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Psychological Function and Serum Vitamin D Concentration in COVID19- Patients: A cross-sectional study

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ABSTRACT

Introduction*:* The pandemic of COVID-19 created a psychological response. So, the psychological function of COVID-19 patients is an important subject that forces us to follow up with them.

Aim: Assess the correlation between vitamin D serum concentrations and psychological functions such as insomnia, stress, and depression through the COVID-19 pandemic

Methods: In this cross-sectional study, blood samples from 120 COVID-19 patients (61 males and 59 females) who had more than 30 years, were taken. Also, 25(OH)D Serum level of COVID-19 patients was analyzed. The Insomnia Severity Index (ISI), Depression anxiety stress scales (DASS), and the Short Form Health Survey (SF-36) were used to analyze insomnia, anxiety, stress, quality of life, and depression.

Results: The relationship between temperature (p=0.039), PCO2 (p=0.022), and serum vitamin D level was significant. Additionally, there was a significant correlation between stress (p=-0.023, OR=0.389, 95% CI for OR=0.047, 0.843), depression (p=0.012, OR=0.659, 95% CI for OR=0.476, 0.913), and the concentration of serum vitamin D.

Conclusion: This study recommends that vitamin D supplementation improve psychological state in COVID-19 patients.

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Introduction

A cluster of previously unknown pneumonia was reported, in Wuhan, China in December 2019 (1). Since, COVID-19 has spread globally, infecting more than 270 million persons. Also, it caused 5≥ million deaths as of December 2021 (2).

To hinder the fast propagation of COVID-19, social distancing and home-office measures were imposed worldwide, reducing outdoor activities and interpersonal interactions (3). The extreme changes caused by the pandemic have contributed

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contributed to the emergence of a psychological health crisis in many countries, as various studies have demonstrated (4,5). Studies have shown an association between economic stagnation and massive lockdowns due to the pandemic and an escalation in suicide rates, and the prevalence of depressive traits has increased more than three times since the pandemic's beginning (6,7,8).

UNICEF has reported, social isolation as a COVID-19 consequence impairs the psychological health of Australian teenagers in terms of increasing their levels of anxiety (9). Social isolation has also contributed to loneliness, boredom, stress, and fear (9, 10). People with psychological health situations before, are even at higher risk for deterioration or recurrence of their symptoms (11,12).

However, the degree of susceptibility to the psychological distress imposed by the pandemic depends on social support, exposure to mass media, duration of isolation, infection conditions, and lifestyle habits, including nutrition (13). Previously, a relationship between neuropsychological situations like depression and bipolar disorder and vitamin D deficiency was reported in several studies (14,15).

Vitamin D (25(OH)D) is a neuroactive substance that modulates cell growth, inflammation, detoxification, neurotransmitter synthesis, and development in the central nervous system (16, 17). Vitamin D regulates mood via increasing brain serotonin availability by increasing the expression of tryptophan hydroxylase two enzymes. This enzyme is needed for sufficient serotonin production (18). Therefore, low levels of vitamin D causes psychological disorder. Also, vitamin D inadequacy boosts the secretion of pro-inflammatory factors like interleukin-6 by increasing nuclear-factor kappa B expression (19).

Inflammation in the brain increases the risk of mental disorders like depression and anxiety (20). Furthermore, decreased vitamin D level is connected with altered responses to stressors and traumatic events (21,22). A meta-analysis revealed a significant connection between insufficiency of vitamin D and the risk of depression. It recommends that the supplementation of vitamin D could be helpful in depressive patients with hypovitaminosis (23). Additionally, vitamin D supplementation has shown a considerable enhancement in symptoms of individuals diagnosed with depression in comparison to placebo, which could highlight a causal association between reduced vitamin D concentration and depressive traits (24,25).

However, vitamin D function in depression is still debated and requires more study (23,26,27). As vitamin D deficiency is noticeably common among the population, with more than a billion individuals affected by it globally, the importance of investigating its different effects cannot be stressed more at the time of the pandemic (28).

Therefore, we aimed to estimate the correlation between vitamin D serum concentrations and mental function in the COVID-19 pandemic.

Materials and Methods

Study design

In 2021, our cross-sectional study was administered in Imam Reza Hospital in Mashhad, on 120 patients with COVID-19 who were aged >30 years. Without anti-depressant drug treatment, hepatic or renal failure, cancer, metabolic bone disease, and autoimmune diseases throughout the previous six months were the exclusion criteria. Informed written consent was provided by all subjects. The trial was confirmed by the Ethics Committee of MUMS (Mashhad University of Medical Sciences), Mashhad, Iran.

All the participants in the main study who met the inclusion criteria were included in this study based on global sampling (29).

General and clinical characteristics

At first, we collected clinical and demographic characteristics such as smoking status, age, and the data of comorbidity from each subject by professional questioner.

Blood Collection and Biochemical Measurements

Blood samples were collected from all subjects following a 12-hour fasting period in plain Vacutainer tubes. All blood samples were centrifuged at 5000 g for 15 minutes at 4° C to isolate serum. 25(OH)D serum levels were evaluated by commercial ELISA kits (Pishgaman Sanjesh- Iran) using an Awareness/Stat Fax 2100 analyzer.

Depression anxiety stress scales (DASS)

To evaluate mood status, we used DASS (30). DASS is a questionnaire that includes three subscales and consists of 7 questions, generally consists 21 items. Every question is on a four-point (0-3) Likert scale to recognize the intensity of affective disorders like stress, anxiety, and depression.

Every item score should be doubled, as DASS 21 is a summarized version of DASS 42. In DASS, a higher score reveals an increased in negative emotion, and a lower score shows a decreased in negative mood status. The validity and reliability of DASS have been reported in the Iranian population before (31). The scores of stress, anxiety, and depression were separated into two classifications: No or minimal scores, and some degree of affective disorders. The scores received from every item were find out as follows: (≤14, No), (>14, some degree of stress), (≤ 9, No), (> 9, some degree of depression), (≤7, No), (>7, some degree of anxiety).

Insomnia Severity Index (ISI)

The ISI is a self-report tool for determining insomnia that has seven items. The dimensions evaluated are the distress caused by sleep problems, noticeability of sleep disorders by others, early morning waking up problems, interference of sleep problems with daytime functioning, sleep dissatisfaction, severity of sleep onset, and sleep preservation (32).

According to the severity, every item scored on a 0–4 scale. The overall scale ranges from 0 to 28 and is defined as follows no insomnia (0–7), sub-threshold insomnia (8–14), mild insomnia (15–21), and severe insomnia (22–28). The reliability and validity of the Persian version of this questionnaire have been proved in the Iranian population (Cronbach's a>0.8 and intra-class correlation coefficient >0.7) (33).

Quality of Life Questionnaire

We used SF-36 validated questionnaire to assess the general quality of life. SF-36 is categorized into eight subscales, including Mental Health, Role Emotional, Vitality, General Health, Physical Functioning, Role Physical, and Bodily Pain Social Functioning. This questionnaire's scoring ranges from 0 to 100. The SF-36 Persian version was evaluated in a prior study and showed construct validity and good reliability (34).

Statistical analysis

We used the statistical package for social sciences (SPSS) version 16 for analyzing data. The normality distribution of continuous variables was estimated using the Kolmogorov-Smirnoff and Shapiro-Wilk tests. Normally and non-normally distributed variables were presented using mean and standard deviation (SD); were presented using mean and standard deviation (SD); and median and interquartile range (IQR), respectively. The data was double-checked to correct errors regarding outliers and missing variables.

For the remaining missing variables, multiple imputation was performed based on gender, age, and other related variables to the missing variables using the SPSS software. We compared usually distributed and non-normally distributed variables between groups using the independent t-test and Mann-Whitney test, respectively. The chi-square test was performed to compare the distribution pattern of categorical variables between groups.

Also, we used Binary logistic regression to evaluate the relationship between achieving serum vitamin D >30 ng/mL after the intervention as the dependent variable, and the scores of DASS-21 subscales, total SF-36, ISI, and sleep quality scores, as independent variables. The statistical significance level was regarded as $p<0.05$.

Results

One hundred twenty patients (59, 49.1% females and 61, 50.9% males) cooperated in the current study. The mean age of the patients was 60.38±13.61 years old. We separated subjects into two groups; 1) the level of serum vitamin D 30 ng/mL or above, and 2) serum vitamin D below 30 ng/mL. Comparison of the demographic and medical history variables between subjects with levels of serum vitamin D above 30 ng/mL and below 30 ng/mL are presented in Table 1.

Table 1. Comparison of demographic and medical history variables between patients with serum vitamin D levels above 30 ng/mL and below 30 ng/mL

Variable		Vitamin D < 30 ng/mL n=68	Vitamin D > 30 ng/mL n=52	p-value
Gender	Male	35 (57.9%)	26 (42.1%)	0.870
	Female	33 (56.4%)	26 (43.6%)	
Residential status	Male	64 (57.1%)	48 (42.9%)	0.395
	Female	5 (62.5%)	3 (37.5%)	
Hypertension		26 (55.3)	21 (44.7%)	0.721
Diabetes		24 (52.2%)	22 (47.8%)	0.359
CVD		14 (56.0%)	11 (44.0%)	0.884
Smoking		57 (60.0%)	38 (40.0%)	0.146

and In Our study the level of serum vitamin D was 30 ng/mL or above in 52 (42.9%) of the patients. There was an insignificant difference in demographic and medical history variables between patients with levels of serum vitamin D below above 30 ng/mL ($p>0.05$).

A comparison of the clinical variables, DASS-21 subscale, SF-36, and sleep quality scores with the levels of serum vitamin D below and above 30 ng/mL is presented in Table 2.

There was a significant difference between temperature ($p=0.039$) and PCO2 ($p=0.022$) of The relationship between DASS-21 subscales, SF-36, and ISI scores and improved serum vitamin D in the study patients are presented in Table 3.

There was a significant correlation between stress ($p=-0.023$, OR=0.389, 95% CI for OR=0.047, 0.843) and depression ($p=0.012$, OR=0.659, 95% CI for OR=0.476, 0.913) and Vitamin D levels.

Table 2. Comparison of clinical variables and scores in DASS21- subscales, SF36-, and insomnia between patients with serum vitamin D levels above 30 ng/mL and below 30 ng/mL

Variable	Vitamin D < 30 ng/mL n=64	Vitamin D > 30 ng/mL n=48	p-value
Pulse rate (/min)	87.00 (14.50)	90.85±10.46	0.201†
Respiratory rate (/min)	21.96±3.65	27.00±5.63	0.326‡
Temperature	37.00 (0.63)	37.15±0.31	0.039*†
SBP (mmHg)	133.27±20.57	131.77±23.61	0.694‡
DBP (mmHg)	80.15±16.26	79.62±13.85	0.854‡
SPO2 (%)	83.50 (12.75)	89.00 (12.00)	0.320†
O2 saturation (%)	73.15 (6.45)	65.40 (37.25)	0.311†
PaO2 (mmHg)	41.65±13.54	33.10 (24.35)	0.418†
PCO2 (mmHg)	40.72±11.15	48.18±17.67	0.022*†
Depression	9.00 (9.25)	7.00 (3.50)	0.090†
Anxiety	13.00 (9.50)	11.92±3.90	0.491†
Stress	10.50 (9.50)	10.00 (6.50)	0.907†
Quality of life	53.77±18.04	59.32±20.25	0.864‡
Insomnia Severity Index	2.00 (10.00)	1.00 (5.50)	0.665†

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SPO2: Blood Oxygen Saturation, PaO2: Arterial Oxygen Pressure, PCO2: Arterial carbon Dioxide Pressure, min: Minute, mmHg: Millimeters Mercury, mEq: Milli Equivalent, L: Liter,

Table 3. Relationship between depression, stress anxiety, quality of life and insomnia scores and improved

Variable	B	Wald	p	OR	95% CI for OR	
					Lower	Upper
Depression	-0.416	6.282	0.012*	0.659	0.476	0.913
Anxiety	-0.105	0.689	0.407	0.901	0.704	1.153
Stress	-0.329	5.191	0.023*	0.389	0.047	0.843
Insomnia	-0.085	1.997	0.158	0.918	0.816	1.033
Quality of Life	-0.009	0.246	0.620	0.991	0.955	1.028

Binary logistic regression was done.

These results revealed that with one point increase in depression scores, the risk of achieving vitamin D levels above 30 mg/mL decreases by 34.1%. Furthermore, with one point increase in stress core, the risk of achieving vitamin D levels above 30 ng/mL decreases by 38.9%. Although we obtained all these results, more studies are required to confirm all of the findings and to determine all the mechanisms that vitamin D affects psychological function.

Discussion

In this cross-sectional study, the correlation between vitamin D concentration and psychophysiological factors among 120 COVID-19 patients was assessed. There was a significant correlation between higher levels of vitamin D and reduced depression and stress in patients. The correlation between vitamin D and mental disorders has been investigated in various studies (35,36,37).

Our data show a significant correlation between the reduced severity of mental effects caused by COVID-19 and 25(OH) D concentrations (at least 30 ng/mL). In line with our study, some experimental studies have shown a significant correlation between increased major depression and vitamin D deficiency (38). Pu et al. showed lower serum 25-OH-D3 levels increase the severity of depression (39). Murphy et al. found that a reduced level of serum 25(OH) D is associated with depression (40).

Also, a meta-analysis of cohort and cross-sectional studies suggested that depressive disorders are related to reduced vitamin D concentrations (41).

It can be due to the extensive impact of Vitamin D on modulating mental function, including neurotransmitter release (42,43,44), neuroprotection (45, 46), maintaining cognitive ability (47, 48), and protection against adverse outcomes of chronic stress (49,50).

Increasing inflammatory factors like TNF-α, IL-1β, and IL-6 change the release and effect of neurotransmitters such as glutamate, serotonin, and dopamine (51).

Vitamin D effectively decreases inflammation and oxidative stress. Selective Serotonin Reuptake Inhibitors (SSRI) are used to reduce the pro-inflammatory cytokine's adverse effects in the brain. (52) Also, oxidative stress is associated with depression by damaging DNA (53). The supplementation of vitamin D increases the gene expression that correlates with antioxidation (glutamate–cysteine ligase modifier subunit and glutathione reductase) (54).

Therefore, vitamin D decreases oxidative stress and improves depression. One of the most COVID-19 outcomes is stress which affects psychological stability (55). Our study revealed that the levels of vitamin D are associated with pressure in COVID-19 patients. Tehrani et al. indicated that adults had higher priority and had lower levels of vitamin D (56).

Another study revealed that higher vitamin D levels reduce stress (57). Also, Trovato et al. found that increased consumption of vitamin D or sunlight exposure is related to lower perceived stress among participants (58). In contrast, insignificant association was found between stress in another study and vitamin D levels (59). Reducing stress may be related to the improvement of depression (57).

So, it helps COVID-19 patient's mental health and decreases stress.

We have some limitations in our study. At first, this is a cross-sectional study that cannot find causality. Also, our study was on Covid-19 patients, which can limit the generalization of the results to other populations. We included patients who had recorded 25(OH) D concentrations. Some confounding factors, like social, economic status and smoking, did not register for all participants and might have a reasonable effect on the severity of COVID-19. Additionally, the RT-PCR test has not been performed on all participants with COVID-19 clinical signs. Second, our study is cross-sectional. Thus, we cannot define the relationship between the sufficiency of vitamin D and the decreased risk of depression or stress among COVID-19 patients.

In conclusion, this study revealed that vitamin D concentrations are related to depression and stress. A higher concentration of serum vitamin D may decrease depression and stress risk among COVID-19 patients. Additional longitudinal large-scale studies are needed to prove our findings. Therefore, these findings might shed more light on the pathophysiology of COVID-19 symptoms.

If these findings are observed in other studies, some of the associated symptoms of COVID-19 may be prevented or improved through nutritional interventions both at the community and hospital levels. Furthermore, physicians might better anticipate of the prognosis of symptoms in COVID-19 patients who present degrees of depression and stress.

Ethical statements

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Availability of data and materials

The datasets collected and/or analyzed during the present study are not publicly accessible due to ethical concerns, but the corresponding author may provide datasets upon reasonable request.

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