 0.01) [20].

However, the results were not found to be in concordance with **Singh,** 2020. Their study evaluated COVID-19 data from various pandemic phases for covariation with predicted zinc insufficiency. They found a negative correlation between zinc deficiency and a steady improvement in covariation [21]. **Joulaei et al.,** 2022, revealed that there seemed to be no correlation between blood Zn levels and COVID-19 death rates [22]. According to NIH guidelines which were last updated in September 2022, there is a lack of proof for the panel to suggest zinc therapy for COVID-19 [23]. Moreover, **Szarpak et al.,** 2021, found that zinc administration did not affect the management of COVID-19 as measured by survival to hospital departure and in-hospital death [24].

Conclusion

Low serum zinc levels may be associated with COVID-19 infection, yet we could not detect a statistically significant correlation with either disease severity or the outcome in the form of mortality.

Study limitations

At the time of recruitment, finding patients who had not received zinc supplementation before being infected seemed rather difficult. Furthermore, informed oral consent was difficult to be taken from critical patients rendering this group discarded from the study. These factors resulted in a small size study population.

Authors' contribution

All authors have substantially contributed to the conception and design, acquisition of data, data analysis, and interpretation. All authors have agreed on the content of the manuscript. Rasha Ahmed: Conceptualization, Writing- original draft, Supervision. ReemElkorashy: Formal analysis, Writing - review & editing. ZeinabAbdellatif: statistical analysis, review & editing. Aya.M.Al-sharif: Investigation, methodology. HananZaghla: Conceptualization, Investigation, Supervision. Manal Mohamed Kamal: Investigation, Formal analysis, Supervision. Yasmine Gaber: Methodology, editing, Investigation. Youssef Soliman: Investigation, editing. Ahmed M. Hashem: Investigation, methodology. Khaled Salem: Investigation, methodology, Hala Ramadan: Writing- original draft, editing.

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Conflict of interest

None of the authors has a conflict of interest to declare.

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