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Original Article

The Effect of Nutrients Intake with an Emphasis on Immune-Boostings in Patients with COVID-19

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ABSTRACT

Background: The immune system plays a vital role in preventing and treating viral infections. One of the most important regulators affecting immune system is nutrition. This study aimed to evaluate the dietary intake of nutrients, especially immune-boosting ones in hospitalized patients with COVID-19.

Methods: Patients with COVID-19 infection (n=50) who were admitted to the COVID-19 Unit of Shahid Jalil Hospital in Yasouj, Iran were enrolled. Nutrients intake was calculated using a validated food frequency questionnaire (FFQ). Demographic information, history of underlying diseases, and clinical symptoms were also collected using a questionnaire completed through face-to-face interviews with the patients or their companions.

Results: The mean intake of vitamins A ($p<0.001$) and D ($p<0.001$) was lower than the dietary intake recommendation (DRI). Also the mean intake of vitamins A ($p<0.001$), C ($p<0.001$), and D ($p<0.001$), omega-3 fatty acid ($p<0.001$), and protein ($p<0.001$) was significantly lower than the recommended amounts for supporting the optimal immune function.

Conclusion: Although many nutrients were in the DRI range, more than recommended amount might be needed to strengthen the immune system and reduce the course of treatment for infectious diseases such as COVID-19. This may indicate the importance of supplement therapy or nutritional therapy in combating such viral infections as COVID-19.

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Introduction

In December 2019, a cluster of pneumonia cases caused by a newly identified β-coronavirus occurred in Wuhan, China. On January 12, 2020, the coronavirus was originally named the new 2019 coronavirus (COVID-19) by the World Health

Organization (WHO) (1). The symptoms of the disease ranged from completely asymptomatic to severe pneumonia and multi-organ dysfunction (2). Clinically, the disease was characterized by fever, shortness of breath, dry cough, and fatigue. Diarrhea was reported by some patients, as well (3). Previous studies demonstrated that such risk factors as chronic diseases including diabetes, hypertension, and cardiovascular diseases, obesity, and male sex were associated with the severity of COVID-19 (4, 5).

Patients with COVID-19 were found to develop inflammation and elevated levels of inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1 (IL-1), and tumor necrosis factor-α (TNF-α). This disease also led to an increase in the production of Reactive Oxygen Species (ROS) and Reactive Nitrogen Species (RNS), eventually resulting in tissue damage, lipid peroxidation, and genetic mutation by changing the structure of nucleic acids (6). Generally, imbalance between the antioxidant system and the production of ROS and RNS leads to oxidative stress. Increased oxidative stress is, in turn, one of the main causes of lung diseases such as Acute Lung Injury (ALI) and Acute Respiratory Distress Syndrome (ARDS), both of which are associated with acute respiratory failure and significant mortality (7).

Viral infections, on the other hand, can trigger a 'cytokine storm' that activates lung capillary endothelial cells, infiltrate neutrophils, and increase oxidative stress (8). Weak immune system is also an important risk factor for viral respiratory infections (9). The immune system is made up of an efficient set of cells and chemical mediators to protect against the attack of external agents and infections (10). Evidence has demonstrated that nutrition is one of the main factors for strengthening the immune system (10). Macro and micro-nutrients deficiencies increase the risk of viral infections such as COVID-19 by weakening the immune system, and the severity of the disease is higher in people with nutritional deficiencies (11).

Moreover, optimal diet plays a vital role in reducing inflammation, oxidative stress, and lung tissue damage in coronavirus infection (12). Therefore, the human body needs a complete diet full of such as vitamins, proteins, and minerals to prevent and fight against viral infections (10). Selected micronutrients such as vitamins C, D, A, E, omega-3 fatty acid and zinc are essential to correct immune function. These nutrients are required for cell processes of immunity like proliferation, differentiation, movement, function and dealing with oxidative and inflammatory situations (13, 14). Also studies have shown that vitamins C, D, A, and zinc are involved in reducing the risk of acute infections (14).

Diet is one of the most important factors in strengthening the immune system as well as in coping with oxidative stress and viral infections, so studies on the intake of macro and micro nutrients in the diet of patients with COVID-19 are essential. Therefore, the present study aimed to evaluate a group of COVID-19 patients with respect to (i) their nutrients intake compared to the dietary intake recommendation, and (ii) their amount of some immune boosting nutrients intake compared with the recommended amount for optimal immune function.

Materials and Methods

The current hospital-based, cross-sectional study was conducted among the patients with COVID-19 hospitalized in Shahid Jalil Hospital, Yasouj in 2020 (from April to June). Sampling was done via census. Accordingly, all adult patients with COVID-19 who referred to the hospital were included in the study. The patients were selected based on a Real-Time Reverse Transcription Polymerase Chain Reaction (rRT-PCR) test for the qualitative detection of nucleic acid from SARS-CoV-2 in upper and lower respiratory specimens. The adult patients with confirmed disease who were able to answer the questions and were willing to participate in the study were enrolled. Children, pregnant and lactating women, intubated patients, patients with dementia and coma, and those on special diets were excluded from the research. Totally, 58 patients with COVID-19 were admitted to the infectious ward and Intensive Care Unit (ICU) of the hospital, 50 of whom were eligible for the study. This study was approved by the Ethics Committee of Shiraz University of Medical Sciences (code: IR.SUMS.REC.1399.1193).

To assess dietary intake, the patients were asked to respond to a 168-item, semi-quantitative Food Frequency Questionnaire (FFQ) that had been validated in the previous studies (15). The participants were asked to mention the amount and frequency of consumption of the food items in the previous year on daily, weekly, monthly, and yearly bases. Additionally, the consumption of energy and nutrients was assayed using the Nutritionist IV diet analysis software (version 7.0; Nsquared computing, Salem, OR, USA). Besides, the mean intake of nutrients was separately compared to DRI amongst males and females. Furthermore, demographic information, history of underlying diseases, and clinical symptoms were collected using a questionnaire completed through face-to-face interviews with the patients or their companions. The data were analyzed using the

SPSS software (SPSS, Inc., Version 20.0, Chicago, IL, USA). Continuous quantitative data were reported as mean±standard deviation (SD). In addition, one sample t-test was used to compare the average nutrients intake to the DRI.

Results

Demographic information, prevalence of underlying diseases, and clinical symptoms of the COVID-19 positive patients have been presented in Table 1. The mean age of the 50 patients including 25 males and 25 females was 46.1 (13.1) years. The patients' mean of Body Mass Index (BMI) was 26.31 (4.21) kg/m^2 while 60% of them were overweight and obese. Furthermore, 54% of the patients had underlying diseases (Table 1) that hypertension (20.83%) and diabetes (12.5%) were more common. Also, the most common symptoms of patients have been reported in Table 1.

The average intake of macronutrients has been presented in Table 2. The average dietary intakes of energy, carbohydrate, and fat were 2811.26 (570.29) Kcal/day, 379.77 (95.70) g/day, and 106.79 (43.29) g/day, respectively. The average protein intake was 91.12 g/d, which accounted for an average of 12.96% of their total energy intake or 1.26 g/kg/d. The mean intake of Eicosapentaenoic Acid (EPA) + Docosahexaenoic Acid (DHA) was also 0.13 g/day.

Daily consumption of micronutrients and its comparison to the DRI have been summarized in Table 3. The results indicated that the mean intake of some micronutrients was significantly different from the DRI. Accordingly, the mean intake of vitamins A (p<0.001), and D (p<0.001), was lower than the DRI. Moreover, compared to the DRI, the mean intake of vitamins B1 (p<0.001), B2 (p<0.001), B3 (p<0.001), B9 (p<0.001), and B12 (p<0.001), and selenium (p<0.001) was higher in both male and female. Mean intake of other nutrients was shown in Table 3. According to Table 4, the mean intake of vitamins A (p<0.001), C (p<0.001), and D (p<0.001), omega-3 fatty acid (p<0.001), and protein (p<0.001) was significantly lower than the recommended amounts to support the optimal immune function in the infectious patients.

Discussion

This was the first study to investigate nutrient intake with emphasis on immune-boosting nutrients amongst patients with COVID-19 in Yasuj, Iran. The results indicated that 60% of the patients were overweight and obese and 54% had underlying diseases. Additionally, the mean intake of some nutrients including vitamins A, C, and D, omega-3 fatty acid, and protein was lower than the recommended amounts for supporting the optimal immune function. Some nutrients including proteins, vitamins A, E, C, and D, omega-3 fatty acids, and minerals such as zinc are important for strengthening and optimal functioning of the immune system (16). Protein is also an essential nutrient for boosting the immune system and preventing or treating viral infections (17). Some amino acids such as arginine play a key role in the production of nitric oxide, which is an important factor in preventing inflammation and strengthening the immune system (17, 18). Recently, 1.5 g/kg/d protein was recommended to maintain a healthy

Table 1: Demographics, comorbidities, and clinical symptoms in patients with COVID-19 in Yasuj, Iran.

Variable	COVID-19 patients (n=50)
Age in years (mean, SD)	46.1 (13.10)
Female sex, n (%)	25 (50)
Weight (kg; mean, SD)	72.14 (12.91)
BMI (kg/m^2; mean, SD)	26.05 (3.35)
Normal weight, n (%)	20 (40)
Overweight*, n (%)	21 (42)
Obese**, n (%)	9 (18)
Comorbidity, n (%)	
HTN	11 (22%)
Diabetes	8 (16%)
IHD	3 (6%)
COPD	3 (6%)
Asthma	2 (4%)
ICU admission	12 (24%)
Clinical symptoms	
GGO-positive, n (%)	40 (80%)
CRP-positive, n (%)	26 (52%)
Fever (%)	98
Cough (%)	82
Dyspnea (%)	60
Fatigue (%)	46
Headache (%)	30
Insomnia (%)	30
Body pain (%)	28
Chills (%)	26
Sore throat (%)	24
Loss of taste and smell (%)	22
Nausea and vomiting (%)	20
Nightmare (%)	16
Loss of appetite (%)	14
Diarrhea (%)	14
Dry mouth and nose (%)	10
Sweating (%)	6

BMI: Body mass index; HTN: Hypertension; IHD: Ischemic heart disease; COPD: Chronic obstructive pulmonary disease; GGO: Ground-glass opacity; CRP: C-reactive protein; SD: Standard deviation; N: Number. *Overweight: BMI=25.0 to 29.9 kg/m^2, **Obese: BMI≥30 kg/m^2.

Table 2: Daily intake of macronutrients in the patients with COVID-19 in Yasuj, Iran.

Macronutrients	Patients (n=50)	DRI
Energy intake (kcal/day) (mean, SD)	2811.26 (570.29)	-
Energy (kcal/kg/day)	38.96	-
Protein (g/day) (mean, SD)	91.12 (23.74)	-
Protein (g/kg/ body weight)	1.26	-
Protein (AMDR) (% total energy)	12.96	10-35
Fat (g/day) (mean, SD)	106.79 (43.29)	
Fat (AMDR) (% total energy)	34.18	20-35
Saturated fat (g/day) (mean, SD)	30.44 (6.32)	-
Saturated fat (% total energy)	9.74	10
Cholesterol (mg/day) (mean, SD)	270.66 (79.03)	<300
MUFA (g/day) (mean, SD)	24.79 (6.96)	-
MUFA (% total energy)	7.93	-
PUFA (g/day) (mean, SD)	30.47 (7.59)	-
PUFA (% total energy)	9.75	-
Omega-3 (EPA+DHA) (g/day) (mean, SD)	0.13 (0.08)	0.6-1.2
Carbohydrates (g/day)	379.77 (95.70)	-
Carbohydrates (AMDR) (% total energy)	53.60	45-65
Fiber (g/day) (AI) (mean, SD)	77.94 (24.10)	30-38 21-25

SD: Standard deviation; N: Number; DRI: Dietary reference intake; AMDR: Acceptable macronutrient distribution range; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; MUFA: Monounsaturated fatty acids; PUFA: Polyunsaturated fatty acids; AI: Adequate intake.

Table 3: Daily consumption of micronutrients in the patients with COVID-19 and its comparison to DRI

Vitamin*s*	Patient*s* (n=50; Mean±SD)		DRI		*p* value	
	M (n=25)	F (n=25)	M	F	M	F
Vitamin A (µg/day)	327.73 (110.08)	325.09 (92.63)	900	700	<0.001	<0.001
Vitamin D (µg/day)	1.06 (0.65)	1.82 (3.97)	15		<0.001	<0.001
Vitamin E (mg/day)	15.95 (5.67)	15.14 (5.31)	15		0.40	0.89
Vitamin K (µg/day)	114.48 (84.99)	95.20 (34.87)	120	90	0.74	0.45
Vitamin C (mg/day)	103.09 (51.72)	87.95 (55.36)	90	75	0.21	0.25
Thiamin, B1 (mg/day)	2.7 (0.73)	2.06 (0.61)	1.2	1.1	<0.001	<0.001
Riboflavin, B2 mg (mg/day)	2.00 (0.48)	2.05 (0.46)	1.3	1.1	<0.001	<0.001
Niacin, B3 (mg/day)	30.74 (8.89)	28.36 (7.79)	16	14	<0.001	<0.001
Pantothenic acid, B5 (mg/day)	5.42 (1.5)	5.16 (1.23)	5		0.18	0.50
Pyridoxine, B6 (mg/day)	2.09 (0.74)	3.14 (5.89)	1.3-1.7	1.3-1.5	<0.001	0.13
Biotin, B7 (mg/day)	30.11 (12.91)	28.64 (12.74)	30		0.96	0.60
Folate, B9 (µg/day)	820.02 (188.45)	750.25 (216.75)	400		<0.001	<0.001
Cobalamin, B12 (µg/day)	3.24	3.18 (0.75)	2.4		<0.001	<0.001
Calcium (mg/day)	1125.33 (241.99)	1084.06 (330.80)	1000-1200		0.6	0.21
Magnesium (mg/day)	402.15 (97.70)	395.58 (87.14)	420	230	0.37	<0.001
Zinc (mg/day)	10.78 (2.12)	11.81 (2.12)	11	8	0.61	<0.001
Iron (mg/day)	21.83 (6.45)	20.90 (4.85)	8	18	<0.001	0.00
Selenium (mg/day)	115.78 (27.46)	112.53 (29.72)	55	45	<0.001	<0.001

One sample t-test was used. SD: Standard deviation; N: Number; DRI: Dietary reference intake; M: Male; F: Female, EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid.

diet in hospitalized COVID-19 patients without malnutrition (9). In this study, the average protein intake was less than the recommended values for hospitalized patients.

Omega-3 is one of the most important nutrients with anti-inflammatory and immune-boosting properties associated with increasing the activity of cells, increasing phagocytosis, and reducing the production of inflammatory cytokines (19-21). A previous research indicated that 2.7 g/day EPA significantly reduced PGE2 production (9). It was also maintained that the presence of EPA and DHA in the formula of patients with severe sepsis, ADRS, and ALI decreased the need for ventilation and

Table 4: Recommendations for the consumption of selected nutrients to support the optimal immune function and comparison to their consumption by the patients.

Nutrients	Recommendation (9)	Patients (n=50; Mean±SD)	*p* value
Vitamins and trace elements including vitamins A, E, D, C, B6, B12, and B9 and trace elements including zinc, iron, selenium, magnesium, and copper	Multivitamin/mineral supplements (e.g., 100% RDA for age and gender)+a well-balanced diet	-	-
Protein	Healthy individuals: 0.8 g/day Hospitalized COVID-19 patients without malnutrition: 1.5 g/day	1.26	<0.001
Vitamin A	Prevention of viral diseases and the flu: 800 μg/day	326.41 (100.70)	<0.001
Vitamin C	Healthy individuals: 200 mg/day (at least) Sick individuals: 1-2 g/day	95.52 (53.57)	<0.001
Vitamin D	2000 IU/day (50 μg/day)	1.44 (2.84)	<0.001
Omega-3 fatty acids (EPA+DHA)	250 mg/day of EPA+DHA	130 (0.08)	<0.001

One sample t-test was used. SD: Standard deviation; N: Number; RDA: Recommended dietary allowance; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic acid; IU: International unit.

improved respiration (10). In the current study, the mean intake of EPA and DHA was much lower than required to support immune function.

Vitamin A, known as the 'anti-infection' vitamin, has anti-inflammatory and immune-boosting properties by controlling the production of inflammatory factors such as IL-2 and TNF-α, regulation of NK cells, and differentiation of Th1 and Th2 cells (16). Vitamin A is useful as a treatment for coronavirus and prevention of lung infection (22). Generally, 800 μg/day of vitamin A has been recommended to prevent viral diseases and the flu (9). Nonetheless, the patients with COVID-19 received much less than the prophylactic dose in the current study.

Vitamin D is an important factor in respiratory infections due to its main role in innate and acquired immunity (23), as well as due to its impact on the production of cytokines and immunoglobulins. Low levels of vitamin D were found to be associated with an increased incidence of viral diseases such as influenza (24), and increased risk of bovine coronavirus infection (25). The optimal levels of this vitamin were linked to a reduction in respiratory tract infections (26). Daily intake of 2000 IU/day has been recommended for boosting the immune function (9) that in the present study, the average dietary vitamin D intake was much less than the recommended amount.

Vitamin C can modulate the accumulation and activation of neutrophils and phagocytes in addition to reducing the degeneration of alveoli by reducing the degradation of protein channels (10). High dose of oral vitamin C (2 g/kg/d) was reported to reduce the average length of ICU stay by 8.6% (27), and the intravenous dose of 200 mg/kg/day decreased the average length of ICU stay by 7.8% (27). Intravenous administration of the high dose of vitamin C (10-20 g/d for 8-10 hours) also improved oxygenation indices and mortality in patients with moderate to severe COVID-19 (7). Overall, human studies revealed the effectiveness of this vitamin in reducing vulnerability to respiratory infections and pneumonia (6). In the present study, the mean intake of vitamin C was lower than recommended amount to reduce the severity and duration of upper and lower respiratory tract infections.

Vitamin E, as one of the most important antioxidants in the diet and the human body, strengthens the immune system by reducing the production of PGE2, inhibiting the activities of COX2 and NK cells, reducing the production of interleukins, and modulating the Th1/Th2 ratio (28). It was shown that taking 200 IU vitamin E reduced the chances of catching common cold through the year (10), and administration of 600 IU vitamin E also improved the conditions of patients with ARDS admitted to ICUs (29).

Zinc is currently being investigated for the prevention and treatment of COVID-19 due to its role in immune function, as well as its potential to reduce the replication of the coronavirus (6). Zinc deficiency increases the concentration of pro-inflammatory cytokines (IL-1, IL-6, and TNF-α) and decreases antibody and white blood cells production (6). In a systematic review, high-dose of zinc was reported to reduce the duration of the disease, but had no effects on the prevention and severity of cold symptoms (6). In the present research, the daily intake of zinc was within the level of RDA.

Since COVID-19 is a novel disease, limited information is available regarding the underlying causes of the disease including nutrition and diet that play a critical role in strengthening the immune system, which were discussed in the present study. We use of a valid and reliable FFQ to accurately measure nutrients intake. However, the study limitations included its small sample size and lack of comparison to a control group. Additionally, physical activity and malnutrition assessment indicators were not evaluated in this study.

Conclusion

The study findings showed that the intake of some nutrients such as vitamins D, and A, and omega-3 fatty acids were even less than the DRI in the patients with COVID-19. The intake of selected immune-boosting nutrients such as protein, vitamins D, and C, and omega-3 fatty acids was also less than the recommended intake to support the optimal immune function. According to a recent study reporting a relationship between the use of dietary supplements and reduced risk of COVID-19 (30), increseed intake of some nutrients more than DRI might help decrease the risk of COVID-19 by strengthening the immune system and improving resistance to infection. Yet, further clinical studies are suggested in this field.

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Conflict of Interest

None declared.

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