

## Supplement Usage Pattern in a Group of COVID-19 Patients in Tehran

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### Abstract

**Objective:** The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection, causes severe acute respiratory syndrome and was spread throughout the world in early 2020. The effects of vitamin and micronutrient supplements on the prevention and treatment of COVID-19 seems challenging in scientific considerations. On the other side generally, experts warn against over-consumption of these supplements.

**Materials and methods:** This study aimed to investigate the vitamin and micronutrient supplementation usage pattern in past history of patients with COVID-19 via a cross-sectional inquiry. Totally 510 patients referring to the infectious disease clinic of Imam Khomeini Hospital in Tehran from March 2020 to May 2020 were recruited. The inclusion criterion was suspected patients for COVID-19 based on clinical findings and CT scans of the lung. The infected patients included both inpatients (171) and outpatients (339). Demographic information, clinical signs, and the supplement pattern use were collected through a questionnaire and the data were statistically analyzed.

**Results:** Vitamin D3 intake was reported in 30% (103 patients) of outpatients and 16.5% (28 patients) of hospitalized patients, which is statistically significant ( $P=0.001$ ). It shows that, the frequency of vitamin D3 consumption in the outpatient group was higher than inpatient group. This significant difference has also been shown in zinc consumption, in 29 patients (9%) outpatients versus 4 patients (2%) inpatients were reported ( $P=0.007$ ). Multi nominal regression showed that vitamin D3 intake has a supportive effect and reduces the risk of exacerbation and worsening of the disease. ( $OR=0.291$ ; 95% CI 0.102-0.834,  $P=0.022$ ).

**Conclusion:** According to the results of the present study and the findings of other studies, considering the supportive effect of vitamin D3 in reducing the severity of infectious diseases; Clinical trials with an appropriate sample size are recommended to investigate the functional role of this vitamin in improving viral diseases of the respiratory tract.

**Keywords:** Supplement; COVID-19; Vitamins; Micronutrients

### Introduction

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The coronavirus disease 19 (COVID-19) is a highly transmittable and pathogenic viral infection that causes severe acute respiratory syndrome and was introduced from Wuhan, Hubei province and was spread throughout the world in early 2020 (1, 2).

The countries around the world experienced numerous problems that threaten public health and have attracted enormous consideration around the world. Also, to date, there are no clinically approved vaccines or antiviral drugs for these human coronavirus infections. However, studies about this new virus are limited (1). Therefore, intensive research on the novel developing human infectious coronaviruses is needed to explain their route of transmission and pathogenic mechanisms and to identify potential drug targets, which would support the development of effective preventive and therapeutic countermeasures (2). Prevention and control of infections and observance of hygienic principles by the general public is a priority. Nutritional and health advice hygiene should be considered more than ever. However, the role of vitamin supplementation in the prevention of many chronic diseases is less well established (3). Evidence is insufficient to prove the presence or absence of benefits from the use of multivitamin and mineral supplements to prevent chronic disease (4). Dietary supplements are widely used and offer the potential to improve health if appropriately targeted to those in need. Inadequate nutrition and micronutrient deficiencies are prevalent conditions that adversely affect global health (5). Some researchers have guessed that people with low serum vitamin D might be at higher risk of infection with COVID-19, or do worse if infected (6). Though, Lee et al. "Found no clinical evidence that vitamin D supplements are beneficial in preventing or treating COVID-19" (7).

A review of randomized clinical trials showed that vitamin D supplementation was associated with reduced respiratory tract infections (8). Numerous clinical data suggest that vitamins, including vitamins A, B6, B12, C, D, E and folate, rare elements, including zinc, iron, selenium, magnesium and copper and omega-3 fatty acids play an important role in supporting the immune system (9, 10).

Also, there is widespread publicity about the effects of vitamin supplements on the prevention and treatment of COVID-19. In other side generally experts warn against over-consumption of these supplements. Therefore, this study aimed to investigate the history of vitamin and micronutrient supplementation pattern use in patients with COVID-19.

## Materials and methods

The Ethics Committee of Tehran University of

Medical Sciences has approved this study (IR.TUMS.VCR.REC.1398.1063). The present study is a cross-sectional study. Totally 510 patients' referring to a university hospital infectious clinic from March to May 2020 was recruited in this study. All patients who referred to our hospital with clinical findings of COVID-19 and their diagnosis were confirmed by reviewing CT scans by two expert radiologists, were entered into our study. Two views of ground glass opacity and consolidation in CT scan confirmed by two different radiologists have been considered as diagnosis of COVID-19 (11). The images of CT sometimes appear bilateral pulmonary parenchymal ground-glass and Consolidative pulmonary opacities with a rounded morphology and a peripheral lung distribution when patients are infected with COVID-19 (12). Symptoms (including fever measured in degrees centigrade, dry cough, productive cough, difficulty speaking, headache, chest tightness, difficulty with exertion, shortness of breath, sore throat, malaise, and diarrhea) will be rated as present, or not. Symptomatic patients who complained of symptoms; in the absence of acute pulmonary symptoms in CT scan, were managed on outpatient setting. Patients were hospitalized if they had shortness of breath (dyspnea) and less than 90 percent of Oxygen saturation (inpatients).

The severity of the disease in patients was divided into three categories: general, severe and critical as follows. General: fever; respiratory symptoms; radiologic findings from pneumonia. Severe: The presence of any of the symptoms of distress (respiratory distress); Respiratory rate more than 30 per minutes, Blood O<sub>2</sub> saturation level less than 90% at rest, the ratio of arterial oxygen pressure to the percentage of inspiration oxygen is less than 300 mm and critical: presence of any of the symptoms: respiratory failure, need for mechanical ventilation or artificial respiration, septic shock, extra pulmonary organ failure and transfer to the intensive care unit.

Data collection method was a researcher-made questionnaire including demographic characteristics, clinical and Para clinical symptoms of the patient. It should be noted that patients are asked about the use of all therapeutic supplements (multivitamin, vitamin C, vitamin E, folic acid, iron, omega 3 and omega 6) in the last three months. In the case of patients with critical disease conditions; these questions were asked of the patient's first-degree relatives or from their medical records.

**Statistical analysis:** After collecting the required information, the data were analyzed using SPSS version 21 software. Frequency and frequency percentages were calculated for qualitative variables. Means and standard deviations were determined for Quantitative variables. The significance level was considered as 0.05 to interpret the relationships among the variables. Distribution of variables in this study was not normal, which was assessed by the Mann–Whitney test instead of t independent -test, and then the p-value were extracted. The quantitative variables were compared between the two groups by t-test and Mann–Whitney test. The qualitative variables were compared using Chi-square.

Adjusted Multivariate binary logistic regression was used to examine the variable in relation to odds of COVID-19 in inpatients compared to outpatients groups. Multi nominal Logistic Regression was also used to obtain factors affecting the severity of this disease.

## Results

The study was performed on 510 patients with acute respiratory symptoms in the infectious department of the Imam Khomeini hospital. Depending on the severity of the clinical symptoms and lung scan, Patients were divided into two groups: 171 patients who were admitted in hospital (inpatient) and 339 patients were treated on an outpatient basis. The highest number of hospitalizations was reported in people over 60 years and non-hospitalized or outpatient in people less than 35 years of age. The majority of cases in both outpatient and inpatient were men ( $P=0.010$ ). In the outpatient group, 48% (163 patients) and in the inpatient group, 64.5% (107 patients) had a history of contact with the infected person, which was a significant difference ( $P=0.001$ ). In other words, in inpatients group, the history of contact with the infected person in the family and workplace has been reported more. The prevalence of hypertension, diabetes, and anemia was higher in hospitalized patients than outpatients ( $P<0.05$ ) (Table 1).

The clinical symptoms in both outpatients and inpatients included fatigue, myalgia, headache, chest pain and sore throat which were more common in the outpatient group. Lung CT scans showed that pulmonary infiltration and ground glass image was reported in 99% of hospitalized patients ( $P = 0.001$ ). As well as, in the majority of hospitalized patients (87%), only ground glass

pattern was reported ( $P=0.001$ ).

Also, Hemoglobin levels were lower in hospitalized patients ( $P = 0.001$ ). This means that 44 patients (26%) of hospitalized patients had anemia compared to 8 patients (2.5%) of the outpatient group.

As we expected the mild clinical and gastrointestinal symptoms were more common in outpatient, however, a high rate of pulmonary infiltration and ground glass in CT scan and images were observed in hospitalized patients. Furthermore, anemia was more common in hospitalized patients.

In the group of hospitalized patients, 80 patients (47%) were in severe condition and 67 (40%) were in critical condition. However, in the group of outpatients, 320 patients (94%) had a normal condition. There was a significant difference between two groups ( $P=0.001$ ). It means that most hospitalized patients were in critical condition (Table 2).

The supplement consumption pattern in the two groups of outpatient and inpatient show that supplementary consumption patterns (daily, weekly, monthly and irregular) are not statistically significant in the two groups with COVID 19 ( $P = 0.162$ ).

However, vitamin D3 intake was reported in 30% (103 patients) of outpatients and 16.5% (28 patients) of hospitalized patients, which is statistically significant ( $P=0.001$ ). It shows that, the frequency of vitamin D3 consumption in the outpatient group was higher than inpatient group. This significant difference has also been shown in zinc consumption, in 29 patients (9%) outpatients versus 4 patients (2%) inpatients were reported ( $P=0.007$ ) (Table 2).

It should be noted that patients were also asked about taking of all supplements such as Multivitamins, Vitamin C, Vitamin E, Acid Folic, Iron, Omega-3 and Omega-6, folic acid. The responses indicated that patients in neither of the two outpatient and inpatient groups had used any of these supplements at all.

According to the large number and high diversity of variables, and some Parameters which independently affected hospitalization, we performed a binary regression test to remove the effect of the disruptors and to eliminate their influence on each other. Finally, it can be concluded that the sex of male, Hemoglobin<10 and hypertension are the risk factors for hospitalization.

**Table 1:** Analysis of Demographic variables in both outpatient and inpatient groups infected with COVID-19

Variable	Outpatient	Inpatient	P-value
Age (mean $\pm$ SD)	43.74 $\pm$ 13.84	58.77 $\pm$ 17.43	0.0001*
Age group (years)			
< 35	117(8.2%)	14(8.2%)	0.0001**
35-60	176(51.9 %)	77(45%)	
> 60	46(13.6%)	80(46.8%)	
Education			
Illiterate	1(0.3%)	24(14%)	0.0001**
High school	126(63.7%)	96(67%)	
Undergraduate	94(28%)	23(14%)	
Postgraduate	28(8%)	9(5%)	
Occupation			
Unemployed	20(6%)	17(10%)	0.0001**
Worker	24(7%)	13(8%)	
Employee	119(35%)	30(17.5%)	
Retired	8(2%)	19(11%)	
House wife	89(26%)	42(25%)	
Free lancer	76(22%)	49(29%)	
Gender			
Yes	195(57.5%)	117(69%)	0.014**
No	144(42.5)	53(31%)	
History of Exposure			
Yes	163(48%)	107(64.5%)	0.001**
No	176(52%)	64(35.5%)	
History of Smoking			
Yes	79(23%)	33(20%)	0.384
No	260(77%)	133(80%)	
History of Drugs			
Yes	13(4%)	10(6%)	0.265
History of Chronic Disease			
Hypertension	55(16%)	68(40%)	0.0001**
Heart disease	30(9%)	40(23%)	0.0001**
Diabetic	38(11%)	51(30%)	0.0001**
Hypothyroid	28(8%)	8(5%)	0.140**
Anemia	8(2.5%)	44(26%)	0.0001**
History of taking supplement in the last three months	148(44%)	55(32%)	0.0001**
Number of supplements type (mean $\pm$ SD)	1 $\pm$ 1.53	0.67 $\pm$ 1.28	0.012**
***Obesity	30(19%)	7(14%)	0.69**

\*Mann-Whitney Test, \*\*Chi- Square Test, \*\*\*Obesity: BMI>30

One of the important and obvious differences between the two groups was their general condition (severe and critical condition). Although some factors did not affect hospitalization and outpatient status, they may affect the patient's condition. Multi nominal regression showed that Hypertension with a probability of 4.9 times (OR=4.997; 95% CI2.433-10.25,  $p$  value=0. 0001) and anemia with a probability of 22 times (OR=22.905; 95% CI9.355-56.083,  $p$  value=0. 000) are effective in the severity of the disease. In addition, vitamin D3

intake has a supportive effect and reduces the risk of exacerbation and worsening of the disease. (OR = 0.291; 95% CI 0.102-.0834,  $p$  value = 0.022) (Table 4).

## Discussion

The results of the present study showed that only vitamin D3 and zinc were used more commonly in outpatients infected with COVID-19 and vitamin D3 intake may be has a supportive effect and reduces the risk of exacerbation and worsening of the disease.

**Table 2:** Analysis of clinical symptoms and intake of supplement pattern in both outpatient and inpatient groups infected with COVID-19

Variable	Outpatient	Inpatient	P-value
<b>Clinical symptom</b>			
Fever & chilly	176(52%)	101(59%)	0.126
Cough	248(73%)	118(70%)	0.326
Sputum	110(32.5%)	60(35%)	0.566
Myalgia	214(63%)	89(52%)	0.016
Fatigue	215(63%)	72(42%)	0.0001
<b>Gastrointestinal symptoms</b>			
Diarrhea	94(28%)	41(24%)	0.365
Nausea	117(34.5%)	56(33)	0.172
Vomiting	60(18%)	38(22%)	0.221
Headache	167(50%)	54(32%)	0.0001
Sweating	41(12%)	18(10.5%)	0.601
Anorexia	141(42%)	74(43%)	0.747
Weakness	86(25.5%)	48(28%)	0.153
Loss of sense of taste	18(5.3%)	12(7%)	0.439
Chest Pain	48(14%)	9(5%)	0.003
Sore throat	56(16.5%)	14(8%)	0.010
<b>Signs in Lung CT scan</b>			
Consolidation	12(5%)	8(5%)	0.8/95
Bilateral Pulmonary Infiltration	51(21%)	43(25%)	0.310
Ground- glass Opacity	138(57%)	147(87%)	0.0001
Bilateral Pulmonary Infiltration & Ground- glass Opacity	2(1.2%)	14(1.7%)	0.445
Hemoglobin level* (mean $\pm$ SD)	13.84 $\pm$ 1.76	12.54 $\pm$ 2.43	0.001
<b>BG&amp;RH</b>			
O	72(36%)	13(47%)	0.198
A	57(28.5%)	12(39%)	
B	42(20.5%)	0	
AB	31(5%)	3(14%)	
<b>General Condition</b>			
General	320(94%)	22(13%)	0.0001
Severe	19(6%)	80(47%)	
Critical	0	67(40%)	
<b>Pattern of Supplement usage</b>			
Daily	50(34%)	26(47%)	0.162
Weekly	24(16%)	9(16%)	
Monthly	32(22%)	9(16%)	
Irregular	42(28%)	11(21%)	
Usage of Vitamin D supplement	103(30%)	28(16.5%)	0.001
Usage of Zinc supplement	29(9%)	4(2%)	0.007
Usage of Multi- vitamin	47(14%)	18(10.5%)	0.286

\* Mann-Whitney Test, Chi- Square Test

In the development of COVID 19 epidemics, the search for possible antiviral strategies for protection and treatment is of particular importance and urgency. Zinc is recognized to control antiviral and antibacterial immunity and regulate the inflammatory response. Despite the lack of clinical data, certain indications suggest that modulation of zinc status may be beneficial in COVID 19 (13).

It is clear that zinc has antiviral properties against a number of viral species. Although there are no exact

studies, it seems that zinc appears to inhibit the enzymatic processes of protease and polymerase viruses, as well as processes such as virus attachment, infection, and non-coverage. In addition, in laboratory conditions, zinc has been shown to inhibit the activity of the RdRp coronavirus, and zinc ionophores prevent coronavirus proliferation (14). Unfortunately, these mechanisms have not been well studied in clinical trials, where zinc supplementations may offer prominent antiviral effects as an adjuvant treatment (15).



**Table 3:** Binary logistic regression analysis was used to examine the Relation of variable levels in two groups

Group		B	P	OR	95% CI for EXP(B)	
					Lower	Upper
Step 1 <sup>a</sup>	Education	.014	.972	1.014	0.456	2.257
	Job	-.699	.135	.497	0.199	1.242
	Exposure	.003	.993	1.003	0.933	1.003
	Smoke History	.672	.153	1.958	0.153	1.958
	Hypothyroid	.159	.830	1.173	0.275	5.007
	Gender	1.333	.003	3.791	1.576	9.119
	Hypertension	-1.078	.025	.340	.133	.873
	Diabetes	.194	.673	1.214	.493	2.990
	Anemia	.053	.933	1.055	.306	3.637
	Vitamin D Intake	.683	.106	1.980	.864	4.541
	Zinc Intake	.727	.374	2.069	.417	10.266
	Multivitamin Intake	-.380	.492	.684	.231	2.022
	Hemoglobin	.365	.004	1.440	1.126	1.842
	Heart	-.419	.448	.658	.223	1.941
	Autoimmune diseases	-.840	.485	.432	.041	4.553
	Constant	-7.526	.000	.001		

Despite some controversial results over the years, Vitamin D appears to play an important role in the regulation of innate immunity in the upper respiratory tract (16). There is also evidence revealing of effects of vitamin D supplementation in the prevention of infections (17). Also, cell culture experiments emphasize that vitamin D has direct anti-viral effects particularly against enveloped viruses. Though vitamin D's anti-viral mechanism has not been fully elucidated, it may be related to the ability of vitamin D to regulate the anti-microbial peptides LL-37 and human beta-defensin (18).

Evidence for supporting the role of vitamin D supplementation in reducing the risk of COVID-19 includes flu prevalence in winter when the 25-hydroxy vitamin D (25 (OH) D) concentration is the lowest rate (6, 19). Also serum 25 (OH) D concentrations decrease with age (20), which may increase the risk of mortality in cases of COVID-19 with increasing age (21). The reasons include less sun exposure time and reduced vitamin D production due

to lower levels of 7-dehydro cholesterol in the skin (22). Also, using some medications usually increases with age some of which reduce serum 25 (OH) D concentration (23). A recent review found that vitamin D loading doses of 200,000-300,000 IU in form of 50,000 IU capsules were used to reduce the risk and severity of COVID-19 (24).

The hypothesis that "vitamin D supplementation can reduce the risk of influenza and COVID-19 incidence and death" should be investigated in trials to determine the appropriate doses, serum 25 (OH) D concentrations, and the presence of any safety issues" (6). However, Vitamin D supplementation has been described as a treatment for people infected with COVID-19. But so far, there is little scientific evidence that seems to be insufficient in this regard (25, 6). Although there is conflicting data, available evidence suggests that supplementation with micronutrients with protective roles in the immune system may modulate immune function and reduce the risk of infection (26).

**Table 4:** Nominal regression analysis was used to examine the relation of general condition of patients with some variables

General Condition	B	P	OR	95% CI for EXP(B)	
				Lower Bound	Upper Bound
Gender	-.362	.335	.696	.334	1.453
Smoking	-.397	.357	.672	.288	1.567
HTN	1.609	.000	4.997	2.433	10.265
Diabetes	.882	.021	2.415	1.140	5.117
Cardiac Disease.	.627	.156	1.871	.787	4.450
Anemia	3.131	.000	22.905	9.355	56.083
Vitamin .D intake	-1.235	.022	.291	.102	.834
Zinc intake	-.927	.407	.396	.044	3.532
Multi vitamin Intake	.167	.768	1.182	.390	3.581

It seems the previous consumption of vitamin D and zinc supplements have been accompanied by the mild condition and lower needs of hospitalization. But, the Randomized controlled trials and large population studies should be conducted to explain the efficacy and mechanism of vitamin D, other Vitamins and micronutrients supplementation as an anti-viral agent.

Limitations include that the data were collected from a single-center study in Tehran and the lack of evaluating variables such as the serum 25 (OH) D concentrations, zinc and other micronutrients in this study. It is recommended to perform the randomized control trials and follow-up studies in two groups of inpatients and outpatients infected with COVID-19 to respond to the preference for using any of Vitamins or micronutrient supplementation.

### Conclusion

Zinc and vitamin D is recognized to have anti COVID effects indirectly via immunologic intermediation. According to clinical findings of this study it is suggested that modulation of zinc or vitamin D status may be beneficial in COVID 19.

### Conflict of Interests

Authors have no conflict of interests.

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