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Original Article

Assessment of Vitamin D, Vitamin B12, Retinol-binding Protein (RBP), Zinc, Selenium, Copper and Magnesium in Iranian COVID-19 Patients and Their Relationships with the Disease Linked Death

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ABSTRACT

Background and Objectives: Clinical evidence on the nutritional statuses of COVID-19 patients and their associations with COVID-19 clinical outcomes are limited. To the best of the authors' knowledge, no studies have been carried out on COVID-19 patients of Iranian population. Therefore, the aim of this study was to assess vitamin D, vitamin B_{12}, RBP, zinc, selenium, copper and magnesium levels in patients with COVID-19. Furthermore, associations of nutrient levels with the disease-linked death were investigated.

Materials and Methods: This cross-sectional study was carried out in hospitals affiliated to Hamadan University of Medical Sciences, Hamadan, Iran, on 98 COVID-19 positive patients, March to May 2020. Demographic and clinical data of the patients were collected from their clinical records. Blood samples of 5 ml were collected from the patients, which were used for hospital routine laboratory assays as well as measuring trace elements and vitamins. Comparison of chemical biomarkers based on the patient's treatment outcomes was carried out using Mann-Whitney U test. For data analysis, Stata Software v.14 was used.

Results: From 98 COVID-19 positive patients, 16 (13.33%) patients died during the treatment. These patients had higher proportions of heart diseases (37.5% against 10.98%, $p = 0.007$). Moreover, the median of white blood cell counts was significantly higher in patients, who died during treatment ($p = 0.002$). For vitamin D_3, vitamin B_{12}, RBP, zinc, selenium, cupper and magnesium, 59.2, 12.24, 53.08, 30.61, 88.71, 16.33 and 26.53% of the patients had values below the reference value ranges of these elements, respectively. Comparison of chemical biomarkers based on the patient's treatment outcomes did not show significant differences ($p > 0.05$).

Conclusions: Although results of this study did not show significant differences between the levels of the trace elements and vitamins with the outcomes in COVID-19 patients due to the small sample size of the present study, assessment of these relationships needs stronger evidence by designing large studies.

Keywords: COVID-19, Vitamin D, Vitamin B_{12}, Zinc, Selenium, Copper, Magnesium, Iran

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a newly-emerged disease caused by a member of beta coronaviruses. It was first reported in December 2019 in Wuhan, Hubei Province, China (1). Then, the disease was named coronavirus disease 2019 (COVID-19), spreading over six continents (2). It quickly spread worldwide and has become a global health threat (3). More than 600,000 of new cases and thousands of deaths are reported worldwide every day. These statistics are nearly 14,000 new cases and more than 400 deaths per

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day for Iran, winter 2022 (4, 5). Nowadays, a very limited numbers of specific antiviral drugs are available for the treatment of coronavirus. Therefore, the major way to fight with COVID-19 seems to focus on preventive measures and isolation and treatment of the patients (4). Moreover, dietary management is recommended as an approach to minimize potential risks of COVID-19 infection and its mortality (6). Numerous trace elements and vitamins are necessary for the normal function of the immune system (7), which could be important weapons against COVID-19 (8). Supplementation with these trace elements and vitamins, including vitamin A, vitamin D, zinc (Zn), selenium (Se), copper (Cu) and magnesium (Mg) can enhance innate and adaptive immune systems against viral infections (9–11). Other important nutrients with positive effects on the immune system include B vitamins (vitamins B_6 and B_{12} and folate) and vitamin C and the trace elements include iron, Mg and Cu (12). These nutrients play essential roles in establishment and maintenance of physical barriers, production of antiviral agents, differentiation and chemotaxis of immune cells (macrophages, neutrophils and lymphocytes) and termination of inflammation. Low numbers of lymphocytes, impaired cytokine productions and poor antibody responses and phagocytoses may occur by the lack of nutrients (13).

Most of the known risk factors from COVID-19 linked to deaths include fundamental associations with essential nutrients and nutritional statuses (14). Researches have indicated that COVID-19 patients have malnutrition signs such as liver and kidney dysfunctions and low levels of serum albumin (15). Deficiency of these nutrients may increase risks of COVID-19 infection and severe diseases. Due to the antioxidant and anti-inflammatory nature of vitamins and nutrients, they may be consumed during COVID-19 (3). Additionally, pathological conditions such as COVID-19 may result in diarrhea and subsequent loss of electrolytes and essential nutrients in the body (16). Under these conditions, patients must receive nutrition as soon as possible, especially those associated to poor prognoses and bad outcomes (17). Therefore, nutritional assessment and support have been suggested for COVID-19 patients, especially for critically ill patients admitted to intensive care units (ICU) (18). Nevertheless, clinical evidence regarding nutritional statuses of COVID-19 patients and their associations with COVID-19 clinical outcomes is very limited. This evidence can provide valuable recommendations and advice for health professionals and governments regarding how to identify vulnerable and at-risk peoples of the population and how to prescribe supplements for patients with poor prognoses. To the best of our knowledge, no such studies have been performed in COVID-19 patients of Iranian populations. Therefore, in this study, we aimed to determine the vitamin D, vitamin B_{12}, RBP, Zn, Se, Cu and Mg levels in patients with COVID-19. Furthermore, associations of nutrients levels with COVID-19 linked death were investigated.

Materials and Methods

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This cross-sectional study was carried out at hospitals affiliated to Hamadan University of Medical Sciences, Hamadan, Iran, on 98 COVID-19 positive patients, March to May 2020.

Participants

Patients admitted to the hospitals, who were verified with SARS-CoV-2 infection using real-time polymerase chain reaction (PCR), were enrolled in this study. Sampling was carried out using non-probability convenience sampling method.

Eligibility Criteria

The inclusion criteria were patients with clinical manifestations of COVID-19, who verified using real-time reverse transcriptase-PCR (real-time RT-PCR) over the age of 18–65 years. Exclusion criteria were disagreement of the patients or their relatives to participate in the study, patients on mechanical ventilation and use of medication supplements within the last 3 m.

Blood Sampling

A blood sample of 5 ml was collected from each patient, which was used for hospital routine laboratory assays (e.g., complete blood count) as well as assessment of the parameters of this study (trace elements and vitamins). Blood sample for complete blood count (CBC) was collected using tubes containing EDTA anticoagulant. Blood samples for trace element and vitamin assessments were collected in plastic tubes with no anticoagulants. Blood samples was set 15–30 min at room temperature (RT) to clot. Then, sera were separated by centrifugation of tubes at 1500 g for 10 min at 20 ºC. Sera were transferred into fresh plastic tubes and stored at -20 ºC until use.

Data Collection

Demographic data of the patients, including age, sex, clinical signs at the time of referral and underlying diseases, were collected from their medical records. White blood cell (WBC), lymphocyte and platelet counts and hemoglobin concentration assay were carried out using fully automated hematology cell counter (Mindray, China). List of the patients was provided to the hospital and patients' life statuses were reported to the research team by the supervisor of the COVID-19 during patients' discharge using telephone contacts. Retinol binding protein (RBP) assay was carried out using nephelometric method (Genrui, China). Assessments of vitamin B_{12} and vitamin D were carried out using ELISA kits (Pishtaz, Iran) and automated ELISA reader (Awareness, USA). Furthermore, Zn, Cu and Mg were assessed using colorimetric assay kits (Pars

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Azmon, Iran) and automated chemistry analyzer (ROCHE, USA). The Se was investigated using atomic absorption spectroscopy (AAS) (Analytica Jena, Germany)

Statistical Analysis

Characteristics of the study participants based on the treatment groups were present as number (%) for categorized variables and median (IQR) for continuous variables. Shapiro-Wilk test was used to check normality distribution of the investigated variables. Chi-square and Mann-Whitney U tests were used for the comparison of background characteristics between the two groups (dead and alive patients). Comparison of chemical biomarkers based on the patients' life statuses was carried out using Mann-Whitney U test. For data analysis, Stata Software v.14 (Stata, USA) was used. A p-value ≤ 0.05 was reported statistically significant.

Ethical Considerations

This study was approved by the Ethics Committee of Hamadan University of Medical Science (Ethical code: IR.UMSHA.REC.1399 300) and written informed consents were collected from all patients for study participation and publishing their anonymized information in articles. All study protocols were based on the world medical association (WMA) Declaration of Helsinki.

Results

A total of 98 COVID-19 patients were first participated in this study. However, 16 (13.33%) of them died during the treatment. The mean duration of diagnosis-to-death of the 16 dead cases was 5.13 d ±2.19. In total, 66.63% of the participants aged more than 60 years and 51.02% were female. Regarding background diseases, 18.37, 35.71, 15.31 and 19.39% of the participants had diabetes, hypertension, heart disease and kidney failure, respectively. In Table 1, demographic, clinical and biochemical variables were compared based on the treatment outcomes.

Table 1. Demographic, clinical and biochemical variables of the patients based on the treatment outcomes

Variable	Total	Treatment outcome		P. Value*
		Alive (N=82)	Dead (N=16)	
Categorical variables: n (%)				
Age group (year)				
<60	33 (33.67)	31 (37.80)	2 (12.50)	0.05
+60	65 (66.63)	51 (62.20)	14 (87.50)	
Gender				
Male	48 (48.98)	40 (48.78)	8 (50.00)	0.93
Female	50 (51.02)	42 (51.22)	8 (50.00)	
Diabetes				
Yes	18 (18.37)	15 (18.29)	3 (18.75)	0.97
No	80 (81.63)	67 (81.71)	13 (81.25)	
Hypertension				
Yes	35 (35.71)	27 (32.93)	8 (50.00)	0.19
No	63 (64.29)	55 (67.07)	8 (50.00)	
Heart disease				
Yes	15 (15.31)	9 (10.98)	6 (37.50)	0.007
No	83 (84.69)	73 (89.02)	10 (62.50)	
Kidney failure				
Yes	19 (19.39)	15 (18.29)	4 (25.00)	0.54
No	79 (80.61)	67 (81.71)	12 (75.00)	
Continuous variables: Median (IQR)**				
WBC	8550 (6600)	7950 (6300)	11000 (3750)	0.002
Lymphocyte	1280 (932)	1275 (993)	1284 (657)	0.87
Hb	12.4 (2.7)	12.5 (2.7)	12.1 (4.1)	0.63
Plt	179.5 (88)	173.5 (94)	192 (46)	0.22
ESR	34.5 (47.5)	34.5 (53)	36.5 (45)	0.57

*Chi square test for categorical variables and *Mann–Whitney U test* for continuous variables
**IQR: interquartile range

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Table 2. The mean, median and proportion of the biomarkers in COVID-19 patients

Biomarker	n	Mean (SD*)	Median (IQR**)	Reference range	n (% above reference range)	n (% below reference range)
Vitamin D3 (ng/ml)	98	44.76 (104.44)	23 (34.8)	30-100	4 (4.1)	58 (59.2)
Vitamin B12 (pmol/L)	98	126.08 (108.9)	88 (147.5)	21-123	43 (43.88)	12 (12.24)
RBP (mg/L)	98	39.28 (41.11)	15.5 (40)	25-70	18 (18.36)	53 (53.08)
Zinc (micg/dL)	98	87.34 (37.76)	99 (62.5)	Men: 72.6-127 Women:70-114	20 (20.41)	30 (30.61)
Se (micg/L)	98	36.45 (72.75)	20.5 (10)	46-143	2 (2.04)	87 (88.78)
Cu (micg/dL)	98	115.99(73.16)	102.5 (44)	Men:70-114 Women:80-155	22 (22.45)	16 (16.33)
Mg (mg/dl)	98	2.11 (1.61)	1.94 (0.6)	1.7-2.4	15 (15.31)	26 (26.53)

*SD: Standard deviation, **IQR: interquartile range

Table 3. Comparison of the chemical biomarkers based on the patients' treatment outcomes

Biomarker	Alive patients Median (IQR*)	Dead patients Median (IQR)	P. Value**
Vitamin D3 (ng/ml)	23.1 (34.8)	20 (34.8)	0.62
Vitamin B12 (pmol/L)	69.25 (137)	172.5 (165.5)	0.1
RBP (mg/L)	15 (33)	33 (107.9)	0.19
Zinc (micg/dL)	99.5 (64)	96.5 (34.35)	0.55
Se (micg/L)	21.6 (10)	20 (3.1)	0.11
Cu (micg/dL)	105.5 (47)	99.5 (24.5)	0.36
Mg (mg/dl)	1.98 (0.65)	1.9 (0.62)	0.61

*IQR: interquartile range, * *Mann–Whitney U test

No significant differences were seen between the two groups regarding their age, gender, diabetes, hypertension, heart disease and kidney failure, lymphocyte, hemoglobin, platelet and ESR ($p > 0.05$). Patients with death outcome had higher proportions of heart diseases (37.5% against 10.98%, p=0.007). Moreover, the median (IQR) of WBC was significantly higher in patients with death outcome (p=0.002). For vitamin D_3, vitamin B_{12}, RBP, Zinc, Se, Cu and Mg, 59.2, 12.24, 53.08, 30.61, 88.71, 16.33 and 26.53% of the patients had values below the reference values of these elements, respectively (Table 2). Comparison of chemical biomarkers based on the patient's treatment outcome is shown in Table 3. As seen in the table, the two groups were homogenous regarding levels of these biomarkers in their sera ($p > 0.05$). Results of Spearman correlation test showed no significant correlations between WBC counts and micronutrients levels.

Discussion

The present study was carried out to assess serum status of vitamins such as D_3, B_{12} and RBP and trace element such as Zn, Se and Mg in patients affected by Covid-19. Results of the present study showed no significant differences between the variables, including age, sex, background diseases (diabetes, hypertension and renal failure) based on dead and alive patients with Covid-19 (Table 1). Regarding patients with heart diseases, significant differences were seen between dead and alive patients ($p < 0.007$). Based on the present study, no significant differences were observed in other blood factors (except WBC biomarkers) of the patients. Vitamins and trace elements are essential for the normal functioning of the immune system, including positive effects on enhancement of immunity in viral infections (19). vitamin D is a fat-soluble vitamin, known for its important performance in immune responses of the humans (20). Although no significant differences were reported in the serum levels of vitamin D based on dead and alive patients with Covid-19 (Table 2), serum levels of vitamin D_3 in 58 patients with Covid-19 were lower than the reference levels (Table 3). No published studies are available similar to the current study on assessment of vitamin D_3 levels in Covid-19 patients. However, several meta-analysis and systematic-review studies have investigated possible roles of vitamin D in patients with Covid-19 (21, 22). General metabolism and actions of vitamin D in Covid-19 are not well known. In a review study by Grant et al. (2020), the authors reported that vitamin D could affect cathelicidin and defensin levels, decreasing viral replication rates and increasing concentrations of anti-inflammatory agents (12). Therefore, vitamin D deficiency could lead to increase host susceptibility to acute viral respiratory infections (13). Several articles have reviewed roles of vitamin D in

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decreasing risks of respiratory tract infections such as influenza (23, 24). In the current study, significant relationships were not seen between serum levels of vitamin D in dead and alive patients; therefore, it is difficult to conclude that vitamin D deficiency directly increases mortality risks.

Similar to vitamin D, vitamin B is a water-soluble vitamin and includes various roles in activating of various coenzymes in the body. For example, vitamin B_2 (riboflavin) plays important roles in energy metabolism of various cells. Vitamin B_{12} (cobalamin) is critical for the production of red blood cells (RBC), maintenance of a healthy nervous system, cell division, production and synthesis of myelin, cellular growth and rapid synthesis of DNA (25, 26). In the present study, significant differences were not detected in B_{12} and RBP vitamin levels between dead and alive patients ($p > 0.05$) while serum concentrations of B_{12} and RBP vitamins in 12 and 33 of patients were respectively lower, compared with the reference concentrations (Tables 2 and 3). Numerous studies have shown that vitamin B can be effective in improving immune systems of patients with Covid-19. Ragan et al. reported that riboflavin-UV can be effective against MERS-CoV virus due to damages to nucleic acids (e.g., DNA and RNA) of the microbial pathogens (27). Using molecular modeling tools, Kandeel et al. suggested that vitamin B_{12} and RBP could be possible candidates for the treatment of Covid-19 (28). Narayanan et al. reported that vitamin B_{12} could decrease severity and burden of Covid-19 via potential inhibitors of the RNA-dependent-RNA polymerase activity of SCV2-nsp12 enzyme (29). The major reasons of vitamin B_{12} deficiency are not clearly understood. Based on various study, vitamin B_{12} deficiency can occur due to factors such as inability in release of B_{12} from food, binding of the vitamin to proteins, disorders in the vitamin absorption due to atrophic gastritis, celiac disease and intestinal microbial proliferation (30, 31).

Similar to vitamins, trace elements include various roles in various cells and deficiency of these elements can cause several disorders in the body. Regarding statuses of trace elements in patients with Covid-19, the present study showed that serum levels of Zn, Se, Cu and Mg in dead and alive patients of Covid-19 varied with no significance. In fact, Zn as an essential micronutrient is critical for enzymatic functions in the human body. Research have shown that Zn includes antiviral effects such as improvement of immune responses and suppressing of viral replications. In addition, effects of ZN on neutrophils, macrophages and B cells controls reactive oxygen species (ROS) production in cells (32, 33). The current study demonstrated that serum levels of Zn in 30 patients were lower than those in references (Table 2). No studies on serum levels of Zn in patients with Covid-19 are available. A meta-analysis and systematic review article reported that Zn supplementation included beneficial effects on decreased duration and symptoms of common cold infections (34). Razzaque et al. suggested that consumption of up to 50 mg Zn per day by improving the host resistance against viral infections might provide protective roles against Covid-19 pandemic (35). Saigal et al. indicated that Zn supplementation at low concentrations can be effective in decreasing symptoms of the viral disease due to inhibiting replication of SARS coronaviruses (SARS-CoV) (34).

Although the current study could not find significant differences in the levels of vitamin B_{12} and Mg in alive and dead patients; however, vitamin B_{12} through increases in numbers of the cells with roles in cell-mediated immunity affects immune functions and Mg decreases oxidative damages to DNAs of peripheral blood lymphocytes in athletes and sedentary young men (13). As seen in this study, serum concentration of Se as a trace element in 87 patients was lower than the standard concentration and patients had selenium deficiency (Table 2). Based on the mechanisms suggested for Se, this element is critical in the body against viral infections because of its roles in redox homeostatic conditions, redox signaling and co-factoring of the enzymes involved in protection against oxidative damages (36). The Se deficiency can cause oxidative stresses and mutations in the viral genome, resulting in further pathogenicity and mortalities (37). It has been reported that high Se intake (50–100 µg/day) can cause better cellular immune responses (38). Although no differences were reported in the levels of Se in live and dead people affected by Covid-19 in the current study, death rates are higher in the presence of low Se concentrations (37).

Technically, Cu is an important trace element in the body due to its critical roles in protecting DNAs from oxidative stresses as well as co-factoring of superoxide dismutase enzymes and electron transport chain and iron transportation proteins. No published studies on the levels of Cu against Covid-19 are available. Moreover, it is unknown if changes due to the serum levels of Cu are beneficial (39). In this study, no significant differences were observed between the serum levels of Cu in various groups. Based on the findings of Raha et al., human immune system responses are weak when Cu level in the body is low (40); therefore, high contents of Cu in the body can be beneficial in improving immune functions of Covid-19 patients due to the element effects on the immune system. The Mg as an essential substance participates in normal physiological functions and metabolism, including effects on immune functions by the immunoglobulin synthesis, antibody-dependent cytolysis, macrophage responses to lymphokines and energy metabolism. Similar to other essential elements in this study, serum levels of Mg were not significant and were low in 26 patients,

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compared with the reference serum levels. No evidence have been reported on serum Mg levels in Covid-19 patients. A cohort study has revealed that use of Mg (150 mg daily) with other essential vitamins significantly decreases the mortality rate of Covid-19 patients with clinical deterioration requiring oxygen support and/or intensive care support (41). Another study has suggested that magnesium can be an adjunctive treatment for the complicated COVID-19 patients (42). Due to numerous contradictory studies, further clinical evidence on beneficial roles of Mg with other recommended trace elements as treatments of COVID-19 patient are necessary. The small sample size can be reported as the major limitation of the present study and the study may not completely show differences between the groups.

Conclusion

Although results of this study did not show significant differences between the levels of trace elements and vitamins with the outcomes of COVID-19 due to the small sample size, assessment of these relationships needs stronger evidence by designing larger studies.

Ethic approval

The protocol was approved by the Committee for Human Research, Hamadan University of Medical Sciences, Iran. Written informed consents were received from all the patients.

Author's contribution

SB, SAS, FK and FAJ developed the original idea and protocol and prepared the manuscript. SK, SB, FM and SB participated in the study design and analyzed data. SB, FTA, RA, SK, SB and FAJ contributed to the study design and data collection. All authors read and approved the final version of the manuscript.

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