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Biochemistry Section

Status of Common Serum Minerals and Trace Elements in COVID-19 Follow-up Cases: A Hospital-based Study from Eastern India

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ABSTRACT

Introduction: Management of post Coronavirus Disease-2019 (COVID-19) complications are the new challenges nowadays. It has been observed that in post COVID-19 cases the serum levels of several electrolytes and trace elements are deranged.

Aim: This study was conducted to estimate the levels of different serum minerals and trace elements in one month post COVID-19 follow-up patients and compared with normal age-sex matched controls.

Materials and Methods: This hospital based cross-sectional study was conducted in the Department of Biochemistry in a tertiary care centre, over a period of six months (from January 2021 to June 2021). After fulfilling proper inclusion criteria, 223 COVID-19 follow-up patients of both genders (134 males and 89 females) were included as 'case' group. Age-sex matched 250 healthy volunteers were recruited as 'control' group. Levels of serum electrolytes (sodium and potassium) and trace elements (zinc, iron, calcium, phosphate, copper, magnesium and selenium) were estimated, analysed and compared against each other. Tables and statistical analysis was done using Statistical Package for the Social Sciences (SPSS) version 20.0.

Results: In this study, the levels of serum zinc and iron were found to be higher and serum calcium, phosphate, copper, magnesium and selenium levels were reduced in post COVID-19 one month follow-up cases in comparison to controls. Female cases were in deficient state of iron, calcium, copper and magnesium but had high serum zinc and phosphate when compared to males. No abnormalities were noted in the level of electrolytes in post COVID-19 cases.

Conclusion: Assessment and monitoring of levels of the mineral throughout the course of post COVID-19 follow-up is advisable for timely and appropriate measures to combat with post COVID-19 complications.

Keywords: Calcium, Coronavirus disease-2019, Electrolytes, Potassium, Zinc

INTRODUCTION

The whole world is fighting against COVID-19 since December, 2019. According to the information, obtained from 'Worldometer' at the end of June 2021, COVID-19 has taken a toll of around 40 lakh lives all over the globe and USA leads the list with more than 6 lakh casualties followed by Brazil (more than 5 lakh) and India (more than 4 lakh). Fever, cough and cold, anosmia are still the first signs and symptoms presenting in the fever clinic of the tertiary care hospitals which may be followed by diarrhoea, vomiting, conjunctivitis, joints pain, malaise and respiratory distress etc in the later phase of infection. Elderly people with co-morbidities like diabetes, hypertension, renal disorders, hepatic dysfunctions etc., and certain habits like smoking etc., trigger up the chances to be infected with COVID-19 [1].

The relationship between immunity and nutrition is well known and its role in Coronavirus Disease 2019 (COVID-19) is also being paid great attention. However, the nutritional status of COVID-19 patients is unknown. In early COVID-19 studies, some evidence has been provided that electrolyte disorders may also be present upon patients' presentation, including sodium, potassium, chloride and calcium abnormalities [2].

Minerals and trace elements have various roles like differentiation and maturation of cells, giving protection by chemotaxis of neutrophils and phagocytosis of macrophages, synthesis and regulation of anti-microbial proteins, reducing inflammatory process, maintaining body homeostasis by balancing synthesis of cytokines, responses from antibodies, damages due to phagocytosis, wound healing etc. Several studies were conducted regarding the status of serum electrolytes, minerals and trace elements during COVID-19 infection or the comparison of the serum levels before and during COVID-19 infection. Evidence suggests that nutrients are involved in the development of COVID-19; however, no studies have been undertaken to assess nutrient deficiencies in COVID-19 patients directly [3].

Therefore, this study was conducted to estimate the levels of various nutrients in COVID-19 patients. Decreased immunity is a significant risk factor for infection with respiratory viruses. The current study was designed to estimate levels of different serum minerals and trace elements in post COVID-19 patients and compare these values with normal age-sex matched controls.

MATERIALS AND METHODS

This hospital based cross-sectional study was conducted in the Department of Biochemistry with the collaboration of Department of Microbiology, in a tertiary care centre, West Bengal, India, over a period of six months (January 2021 to June 2021). This study protocol was approved by the Institutional Ethics Committee (IEC), in a tertiary care hospital in Kolkata, West Bengal, India. Filled up informed consent form was taken from all the willing participants of case and control groups. The study principles and procedures adhered to the ethical standards formulated in the (1975, revised in 1983) Helsinki declaration.

Inclusion criteria: Adult COVID-19 patients, visiting the Outpatient Department (OPD) of the tertiary care hospital, aged between 41-70 years of both the sexes, detected positive by RT-PCR test who were on treatment as per treatment guidelines laid down by

National Centre for disease control and completed the treatment either in home isolation or in safe-home or in hospital, attending the hospital OPD after one month were included in this study as the 'case group' [4]. Age-sex matched healthy volunteers from same peer group were included in this study as 'control' group.

Exclusion criteria: COVID-19 patients in paediatric age group, young adult (age group of 18-40 years), or advanced elderly (>70 years of age) with cancer or being treated with immune-suppressive drugs, pregnant ladies on multivitamin and multimineral supplements were excluded from this study.

Sample size calculation: In the current year, almost 70-75 percent of adult population suffering from viral fever were infected by COVID-19 virus. So minimum sample size considered was (1.96×1.96×72×20)/(5×5)=223. Age-sex matched 250 healthy volunteers from same peer group were included in this study as 'Control' group.

Study Procedure

A 5 mL of blood sample was collected from the antecubital vein by venipuncture under strict and proper aseptic technique. Serum and plasma from the samples were separated by centrifugation at 3000 rpm for three minutes.

Serum sodium and potassium were estimated by Ion-Selective Electrode (ISE) method in electrolyte analyser machine (9180 Electrolyte Analyser, Roche). Serum levels of various minerals like zinc (nitro-phospho adenosyl phospho-sulphate method), iron (ferrozine method), calcium (arsenazo III), phosphate levels (ammonium molybdate method), copper levels (di-bromo-pyridylazo-ethyl-sulphopropyl-aniline method), magnesium (calmagite method) and selenium levels (by colorimetric method) were analysed colorimetrically using semi-auto analyser (ERBA CHEM V2 PLUS, TransAsia).

STATISTICAL ANALYSIS

The whole data was put into MS-Excel spread sheet and checked for entry errors. Then it was imported into IBM SPSS version 20.0 in Windows 10 for analysis of the data. All values are expressed in a manner of mean±Standard Deviation (SD). Pearson's Chi-square (χ^2) test was used to compare categorical variables. In cases of continuous variables, the data was compared by using independent sample student's t-test. The p (probability) value less than 0.05 was considered as statistically significant.

RESULTS

Age-gender wise frequency distribution of cases and controls was done and the difference was statistically insignificant [Table/Fig-1]. Most affected age group was of 51-60 years. The levels of serum electrolytes, minerals and trace elements of case and control groups were compared [Table/Fig-2].

Groups	Cases			Control			p-value
	Male	Female	Total	Male	Female	Total	
40-50 years	38	30	68	41	33	74	0.822
51-60 years	71	48	119	75	53	128	
61-70 years	25	11	36	29	19	48	
Total	134	89	223	145	105	250	

[Table/Fig-1]: Age-gender wise distribution amongst case and control groups..

Serum parameters	Case group (n=223)		Control group (n=250)		p-value
	Mean	SD	Mean	SD	
Sodium (mEq/L)	138.7	±4.3	139.2	±3.73	0.23
Potassium (mEq/L)	4.38	±0.64	4.12	±0.71	0.27
Zinc (µg/mL)	1.58	±0.83	0.83	±0.19	<0.001
Iron (µg/dL)	238.2	±51.3	135.2	±26.27	<0.001
Calcium (mg/dL)	7.2	±1.9	10.0	±1.59	0.02
Phosphate (mg/dL)	2.7	±0.72	4.1	±0.55	0.001
Copper (µg/dL)	62.6	±14.4	162.3	±10.26	0.001
Magnesium (mg/dL)	1.18	±0.55	1.9	±0.21	0.01
Selenium (ng/dL)	53.7	±16.2	123.6	±23.5	0.001

[Table/Fig-2]: Summarised data and comparison of serum electrolytes, minerals and trace elements between case and control groups.

In case group, serum zinc and iron levels were higher and serum levels of calcium, phosphate, copper, magnesium and selenium were lower than those in the control group. The differences were statistically significant. In comparison, serum electrolyte levels were similar in both groups. In cases the data from male and female were summarised and compared. In males, serum iron, calcium, copper and magnesium levels were increased while serum zinc and phosphate were decreased in comparison to female cases [Table/Fig-3].

Serum parameters	Male (n=134)		Female (n=89)		p-value
	Mean	SD	Mean	SD	
Sodium (mEq/L)	139.2	±5.1	136.7	±5.7	0.13
Potassium (mEq/L)	4.17	±0.52	4.42	±0.53	0.17
Zinc (µg/mL)	1.49	±0.81	1.67	±0.92	0.01
Iron (µg/dL)	247.2	±49.3	231.5	±37.9	0.03
Calcium (mg/dL)	7.9	±1.8	6.8	±1.5	<0.001
Phosphate (mg/dL)	2.4	±0.86	3.1	±0.74	0.02
Copper (µg/dL)	64.9	±12.4	55.2	±18.3	0.03
Magnesium (mg/dL)	1.44	±0.49	1.04	±0.41	<0.001
Selenium (ng/dL)	53.2	±16.3	54.1	±15.9	0.09

[Table/Fig-3]: Comparison of serum electrolytes, minerals and trace elements between male and female cases.

DISCUSSION

Coronavirus or Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) we are collecting the related information regarding this virus each and every day and trying to overcome the hazards and side effects caused by it. The researchers of all over the world are fully engaged in detecting its character, pathogenicity and to find out the exact cause of problems [3]. Proper diet with sufficient amount of minerals, trace elements and vitamins along with proper balance in electrolytes build up strong immune system. During the COVID-19 infection, changes in electrolytes, minerals, trace elements and vitamins have been discussed in several articles. In this study, we have accumulated the data of levels of electrolytes, minerals and trace elements in serum in post COVID-19 phase.

Amongst the imbalances of electrolytes and trace elements, hyponatremia is most common, and most often it is found in Syndrome of Inappropriate Anti-Diuresis (SIAD). In the condition of COVID-19 infection, high levels of Interleukin-6 (IL-6) and cytokines induce non osmotic release of vasopressin causing electrolyte imbalance. So increased level of IL-6 has a negative correlation with serum sodium concentration (Na^+) and PaO_2/FiO_2 (P/F) ratio [5]. Presence and expression of Angiotensin Converting Enzyme-2 (ACE-2) is observed not only in lungs but it has a role in kidneys also. So, recently state of kidneys are also taken as a matter of great concern in COVID-19 infection. It has been observed that increased sodium intake is responsible for the downregulation of ACE-2 and the reduction of the activity of ACE-2 affects the smooth entry of coronavirus inside the cell. The progress of severity and virulence of COVID-19 infection is strongly associated with hyponatremia [6,7].

In COVID-19 infection, the virus affects the activity of ACE-2 and hampers angiotensin-II decay. Increased aldosterone secretion is responsible for loss of potassium through urine, causing hypokalemia [8]. Moreover, in COVID-19 patients, increased amount of potassium is excreted through Gastro-intestinal (GI) and urinary route leading to hypokalemia. Potassium has immense role in contraction and

relaxation of myocardia. Adequate amount of plasma potassium prevents myocardial failure. Though the current study did not document hypokalemia, regular electrolyte assessment is probably required to identify cases with dyselectrolytemia, and to monitor in the long run in order to prevent cardiac failure [9].

In comparison, the levels (mean±SD) of serum sodium and potassium of case group, were similar to those of control group (p-value 0.23, 0.27, respectively). When in male case group, levels of sodium and potassium were compared with levels in female case group, no significant difference was noted (p-value: 0.13 and 0.17, respectively).

Zinc has several important roles like synthesis and functions of neutrophil, macrophage, NK-cell, T-cell, B-Cell and prevents viral infection by inhibiting replication mechanism of rhinovirus, respiratory syncytial virus, SARS-CoV etc., [10,11]. It is evident that RNA-dependent RNA polymerase (RdRp) enzymatic activity is inhibited by the ionophoric action of zinc [12,13]. Zinc has a synergistic effect when it is used either with anti-malarial drugs (chloroquine; CQ, hydroxyl-chloroquine; HCQ) or with some anti-viral drugs [10]. In analysis, serum zinc level was higher in case group in comparison to control group (p-value <0.001). But, in female case group, serum zinc level was more in compared to that of male case group (p-value=0.01).

In this study, serum iron level was elevated in female case group in comparison to control group (p-value <0.001). In male case group, serum iron level was even higher when compared to that of female case group (p-value=0.03). Homeostasis of serum iron is associated with synthesis and functions of regulatory molecules like hepcidine. In COVID-19 patients, the levels of cytokines like IL-6, interferon-γ (IFN-γ), Interleukin-1B (IL-B), Tumour Necrosis Factor-α (TNF-α) are increased causing high hepcidin mediated iron storage in macrophages and hepatocytes. Increased iron storage helps in viral replication by the process of synthesis of Adenosine Tri-Phosphate (ATP) [14]. Drugs like tocilizumab used in the treatment of COVID-19 suppresses the production of hepcidine [15]. In the treatment of COVID-19, serum iron level should be checked regularly, and on necessity, iron chelators can be used as a treatment protocol. Higher iron level triggers the severity of pulmonary fibrosis. In the treatment of lung fibrosis, iron chelators are thought to be useful to control iron level. This justifies the estimation of serum iron in laboratory assessment of COVID-19 cases.

In the SARS-CoV, this calcium is responsible for the formation of structure, entry into the host cells and the replication of virus inside the eukaryotic cells and also responsible for the release of virion [16]. It has been reported that lipid metabolism is disturbed in COVID-19 infection. Increased levels of unsaturated as well as unbound fatty acids are seen in COVID-19 patients. These fatty acids bind with calcium ions resulting in hypocalcemia [17]. Another explanation reveals that hypocalcemia occurs in COVID-19 patients due to the reduced activity of 1 α-hydroxylase in the proximal part of renal tubules of kidneys. Activity of enzyme is hampered due to the expression of ACE2, also expressed in the same site [18].

The same mechanism also explains the imbalance of serum phosphate levels in COVID-19 infection. In conformance to the above hypothesis, levels of serum calcium and inorganic phosphate of case group, remained lower than with those of controls (p-value:0.02 and 0.001, respectively). Sex based comparison revealed a lower serum calcium and inorganic phosphate levels in females and males respectively (p-value: <0.001 and 0.02 respectively).

Copper, an essential micro-element, protects DNA from oxidative stress, strengthens immune system, regulates the normal activity of ceruloplasmin and several enzymatic activities of benzylamine oxidase, super-oxide dismutase etc. Previous studies reveal, deficiency of copper may lead to chronic TNF-α induced pulmonary infection [19]. It is also revealed, serum copper ion and nano-particles of copper oxide, remdesivir (RDV; an analog of nucleotide) and nitric oxide (NO) combinedly prevent entry of coronavirus and its RNA replication by impairing viral mRNA and cuspid protection. So it indicates that adding of therapeutic dose of copper in COVID-19 patients' treatment is beneficial. It is a well known fact that in jejunum of GI tract, copper and zinc ions, both are absorbed competitively. It means high doses of zinc (>150 mg/day) for a longer period of time, may cause copper deficiency. So, people who are taking zinc supplementation on regular basis, are identified as population at risk of being infected with coronavirus, due to the malabsorption of copper ions [20]. In analysis, serum copper level was low in the case group in comparison to control group. In male cases, serum copper level was higher when compared with that of female case group (p-value:0.03).

Proper concentration of magnesium improves metabolism inside myocardium, prevents cardiac myocytes' death and also prevents accumulation of calcium and thus atherosclerosis. Magnesium has also has a role in minimising peripheral vascular resistance to reduce cardiac arrhythmia and to regulate lipid metabolism. It also prevents platelet adhesion and aggression; and improves endothelial function [21]. In the immune system, magnesium has various important roles through several. mechanisms like synthesis of immunoglobulins, adherences of immune cells, binding of Immunoglobulin-M (IgM) with lymphocytes, induction of antibody dependent cytolysis, recognition of response of macrophage to lymphokines and adherence of T helper and B cells all of which are important for resistance against viral infection [22]. Study results showed that serum magnesium level was decreased in case group in comparison to control group (p-value 0.01). In males, serum magnesium level was higher than in female case group (p-value <0.001).

Selenium constitutes the normal structures of enzymes to maintain the body homeostasis. Along with vitamin E, selenium inhibits the synthesis of free radicals. Proper concentration of serum selenium strengthens cellular immunity and prevents viral genome mutation [23]. It has been observed that proper dose of selenium (50-100 µg/day) reduces the chance of COVID-19 infection by cellular immune response [24]. It has also been noted that increased intake of selenium for a longer period of time causes synthesis of certain cytokines like IL-8, IL-10 and T-cells causing hyperimmune mediated complications [25,26]. Study results showed a decreased level in cases in comparison to controls (p-value <0.001). Sex based difference was not evident (p-value=0.09).

These serum electrolytes and trace elements remain involved in thermogenesis, osmotic regulation, enzymatic activity, bone metabolism, conduction through nerve ending, maintenance and normal functions of cardiac muscles, protection from free radicals and formation of blood cells. So, proper levels of above parameters in post COVID-19 scenario are essential for the normal harmony of different organ systems. As the imbalance of sodium and potassium is most common, their signs and symptoms are well known, detection process is very rapid and treatment protocol is standardised and well versed. But, detection of imbalance of other minerals and trace elements is an insidious process. But this imbalance gives rise to health complications in due course of time. So these are to be monitored repeatedly at regular interval and to be treated accordingly.

Limitation(s)

It is a single centre, cross-sectional study conducted within a short period of time with a specific age group from both genders. To get the better result and draw the particular conclusion, multicentric prospective study is required where several follow-ups in regular interval and their results will be discussed and any health related issues and side effects may be the consequences of COVID-19 infection will be noted. Moreover, bigger study population with different age groups should be included in the study for the better result in future; on that basis the future trends of treatment protocol

of COVID-19 infection can be determined. Lack of infrastructure like absence of Atomic absorption spectrometer had compelled the investigators to measure trace elements by colorimetric methods using commercial reagents as an alternative.

CONCLUSION(S)

In this study, it has been observed that the levels of serum zinc and iron remained higher and serum calcium, phosphate, copper, magnesium and selenium levels were reduced in post COVID-19 follow-up cases. During this phase, amongst the patients, females were in a deficient state of iron, calcium, copper and magnesium and in the higher side of serum zinc and phosphate in comparison to male patients. Considering all these factors, we have to make our treatment protocol in future to combat against post COVID-19 complications.

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