Association of serum zinc level and clinical outcome in Egyptian COVID-19 patients

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Abstract

Background: Zinc is an anti-inflammatory and antioxidant micronutrient found in food. Due to its well-established role in immunity, it is currently being used in some clinical trials against coronavirus disease-2019 (COVID-19). This study aimed to assess the association between the mean serum zinc level in COVID-19 Egyptian patients and its relationship with disease severity. This cross-sectional study was conducted on sixty patients with confirmed COVID-19 infection. These patients were divided into two groups according to clinical outcome, group 1 which included 30 intensive care unit (ICU) patients and group 2 which included 30 patients who were admitted to the ward. Mean serum levels of zinc were compared between the two groups.

Results: There was a statistically significant difference noted among study groups regarding the serum zinc level ($p < 0.039$), where lower mean serum zinc levels were noted in ICU patients compared to ward patients (70.6 ± 5.7 vs 73.8 ± 6.1).

Conclusion: Low serum zinc level is associated with the severe outcome of COVID-19 infection.

Keywords: COVID-19, Zinc, Zn, Immunity

Background

Through the last 2 years, the world was devastated by a serious pandemic of COVID-19 caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). Since then, researchers from all over the world carefully studied any possible aetiologies or risk factors to help in finding effective treatment regimens based on current knowledge that can help control the spread of the disease with the help of currently available vaccines in the hope to prevent further pandemic flares [1].

Therapeutic approaches against COVID-19 are currently focusing on the management of its immunopathology and/or tailored to directly control viral replication. Several human trials are currently in progress to assess the therapeutic indices of different drugs, and in combination with dietary supplements like vitamin C, vitamin D, vitamin B12, probiotics, and zinc [1].

Zinc is the second most common trace element that is vital for the growth, development, and maintenance of immune function, in addition to its critical role in antiviral immunity. Its influence reaches all organs and cell types, representing an essential component of approximately 10% of the human proteome and encompassing hundreds of key enzymes and transcription factors [2, 3]. Many foods are considered rich in zinc including meat, poultry, shellfish, legumes, nuts, eggs, and dairy products [4]. The recommended daily intake of zinc for adult males and females is 11 mg and 8 mg, respectively. Pregnant and breastfeeding females need higher daily intake reaching 11 mg and 12 mg, respectively [5].

Zinc deficiency is common. The global prevalence of zinc deficiency is estimated to range from 17 to 20% [6, 7], with the vast majority occurring in developing countries of Africa and Asia. High-risk factors for zinc deficiency include patients with gastrointestinal diseases such as

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Mansour *et al. The Egyptian Journal of Internal Medicine*   (2022) 34:72

Page 2 of 6

Crohn's disease; patients with sickle cell anemia, malnutrition, or chronic kidney disease; and vegetarians and vegans, in addition to pregnant and breastfeeding females [7].

Zinc is a common theme in both prophylactic and curative COVID-19 clinical studies using nutritional supplements. Thus, this study aimed to assess the possible association between mean levels of serum Zn and clinical outcomes in Egyptian COVID-19 patients.

Methods

This comparative cross-sectional study was conducted on 60 Egyptian COVID-19 patients (35 males (58.3%) and 25 females (41.7%), mean age: 59.2 ± 15.3 years) recruited from our institution's quarantine field hospital and quarantine university hospital ICU and inpatient wards during the period from July to December 2021. These patients were divided into two groups according to the severity of COVID-19 infection; the ICU group included 30 patients with severe COVID-19 infection who were admitted to ICU, while the Word group included 30 patients with moderate COVID-19 infection admitted to inpatient wards.

All patients were diagnosed with COVID-19 infection by polymerase chain reaction (PCR) of oropharyngeal and nasopharyngeal swabs. Laboratory investigations were carried out for all recruited patients and included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum albumin, serum ferritin, lactate dehydrogenase (LDH), and D-dimer, in addition to serum zinc level. All patients underwent high-resolution computed tomography (HRCT) of the chest to assess the severity of lung affection due to COVID-19 infection. All patients were receiving zinc supplements in the form of zinc sulfate heptahydrate equivalent to 75–100 mg elemental zinc as per COVID-19 national guidelines. All collected data was tabulated, interpreted, and statistically analyzed.

Results

Patients included in this study were 21 smokers (35%) and 39 non-smokers (65%). Other co-morbidities were noted, where 43 patients (71.7%) had co-morbidities such as hypertension, diabetes mellitus, or both, in addition to atrial fibrillation (AF). Seventeen patients (28.3%) had no co-morbidities.

Comparison between both groups as regards demographic data showed that there was no statistically significant difference found between the two groups regarding gender, age, and smoking.

Comparison between both groups as regards co-morbidities revealed a statistically significant difference ($p < 0.005$). Moreover, it was noted that patients with combined diabetes and hypertension ($n = 15$) had a more severe course of infection demanding admission to ICU ($n = 11$, 73.3%) rather than the inpatient ward ($n = 4$, 26.7%). This was also similar to patients with both hypertension and AF, where they were all admitted to ICU ($n = 3$, 100%). This can elucidate the possible risk multiple co-morbidities convey on the course of infection in COVID-19 patients (Table 1).

Similarly, a comparison between study groups as regards CO-RADS classification revealed a statistically significant difference ($p < 0.025$). It was also noted that the risk for admission to ICU increased as CO-RADS grade increased. This goes with the fact that a higher CO-RADS grade indicated more severe infection, which necessitated more intensive management in critical care settings. Patients with CO-RADS grade 5 had a much higher risk of being admitted to ICU ($n = 13$, 72.2%) rather than the inpatient ward ($n = 5$, 27.8%) (Table 1).

Table 1 Comparison between ward and ICU patients regarding CO-RADS classification

		Admission						Chi-square	
		Ward		ICU		Total			
		N	%	N	%	N	%	X^2	p
Medical history	**Free**	11	36.67	6	20.00	17	28.33	14.959	0.005
	DM	7	23.33	0	0.00	7	11.67		
	HTN	8	26.67	10	33.33	18	30.00		
	DM + HTN	4	13.33	11	36.67	15	25.00		
	HTN + AF	0	0.00	3	10.00	3	5.00		
CO-RADS classification	**CO-RADS 3**	19	63.33	9	30.00	28	46.67	7.413	0.025
	CO-RADS 4	6	20.00	8	26.67	14	23.33		
	CO-RADS 5	5	16.67	13	43.33	18	30.00		

$p > 0.05$: non-significant (NS); $p < 0.05$: significant (S); $p < 0.001$: highly significant (HS)

Mansour *et al. The Egyptian Journal of Internal Medicine*   (2022) 34:72

Page 3 of 6

A comparison of different laboratory parameters of both study groups showed a significant statistical difference among patients as regards total leucocytic count (TLC), neutrophil count, neutrophil/lymphocyte ratio, CRP, and ESR ($p < 0.005$, $p < 0.004$, $p < 0.015$, $p < 0.048$, and $p < 0.029$, respectively). Moreover, there was a statistically significant difference between study groups as regards ferritin, LDH, and D-dimer ($p < 0.013$, $p < 0.042$, and $p < 0.002$, respectively), indicating a more severe course of COVID-19 in ICU patients. There was also a significant statistical difference between study groups as regards AST and ALT ($p < 0.052$ and $p < 0.027$, respectively), in addition to a highly significant statistical difference among study groups as regards vitamin D levels ($p < 0.001$), where a significant decline in mean vitamin D levels was noticed in ICU patients compared to ward patients (18.3 ± 4.8 vs 23.1 ± 3.9) (Table 2).

As regards serum zinc levels, there was a statistically significant difference noted among study groups ($p < 0.039$), where lower mean serum zinc levels were noted in ICU patients compared to ward patients (70.6 ± 5.7 vs 73.8 ± 6.1). These results further elucidate the potential protective role of serum zinc due to its significant role in the maintenance of host's immune functions in addition to its potential antiviral effects. Moreover, observations from this study point towards

Table 2 Comparison between study groups as regards different laboratory parameters

		Admission						*t*-test	
		Ward			ICU			t	p
TLC	Range	2.3	–	20.8	3.3	–	33	− 2.922	0.005
	Mean ± SD	7.650	±	4.491	12.520	±	7.948		
Lymphocytes	Range	0.3	–	2	0.2	–	1.7	0.822	0.415
	Mean ± SD	0.750	±	0.432	0.657	±	0.448		
Neutrophils	Range	1	–	18	2.2	–	31.9	− 2.981	0.004
	Mean ± SD	6.303	±	4.261	11.050	±	7.610		
Hemoglobin	Range	6.5	–	18.5	7	–	18	0.334	0.739
	Mean ± SD	12.320	±	2.621	12.110	±	2.229		
Platelets	Range	17	–	515	112	–	398	− 0.412	0.682
	Mean ± SD	200.433	±	91.409	209.267	±	73.555		
Neutrophil-lymphocyte ratio	Range	1	–	43	2	–	106	− 2.498	0.015
	Mean ± SD	12.967	±	13.330	25.567	±	24.196		
CRP	Range	0.1	–	300	4.5	–	330	− 2.019	0.048
	Mean ± SD	47.049	±	70.470	92.331	±	100.650		
ESR	Range	5.1	–	120	2	–	300	− 2.242	0.029
	Mean ± SD	30.617	±	32.174	62.190	±	70.114		
Creatinine	Range	0.3	–	9	0.4	–	6.1	− 0.607	0.546
	Mean ± SD	1.273	±	1.594	1.490	±	1.132		
AST	Range	9	–	215	4	–	212	− 1.988	0.052
	Mean ± SD	38.067	±	41.047	61.700	±	50.545		
ALT	Range	9	–	185	13	–	338	− 2.272	0.027
	Mean ± SD	37.033	±	35.762	76.500	±	88.160		
Albumin	Range	1.8	–	3.9	2.1	–	4.2	1.556	0.125
	Mean ± SD	3.327	±	0.470	3.123	±	0.540		
Ferritin	Range	56	–	1255	26.7	–	2100	− 2.569	0.013
	Mean ± SD	369.773	±	302.147	642.770	±	497.362		
LDH	Range	110	–	963	125	–	986	− 2.081	0.042
	Mean ± SD	379.667	±	256.082	518.967	±	262.309		
D-dimer	Range	0.2	–	2.9	0.212	–	6.9	− 3.303	0.002
	Mean ± SD	0.737	±	0.715	1.806	±	1.621		
Vitamin D	Range	15	–	30	7	–	27	4.310	< 0.001
	Mean ± SD	23.133	±	3.902	18.267	±	4.799		

$p > 0.05$: non-significant (NS); $p < 0.05$: significant (S); $p < 0.001$: highly significant (HS)

Mansour *et al. The Egyptian Journal of Internal Medicine*   (2022) 34:72

Page 4 of 6

the effects of zinc deficiency on the natural course of COVID-19 infection and the possibilities of poor prognosis in patients due to severe infection (Table 3).

Discussion

SARS-CoV is a virus which is capable to bind the angiotensin-converting enzyme 2 receptors that are present in several locations such as lung alveolar epithelial cells, enterocytes, endothelial cells, and arterial smooth muscle cells in the human body. This novel coronavirus has caused many deaths in the recent pandemic. Evidence suggested that in severe COVID-19 cases, a cytokine storm accompanies the infection [8]. Several studies focused on possible risk factors that may contribute to immunopathogenesis or the natural course of infection in COVID-19 patients. The present study aimed to assess the association between mean serum levels of zinc and the severity of infection in Egyptian COVID-19 patients.

Earlier studies demonstrated that a decreased zinc level favors the interaction of ACE2 with SARS-CoV-2 spike protein and likewise that an increased zinc level inhibits ACE2 expression resulting in reduced viral interaction [9, 10]. On the other hand, the first clinical study correlating lower baseline zinc levels in patients with COVID-19 was done by Jothimani et al., and it was compared to healthy controls showing a highly significant statistical difference between the two groups as regards mean serum zinc levels (74.5 vs 105.8 µg/dL, $p < 0.001$). Among COVID-19 patients in that study, 57.4% ($n = 27$) were zinc deficient [11].

Moreover, Shakoor and his colleagues recently discussed zinc's role in immunity and its effect on patients with COVID-19. They also discussed consuming this nutrient as a potential therapeutic method for reducing the complications and mortality rate of patients with COVID-19 [12]. This agreed with results from another study by Foster et al., where they proved that zinc supplements positively affected reducing fever duration in patients with respiratory infections. Still, it had no significant effect on respiratory rate, cough duration, and hospitalization time [13].

Based on Abdolahi et al. study findings, zinc's serum level had a significant difference between 93 hospitalized COVID-19 patients compared to 186 healthy subjects,

where the case group had a lower serum zinc level than the control group, and the study suggested that zinc deficiency could be a predictor for a critical illness of COVID-19. Moreover, the study recommended using zinc supplements for non-patients for prevention and for patients who may have lower than normal serum zinc levels. However, trials with an increased number of patients should still be evaluated [14].

Several surveys conducted have claimed that zinc consumption is likely to reduce the intensity of COVID-19 infection due to its antiviral properties; it also helps to alleviate respiratory tract infections [3, 15].

There are few published studies that illustrate the efficacy of zinc therapy in managing COVID-19 patients [16–18]. Many individuals globally consume zinc tablets and vitamins C and B due to possible immune booster effects for protection against COVID-19 infection [19, 20].

However, a recent retrospective analysis utilizing electronic medical records found that patients treated with hydroxychloroquine and azithromycin with the addition of zinc sulfate had a higher recovery rate. Interestingly, additional input of zinc sulfate was claimed to be associated with lower mortality rate, need for hospice care, and less invasive ventilation requirements. However, this association was not observed among ICU patients [21].

González and his colleagues demonstrated in their study a correlation between serum zinc levels and COVID-19 outcome. Serum zinc levels lower than < 50 µg/dL at admission correlated with worse clinical presentation, longer time to recovery, and higher mortality. These results, in addition to several other recent studies, might suggest that serum zinc impacts COVID-19 severity, and its adjustment might also constitute an early therapeutic intervention point [22–24]. Another in vitro study by Velthuis et al. showed that Zn^{+2} cations especially in combination with zinc ionophore pyrithione were shown to inhibit SARS-coronavirus RNA polymerase activity by decreasing its replication [25].

Conclusion

Low serum zinc level is associated with severe COVID-19 infection. This is likely due to a combination of immune system imbalance and a direct benefit of viral replication. Thus, we propose serum zinc level as a novel and

Table 3 Comparison between ward and ICU regarding serum zinc level

Zinc level	Admission						t-test	
	Ward			ICU			t	p
Range	65	–	89	56	–	81	2.114	0.039
Mean ± SD	73.800	±	6.059	70.600	±	5.661		

$p > 0.05$: non-significant (NS); $p < 0.05$: significant (S); $p < 0.001$: highly significant (HS)

Mansour *et al. The Egyptian Journal of Internal Medicine*   (2022) 34:72

Page 5 of 6

additional parameter to predict COVID-19 outcomes. Moreover, this study recommends implementing nutritional education programs for healthcare professionals, nursing staff, and dieticians to help raise public awareness concerning healthy foods and eating habits, including zinc-rich food sources. It is also recommended to implement good physician-pharmacist teamwork when using food supplements to maximize benefits and avoid potential drug-drug interactions.

Abbreviations
AF: Atrial fibrillation; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; COVID-19: Coronavirus disease-2019; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; HRCT: High-resolution computed tomography; ICU: Intensive care unit; LDH: Lactate dehydrogenase; PCR: Polymerase chain reaction; SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2.

Authors' contributions
NE, AME, and AMFM made the design for the study. NMMK collected the data of the patients. Analysis of the data was done by AME and AMFM. All authors provided critical feedback and helped shape the research, analysis, and manuscript. All authors have read and approved the final manuscript.

Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the Research Ethics Committee of Ain Shams University (No. FMASU M S 82/2021). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

References
1. Maret W (2013) Zinc and the zinc proteome. Met Ions Life Sci 12:479–501
2. Gupta S, Read SA, Shackel NA, Hebbard L, George J, Ahlenstiel G (2019) The role of micronutrients in the infection and subsequent response to hepatitis C virus. Cells 8(6):603
3. Read SA, Obeid S, Ahlenstiel C, Ahlenstiel G (2019) The role of zinc in antiviral immunity. Adv Nutr 10(4):696–710
4. U.S. Department of Agriculture (2022) Food Data Central
5. Institute of Medicine (US) Panel on Micronutrients (2001) Dietary reference intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington: National Academies Press (US). 12, Zinc. Available from: https://www.ncbi.nlm.nih.gov/books/NBK222317/
6. Wessells KR, Brown KH (2012) Estimating the global prevalence of zinc deficiency: results based on zinc availability in national food supplies and the prevalence of stunting. PLoS ONE 7(11):e50568
7. Kumssa DB, Joy EJ, Ander EL, Watts MJ, Young SD, Walker S, Broadley MR (2015) Dietary calcium and zinc deficiency risks are decreasing but remain prevalent. Sci Rep 5:10974
8. Anuk AT, Polat N, Akdas S et al (2020) The relation between trace element status (zinc, copper, magnesium) and clinical outcomes in COVID-19 infection during pregnancy. Biol Trace Elem Res. https://doi.org/10.1007/s12011-020-02496-y
9. Devaux CA, Rolain JM, Raoult D (2020) ACE2 receptor polymorphism: susceptibility to SARS-CoV-2, hypertension, multi-organ failure, and COVID-19 disease outcome. J Microbiol Immunol Infect 53(3):425–435
10. Li MY, Li L, Zhang Y, Wang XS (2020) Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty 9(1):45
11. Jothimani D, Kailasam E, Danielraj S, Nallathambi B, Ramachandran H, Sekar P, Manoharan S, Ramani V, Narasimhan G, Kaliamoorthy I, Rela M (2020) COVID-19: poor outcomes in patients with zinc deficiency. Int J Infect Dis 100:343–349
12. Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, et al (2020) Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: could they help against COVID-19? Maturitas. 143:1-9
13. Foster M, Samman S (2012) Zinc and regulation of inflammatory cytokines: implications for cardiometabolic disease. Nutrients 4(7):676e94
14. Elhama AS, Azamb K, Azam J et al (2021) Serum vitamin D, calcium, and zinc levels in patients with COVID-19. Clinical Nutrition ESPEN. 43:276–282
15. Hemilä H (2015) Common cold treatment using zinc. JAMA 314(7):730
16. Abd-Elsalam S, Soliman S, Esmail ES, et al (2020) Do zinc supplements enhance the clinical efficacy of hydroxychloroquine? A randomized, multicenter trial. Biol Trace Elem Res 1–5. 199(10):3642–3646
17. Alexander J, Tinkov A, Strand TA, Alehagen U, Skalny A, Aaseth J (2020) Early nutritional interventions with zinc, selenium, and vitamin D for raising anti-viral resistance against progressive COVID-19. Nutrients 12(8):2358
18. Arentz S, Hunter J, Yang G et al (2020) Zinc for the prevention and treatment of SARS-CoV-2 and other acute viral respiratory infections: a rapid review. Adv Integr Med 7(4):252–260
19. Rondanelli M, Miccono A, Lamburghini S et al (2018) Self-care for common colds: the pivotal role of vitamin D, vitamin C, zinc, and echinacea in three main immune interactive clusters (physical barriers, innate and adaptive immunity) involved during an episode of common colds-practical advice on dosages and on the time to take these nutrients/botanicals in order to prevent or treat common colds. Evid Based Complement Alternat Med 2018:5813095
20. Name JJ, Souza ACR, Vasconcelos AR, Prado PS, Pereira CPM (2020) Zinc, vitamin D, and vitamin C: perspectives for COVID-19 with a focus on physical tissue barrier integrity. Front Nutr 7:606398
21. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J (2020) Zinc sulfate, in combination with a zinc ionophore, may improve outcomes in hospitalized COVID-19 patients. J Med Microbiol 69(10):1228–1234
22. Taheri M, Bahrami A, Habibi P et al (2020) A review on the serum electrolytes and trace elements role in the pathophysiology of COVID-19. Biol Trace Elem Res 8:1–7
23. Yasui Y, Yasui H, Suzuki K et al (2020) Analysis of the predictive factors for a critical illness of COVID-19 during treatment—relationship between serum zinc level and critical illness of COVID-19. Int J Infect Dis 100:230–236
24. González M, Talló-Parra M, Herrera-Fernández V, Pérez-Vilaró G, Chillón M, Nogués X, Gómez-Zorrilla S, López-Montesinos I, Arnau-Barrés I, Sorli-Redó ML, Horcajada JP (2021) Low zinc levels at admission

Mansour *et al. The Egyptian Journal of Internal Medicine*   (2022) 34:72

Page 6 of 6

associates with poor clinical outcomes in SARS-CoV-2 infection. Nutrients 13(2):562

25. Velthuis AJ, van den Worm SH, Sims AC, Baric RS, Snijder EJ, van Hemert MJ (2010) Zn2+ inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. PLoS Pathog 6(11):e1001176

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