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Importance of Microminerals for Maintaining Antioxidant Function after COVID-19-induced Oxidative Stress

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Abstract

Background: COVID-19 is caused by the Severe Acute Respiratory Distress Syndrome Coronavirus 2. Since the antioxidant mechanisms such as glutathione peroxidase or superoxide dismutase are downregulated during infection by the virus, there is an imbalance in the oxidant-antioxidant system. In this study we aimed to identify the effect of COVID-19 on the antioxidant defense mechanism by comparing the concentrations of antioxidants and microminerals in COVID-19 patients and healthy controls.

Methods: This cross-sectional analytical study involved 200 patients at Kasturba Hospital, Manipal University. The serum concentrations of antioxidants and minerals were determined to establish the impact of COVID-19 on antioxidants mechanism and nutrient status in COVID-19 patients.

Results: The serum concentrations of GPX ($10.36 \pm 2.70 \geq 5.82 \pm 1.64$ mKAT/L, $p < 0.0001$) and copper ($2192.5 \pm 449.8 \geq 782.15 \pm 106.5$ µg/dL, $p < 0.0001$) were significantly greater, and zinc ($34.78 \pm 4.5 \leq 81.07 \pm 10.13$ µg/dL, $p < 0.0001$) was significantly less, in the study group than in controls. The Pearson correlation between serum SOD and zinc was significant ($r = 0.491$, $p < 0.0001$) indicating the importance of zinc in maintaining and improving SOD activity. No significant correlations were observed between copper and SOD ($r = -0.089$) or iron and CAT ($r = -0.027$).

Conclusions: Our study demonstrated the expected increase in oxidant-radical production during COVID-19 by estimating the altered concentrations of antioxidants and the minerals required to neutralize the elevated ROS. This finding is not novel but adds to the existing literature, which recommends nutritional supplementation of microminerals and antioxidants.

Keywords: COVID-19, Cytokines, Glutathione Peroxidase, Minerals, Reactive oxygen species, Zinc.

Introduction

The novel coronavirus disease or COVID-19 was first discovered in Wuhan, China in 2019, then spread to most countries worldwide and was later declared a global pandemic by the World Health Organization (WHO). Exposure to this coronavirus from the inhalation of infectious droplets via nose or mouth can cause severe acute respiratory distress syndrome (SARS CoV-2), which can present with a wide range of clinical symptoms from mild flu-like, diarrhea, headache, dyspnea, and conjunctival congestion (1). It is established that patients with documented comorbidities including diabetes, chronic kidney disease, chronic liver disease, and chronic obstructive pulmonary diseases

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(COPD) were more vulnerable to infection with COVID-19 than those without (2).

SARS-CoV-2 is an enveloped single-stranded ribonucleic acid (RNA) virus. The 5' terminus of the virus is responsible for viral replication and the 3' end contains the genes encoding five structural proteins; these include the spike (S), membrane (M), nucleocapsid (N), envelope (E), and hemagglutinin esterase (HE) proteins (3,4). The S proteins present on the envelope mediate viral entry into the host cell by binding to the angiotensin-converting enzyme (ACE) 2 receptor. Variations in key amino acid residues at the receptor-binding site for SARS-CoV-2 allows for a stronger binding affinity than SARS-CoV with the human ACE2 receptor (5,6). This accounts for greater pathogenicity of SARS-CoV-2 compared with SARS-CoV and the expression of ACE2 receptors on the host cells correlates with susceptibility to SARS-CoV-2 infection (7-9)**.**

Viral entry into the cell triggers an immune response and the release of proinflammatory cytokines including interleukin 6 (IL-6), interleukin 1 (IL-1), and tumor necrosis factor-α (TNF-α), which in turn activates neutrophils (10). The above steps increase the oxidative stress on the cells and activate inflammasome pathways leading to activation of pyroptosis. Pyroptosis causes programmed cell death leading to efflux of cytokines, which induce reactive oxygen species (ROS) production including O_2^{0-}, H_2O_2, OH^-, and HOO^{o}, resulting in organ failure, further enhancing oxidative stress (11-14).

Oxidative Stress Response

Studies have established that COVID-19 patients have elevated oxidative stress response, causing increased ROS levels (15,16)**,** which in turn induce the expression of antioxidant response elements (AREs). The AREs then activate the production of antioxidant enzymes including superoxide dismutase (SOD), catalases (CAT), and glutathione peroxidase (GPX). These enzymes will then convert the ROS into molecular water, thus neutralizing them (17,18).

Studies have demonstrated significant downregulation of redox-sensitive enzymes in elderly individuals compared to young adults (17-20). This may indicate why SARS-CoV-2 infection is more severe in elderly than in younger individuals (13).

GPx is an intracellular antioxidant. Its activity increases in response to lung inflammation following exposure to an allergen or infection (21). CAT are iron-containing antioxidants that protect tissue against oxidative damage caused by peroxides. Von Kimm et al. reported that CAT supplementation may confer protection and significantly improve patient conditions during respiratory infections and lung diseases (20).

Microminerals including zinc (Zn), copper (Cu), and iron (Fe) have essential functions in maintaining and improving the activity of these antioxidants. Important cofactors associated with SOD are Cu and Zn, hence known as Cu/Zn SOD. Zinc inhibits RNA polymerase activity and reduces viral replication (21). Recent studies indicate Zn deficiency is strongly linked to infection severity, and modulation of the Zn status may be advantageous in COVID-19 (22). Previous studies have demonstrated that decreased serum Cu and Zn concentrations can predispose patients to increased infection risk and inflammation (23). It is also known that systemic infection and inflammation can lead to an increase in serum Cu concentration. Several reports have demonstrated a positive correlation between the Cu/Zn ratio and the severity of respiratory or systemic infections, including COVID-19 (24).

Iron is essential for growth and metabolism, and has a structural role, especially in microbial life. Based on existing information, it can be presumed that COVID-19 infection exacerbates the oxidative stress on cells leading to an imbalance between oxidant and antioxidant status (23). Our aim was to demonstrate this imbalance between oxidant and antioxidant mechanisms due to COVID-19

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infection and its relationship to the concentrations of the associated microminerals. In this study we indirectly analyzed oxidative stress in COVID-19 patients by determining the antioxidant concentrations that are active in neutralizing the ROS formed and their impact on the concentrations of minerals responsible for their adequate action.

Materials and Methods

Study Design

This was a monocentric 5-month cross-sectional and analytical study, conducted at the Department of Biochemistry, Manipal Academy of Higher Education, Manipal, India. The study was approved by the Institutional Ethics Committee, Kasturba Hospital, Manipal. The first participant in this study was enrolled after registration in the Clinical Trial Registration of India.

Participants

200 patients registered at Kasturba Hospital were enrolled in the study. They were divided into healthy control (n=100) and study groups (n=100). The required sample size calculated by the statistical analysis was determined to be 196 (n=196); hence, the sample size is appropriate for the study design and implementation. The eligible patients in the control group were healthy volunteers with no known history of any chronic disorder or patients who had visited the hospital for a regular health checkup and were COVID-19-negative at the time of enrollment. The study group consisted of symptomatic COVID-19 patients. Subject ages in both groups were 18-70 years. COVID-19 was diagnosed using the RT-PCR (polymerase chain reaction) -based Nucleic Acid Amplification Test (NAAT). Written informed consent was obtained from all the patients for participating in the research and utilization of the biochemical data derived from the blood sample collected for biochemical analyses of antioxidants and minerals.

Exclusion Criteria

COVID-19-negative patients who at the time of the research were suffering from clinically diagnosed psychological disorders including anxiety and depression were excluded from this study. COVID-19-positive patients who were pregnant or had pre-existing liver or kidney diseases, thyroid disorder (hypothyroidism), biliary tract obstruction, or previous history of gastrectomy were excluded from the study.

Biochemical Measurements

Fasting blood samples were collected from the participants into vacutainer tubes with a clot activator. Samples were analyzed for serum GPX, SOD, CAT, Cu, Zn and Fe concentrations. The clotted samples were centrifuged at 2300 x g. Sera were collected and stored at -20 ^{o}C until further analysis (21,24). Phosphate buffer and ethylenediaminetetraacetic acid (EDTA) were added to the serum samples for analyses. Serum copper levels were determined colorimetric analysis using the Bathocuproin desulphonated method. Serum zinc (using Nitro-PAPS) and iron (using ferrozine) concentrations were determined by colorimetric methods using kits. GPX was estimated using the Gunzler et. al. method, SOD by a modified Beyer and Fridovich method, and CAT by a modified Goth method using colorimetric analysis. The established procedural steps were replicated during the GPX, SOD, CAT, Cu, Zn and Fe analyses and the procedures are referenced in the citations (24).

Statistical Analysis

Statistics were analyzed using Microsoft Office Excel 2007 (Microsoft Corp, Redmond, WA). Further data analysis was performed utilizing Statistical Package for Social Science (SPSS) version 25. The relationship between the study and control groups for the univariate variables was determined by the Student T-test.

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The correlations between the antioxidant and mineral concentrations in sera were determined using Pearson's correlation test to measure the bivariate linear correlation between the two. The mean values were represented using the means ± SDs. The data are represented using the table diagram. The variables representing p values < 0.05 were considered significant for this study.

Results

Glycemic parameters

GPX activity and copper were significantly greater, while the Zn concentration was significantly less, in the study group than in controls (P < 0.0001). SOD, CAT activity, and Fe concentrations did not differ significantly between the two groups (Table 1).

The Pearson correlation studies were significant with a strong correlation observed between SOD and Zn concentrations in the study group ("r" = 0.4916 and p < 0.0001), but the other correlation study showed a very weak correlation between iron and catalase ("r" = 0.0974, p = 0.345) in both subjects and controls. No statistically significant correlation was found between Cu concentration and SOD ("r" = -0.0275, p = NS, Table 2).

Table 1. Pearson Correlation showing the correlation between the antioxidants and related micronutrients in the Control and Study groups.

Variable	Group		Mean	SD	CI
Glutathione peroxidase (mKAT/L)	Control	P<0.0001* (S)	5.82	1.64	5.82 ±0.32
	Study		10.36	2.7	10.36 ±0.52
Zinc (µg/dL)	Control	P<0.0001* (S)	81.07	10.13	81.07 ±1.98
	Study		34.78	4.5	34.78 ±0.88
Copper (µg/L)	Control	P<0.0001* (S)	782.15	106.5	782.15 ±20.87
	Study		2192.5	449.8	2192.5 ±48.96
SOD (U/ml)	Control	0.918 (NS)	14.45	2.68	14.45 ±0.525
	Study		14.19	2.21	14.19 ±0.433
Iron (µg/dL)	Control	0.854 (NS)	73.74	7.79	73.74 ±1.52
	Study		71.70	5.86	71.70±1.14
Catalase (kU/L)	Control	0.528 (NS)	0.061	0.016	0.06±0.003
	Study		0.0695	0.036	0.06±0.007

SD – Standard Deviation, * – Significant, NS – Not significant.

Table 2. Pearson Correlation showing the correlation between the antioxidants and related micronutrients in the Control and Study groups.

	Control group		Study Group	
	Correlation coefficient (r)	**P value**	**Correlation coefficient (r)**	**P value**
Zinc and SOD	0.0457	0.6559	0.4916	< 0.0001*
Copper and SOD	-0.0181	NS	-0.0896	NS
Iron and Catalase	0.0974	0.3450	-0.0275	NS

*S – Significant, NS – Not significant.

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Discussion

In this study, we aimed to estimate the concentrations of the essential antioxidants GPX, SOD, and CAT following COVID-19 infection and how they may affect the status of the microminerals Zn, Cu, and Fe. COVID-19 is characterized by an immune response leading to enhanced ROS production subsequently leading to increased activity of essential antioxidants, which play a significant role in neutralizing oxidative stress. Hence, low antioxidant levels could lead to unchallenged damage caused by ROS, which may further increase disease severity and result in poorer disease outcomes in patients (23). The micronutrients copper, zinc, and iron act as cofactors to the antioxidant enzymes and are therefore essential for these enzymes' optimal function (25,26). Mritunjay et al., demonstrated that Zn and Fe deficiencies and elevated copper are associated with increased COVID-19-associated morbidity and mortality (27,28).

Muhammad et al. reported that GPX ($p < 0.001$), SOD ($p < 0.001$), and CAT ($p < 0.001$) were significantly less in COVID-19 patients than in controls (29). We did not observe a similar trend. Serum activity of GPX and CAT were significantly greater, but SOD was significantly less, in subjects than controls. Zinc was less and Cu was greater in subjects than in controls, which was also observed by other researchers. Anuk et al, showed that serum Zn was less, and serum Cu was greater in COVID-19 patients than in controls (30). High Cu levels have been established to have an adverse effect on the respiratory tract, therefore an imbalance in the serum Cu/Zn ratio can lead to poor patient outcomes during respiratory infections such as SARS CoV-19 (23,24). As reported by Bastin et al. serum Fe strongly correlates with disease severity in COVID-19 patients (31,32); however, in our study the serum Fe concentration was slightly but not significantly, greater in controls than in the study group, which is a deviation from the normally expected pattern. Zinc deficiency is strongly linked to infection severity by previous literature. Despite the lack of clinical data, modulation of Zn status is beneficial in respiratory infections. During the acute phase of infection, Zn is readily absorbed by the cells and stored in zincosomes or organelles, which may lead to decreased serum Zn levels (21). Mariani et al. reported elevated plasma SOD and Zn levels following Zn supplementation in the elderly with Zn deficiency (25). Te Velthuis et al. established the inhibitory effect of increased intracellular Zn on SARS-CoV2 replication (23). Our study was the first to demonstrate a significant correlation between serum SOD and Zn in COVID-19 patients. Zinc was significantly less in subjects than in controls, although SOD concentrations did not vary significantly between the two groups; however, both were more strongly correlated in subjects than in controls, indicating a significant impact of Zn on SOD concentration.

The correlation between serum zinc and SOD was statistically significant in the study group but not in controls. Little data exists to compare this result with other literature. Serum Fe concentration is significantly associated with the oxidative stress on cells, especially erythrocytes. Jong-Yoo et al. showed that total antioxidant capacity was less in patients with Fe deficiency (0.654 ± 0.81 g/dL, $p<0.001$) than in those without, but the correlation between serum iron and CAT was not significant ($p = 0.543$) (31). CAT contains Fe, and a strong correlation is expected between them, but was not evident in this study. Only one study has reported a strong association between Fe and CAT activity (33).

The major limitation of this research was the lack of estimation of selenium and the cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-α in the serum samples, which was due to financial constraints. It has also been established in previous studies that selenium is effective in upregulating GPX activity in patients with lung infection or injury. Several studies have already established a positive correlation between low

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GPX levels and selenium in lung injury patients (27,28). The other major limitation was the lack of access to patient files, which would assist in subcategorizing the cases based on COVID-19 infection severity and determine the correlation of antioxidants and minerals based on the disease severity.

It is not easy to correlate the biochemistry of nutritional or pathological deficiency of micronutrients and the clinical symptoms and the prognostic outcome following a severe pathological condition such as SARS-CoV-2 infection or other ARDS. SARS-CoV-2 infections result in ROS production, which can lead to disturbances in the oxidant/antioxidant equilibrium. Our study established increased oxidative stress in the patients after COVID-19 infection. These finding establish the importance of the significant role played by copper, zinc, and iron in chronic debilitating infections such as COVID-19 and argues in favor of possible supplementation of the minerals during their treatment. Evidence from previous literature and this study establishes the importance of minerals in antioxidant mechanisms. This research does not provide a novel finding but supports previous evidence, which reports the effect of mineral supplementation to enhance antioxidant function during active infections including COVID-19, and possibly during the post-infection recuperative phase.

The evidence indicates that supplementing patients with minerals will improve outcomes following infections, as the oxidative stress due to increased ROS production is known to cause long-term pathological complications and delay in disease resolution. However, further interventional studies are required to verify that antioxidant supplementation along with supplementation of the related minerals accelerates ROS decline, thus leading to early termination of disease and shortening hospital stays. Researchers have also recommended that the serum copper/zinc ratio can be used as a prognostic marker for other pathological conditions including cardiovascular diseases, respiratory infections, and chronic hepatitis, and may also be of value in determining the effects of oxidative stress in COVID-19 patients. This study could also be expanded by subcategorizing the COVID-19 patients based on disease severity, determining the ROS level in each subcategory and analyzing the effects of antioxidant and mineral supplementation in these patients.

We assume that antioxidant supplementation has an optimum window period and may be more effective early in the disease process before a significant pro-inflammatory response is triggered than in the later period when severe ARDS has developed.

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Conflict of Interest

There is no conflict of interest with anyone.

Ethical Approval

The study was carried out after obtaining approval from the Institutional Ethics Committee, Kasturba Hospital, Manipal. The first participant in the study was enrolled after registration in the Clinical Trial Registration of India.

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