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Plasma Vitamin D level in Patients with SARS-CoV-2 Infection: Does it Correlates With the Increased Risk of Infection?

Nasrin Saberi [1], Behnam Dalfardi [2], Mitra Samareh Fekri [3], Meysam Yousefi [4], Mehrdad Farrokhnia [5], Mohammad Reza Shakibi [6], Mohamad Hasan Tajadini [7], Mohsen Shafiepour [5*]

1. Student Research Committee, Kerman University of Medical Sciences, Kerman, Iran
2. Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
3. Cardiovascular Research Center, Institute of Basic and Clinical Physiology Sciences, Kerman University of Medical Sciences, Kerman, Iran
4. Research Center of Tropical and Infectious Diseases, Kerman University of Medical Sciences, Kerman, Iran
5. Clinical Research Development Unit, Afzalipour Hospital, Kerman University of Medical Sciences, Kerman, Iran
6. Physiology Research Center, Institute of Neuropharmacology, Kerman University of Medical Sciences, Kerman, Iran
7. Department of Clinical Biochemistry, school of Medicine, Tarbiat Modares University, Tehran, Iran

ABSTRACT

Background: COVID-19 is a widespread viral disease that has severely affected our world. Although beneficial effects of vitamin D on immune system are well known, there are ongoing discussions about its role in patients suffering from SARS-CoV-2 infection. In this study, we examined the relationship between risk of COVID-19 infection and plasma vitamin D level.

Methods: This case-control study was conducted on 133 participants in Kerman city, Iran. SARS-CoV-2 infection was confirmed by positive RT-Real time PCR test in 69 cases and another 64 participants were considered as - non-infected - control group. Plasma vitamin D levels were measured among all, and compared.

Results: Sub-normal plasma vitamin D level were reported in about 51% of participants; however, there was no significant difference in the mean plasma vitamin D levels between COVID-19 and control groups. Mean plasma levels of vitamin D were significantly higher in females than males (P-value: 0.017).

Conclusion: According to our results, risk of COVID-19 infection does not correlate with plasma level of vitamin D.

Keywords: COVID-19, Disease Severity, Pneumonia, SARS-CoV-2, Vitamin D Deficiency

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***Correspondence:** Mohsen Shafiepour; Email: m.shafiepour@kmu.ac.ir

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Introduction

Coronavirus disease 2019 (COVID-19) is a major catastrophe for humanity (1, 2). It is a viral infectious disease caused by severe acute respiratory syndrome corona virus 2 (SARS-CoV-2), a member of the Coronaviridae family (3, 4). To date, millions have been infected, and many have died due to this disease (5, 6). The novelty of SARS-CoV-2 virus, its mutations and high rate of transmission, lack of effective antiviral drugs, and large asymptomatic population have made COVID-19 management very challenging (7, 8).

SARS-CoV-2 virus entry to the upper respiratory tract cells depends on the binding of its spike protein (S) to the angiotensin-converting enzyme 2 (ACE2), and the priming of S protein by host cell protease, called transmembrane serine protease 2 (TMPRSS2). After propagation, virus travel through the airways may trigger a very stronger immune response causing subsequent complications (9).

The immune system plays a pivotal role in preventing COVID-19 infection, and its late complications. Therefore, use of immune boosters, such as vitamin D, has increased sharply (10). Vitamin D is a fat-soluble substance with diverse biological roles. In addition to its effective role in the homeostasis of calcium, magnesium, and phosphate, it plays an important role in cell proliferation and differentiation, and the function of the immune system. The relationship between plasma level of Vitamin D, immune function of the respiratory system, and incidence of some viral infections has been proven (11-13).

Considering the aforementioned facts, we designed this study to investigate the association of plasma vitamin D level and COVID-19 severity in a population from Iran, a country with high prevalence of vitamin D deficiency (14).

Materials and Methods

This case-control study was performed during March and April 2020. In this time-frame all suspected cases of COVID-19 referred to Afzalipour Hospital (a referral hospital located in Kerman city, Iran) were included and evaluated. Probability of COVID-19 was assessed after an initial physical examination and history taking according to the WHO guideline (15). Patients' definitive diagnosis was made by Real time PCR test from nasopharyngeal swab specimens.

All the included patients were in sever category of COVID-19 pneumonia according to the WHO guideline. They met the following criteria: having clinical symptoms, including, that of pneumonia (fever, cough, dyspnea, fast breathing) plus one of the followings: respiratory rate > 30 breaths/min; severe respiratory distress; or a SpO2 < 90% on room air.

Viral RNA was extracted by RNJia Virus Kit (Rojetechnologies, Iran). RT-Real time PCR test was done in a Rotor-Gene Q (Qiagen, Germany) machine using COVID-19 One-Step RT-PCR kit (Pishtaz Teb Zaman, Iran).

Study participants were categorized into the two following groups: (1). Case: those with confirmed SARS-CoV-2 infection; and (2) Control: non-infected participants. After obtaining informed consent and demographic data, blood samples were taken and sent to the laboratory to measure plasma vitamin D levels. Vitamin D was measured using Vit D AccuBind ELISA Kit (Monobind, USA) and a NEOGEN Stat-Fax 4700 Microwell Reader (NEOGEN, USA). Serum C - reactive protein (CRP) was measured by Roche high sensitive CRP kit (Roche Diagnostics, Germany) using Cobas C313 instrument (Roche Diagnostics, Germany). Serum Lactate Dehydrogenase (LDH) was measured by LDH kit (Pars Azmoon, Iran) using a Hitachi 911 Autoanalyzer Machine (Hitachi, Japan). Erythrocyte Sedimentation Rate (ESR) test was performed on fresh anticoagulated blood samples using Sedimex instrument (Parsian Teb Zaman, Iran). White blood cell (WBC) count was performed as a part of Complete Blood Count test using fresh anticoagulated blood samples using a Sysmex kx21 instrument (Sysmex, Japan). All statistical analyses were done using IBM SPSS Statistics version 22 (IBM, USA). Descriptive methods were used to examine demographic information of case and control groups. T-test was used for comparing mean values of groups and bivariate correlation was used for assessing the correlation between parameters.

Results

A total number of 133 persons were included. As it is seen in the flowchart, 69 patients with confirmed SARS-CoV-2 infection were placed in the case group (mean age: 51.75 ± 19.78 years) and 64 non-infected participants were considered as the control group (mean age: 52.34 ± 19.35 years). On-admission data of participants' vital signs have been summarized in Tables 1 and 2.

Table 1. Demographic and basic information of study participants

			Study Groups	
			Case n=69	**Control n=64**
Basic information		Age (year)	51.75±19.78	52.34±19.35
		Sex (female/male)	36/33	31/33
		SpO2 in room air	87.18±7.88	89.49±7.21
		Systolic blood pressure	127.14±20.84	126.63±17.03
		Diastolic blood pressure	87.15±11.47	79.91±17.04
		Heart Rate	91.89±23.55	99.57±17.41
WHO severity criteria	Sings of pneumonia	Fever (%)	59 (86)	21 (33)
		Cough (%)	62 (90)	58 (91)
		Dyspnea (%)	51 (74)	56 (88)
		Fast breathing (%)	57 (83)	58 (91)
		Respiratory rate>30 (%)	55 (80)	51 (80)
		Severe respiratory distress (%)	31 (45)	33 (52)
		SpO2 < 90 in room air (%)	69 (100)	53 (83)

Age, sex, O_2 saturation (SpO2) in room air, systolic blood pressure, diastolic blood pressure and heart rate are showed as basic information. Heart rate is defined as beats/min.; blood pressures are defined as millimeters of mercury (mmHg).; Fever is defined as an abnormal body temperature above 38.5 °C.; Fast breathing is defined as respiratory rate above 24 breaths/min.; Severe respiratory distress is defined as accessory muscle use for breathing and inability to complete full sentences

Table 2. Correlation of serum level of Vitamin D and basic physiology characteristics in COVID-19 and control groups

Measure	**Vitamin D**			
	COVID19		**Control**	
	r	**p-value**	**r**	**p-value**
SpO2 %	0.01	0.97	-0.08	0.56
Systolic Blood Pressure	-0.01	0.94	0.18	0.21
Diastolic Blood Pressure	-0.06	0.61	0.09	0.47
Heart Rate	0.06	0.59	0.09	0.58

r: correlation coefficient, Saturation of oxygen was measured by finger pulse oximetry and showed as SpO2. Heart rate is defined as beats/min. blood pressures are defined as millimeters of mercury (mmHg)

Our results showed that among all participants, 12.5 percent suffered from severe vitamin D deficiency (plasma level: <5 ng/ml), about 20 percent had deficiency (10-20 ng/ml), 18.5 percent had insufficient levels (21-30 ng/ml), and 49 percent of all participants had normal levels (>50 ng/ml). The results showed that the mean plasma vitamin D level was significantly (p-value 0.017) higher in female participants (35.02 ± 22.11 ng/ml) than males (27.30 ± 12.83 ng/ml).

Mean plasma levels of vitamin D in COVID-19 groups was 31.15 ± 17.70 ng/ml, slightly higher than 30.10 ± 19.26 ng/ml in the control group, but this difference was not statistically significant (p-value 0.53).

Serum vitamin D level had no significant correlation with patients' respiratory manifestations, their arterial oxygen saturations, and laboratory values including white blood cell (WBC) count, and levels of serum C - reactive protein (CRP), and lactate dehydrogenase (LDH). However, it showed a significant correlation (p-value less than 0.05) with erythrocyte sedimentation rate (ESR).

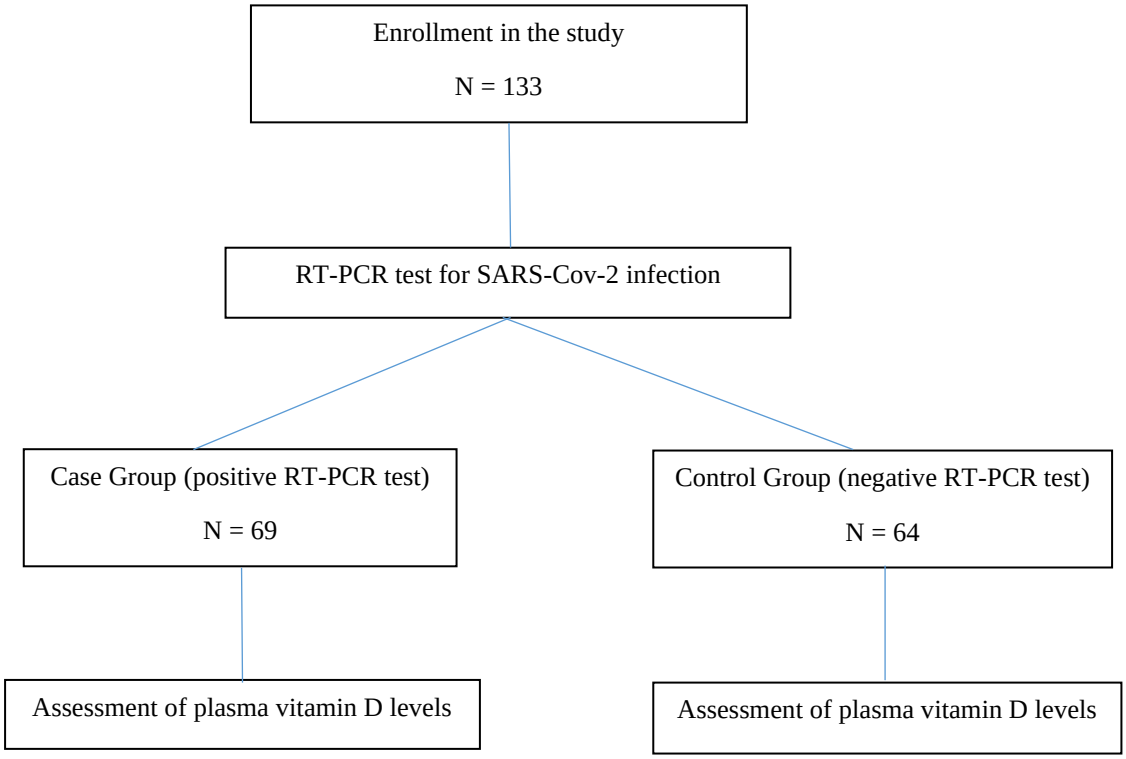

Fig 1. Research protocol.

Discussion

COVID-19 is a major challenge for our helpless world. There are many facts and rumors about the factors that affect risk, severity, and outcome of this disease (16, 17). One of these is about vitamin D, which has received lots of attention since the beginning of COVID-19 pandemic. Initially, in the pandemic, some unsubstantiated claims about the positive effects of vitamin D in prevention and treatment of SARS-CoV-2 infection (18) have greatly increased vitamin D consumption by the help of social networks domination. Nevertheless, there are still ongoing discussions about the role of this vitamin in SARS-CoV-2 infection

The impact of plasma vitamin D level on patients with COVID-19 can be discussed in aspects of risk of SARS-CoV-2 infection, disease severity, and patients' outcome. There are previous reports that suggest vitamin D supplementation reduces the risk of SARS-CoV-2 infection; as its deficiency increases the risk of COVID-19 and its severity (19-24). Nevertheless, consistent with our findings, some of previous works showed no significant association between plasma levels of vitamin D and the risk of SARS-CoV-2 infection (25, 26). A meta-analysis by Pereira and colleagues concluded that vitamin D deficiency did not increase vulnerability of people to SARS-Cov-2 infection; nevertheless, its deficiency was associated with a more severe disease and higher mortality rate (27). In our study, not only there was no significant difference in plasma levels of vitamin D between the two studied groups, but also plasma levels of vitamin D was slightly higher in the COVID-19 group. The high prevalence of vitamin D deficiency and insufficiency among Iranian population, and our limited sample size may justify this finding.

It has been suggested that vitamin D can have two beneficial effects in SARS-CoV-2 infection. Vitamin D plays a role in the production of antimicrobial peptides in epithelial tissue of respiratory tract. Vitamin D positively affects our cellular and adaptive immune systems and improves gene expression of antioxidation mediators. In addition, it may help to prevent dysregulation of inflammatory response in patients with COVID-19 (21, 28, 29). Even if there are positive effects, we do not know what plasma levels of vitamin D are needed to have prophylactic or therapeutic effects, or how long these levels should be stable to achieve these goals. Furthermore, the net results of increasing vitamin D intake cannot be easily assessed.

Another finding of our study was that the prevalence of sub-normal plasma vitamin D levels, including severe deficiency, deficiency and insufficiency, was considerably high (51%) among all participants. This finding was consistent with the results of some other studies conducted in Iran (14). In contrast to our results that showed the average plasma vitamin D level was significantly higher in females, there are previous works that found lower plasma vitamin D levels in females than males (14). It is noteworthy that Iran is one of the countries with high levels of sunlight; however, for reasons including lack of sufficient exposure to sunlight and limited use of vitamin D-containing foods and supplements, vitamin D deficiency is prevalent in Iranian population (14).

Although this increase can lead to the adjustment of low initial levels, negative effects of sudden intake of large amounts of vitamin D and the damage caused by it should not be ignored (30). Therefore, any use of such compounds should be done with care. We strongly recommend conducting clinical trials to investigate the effects of vitamin D and other known compounds in the field of COVID-19 prevention and treatment. The results of such studies increase the possibility of identifying effective and useful compounds and prevent the spread of superstitions and false claims.

This study had some limitations. Our sample size was low. We did not record data on participants' BMI, a potential confounder of the work.

Conclusion

We found that there is no significant difference in the serum levels of vitamin D between COVID-19 infected and non-infected groups. It could be said that serum vitamin D level does not affect the risk of SARS-CoV-2 infection.

Availability of data and materials

All data analyzed during this study are included in this published article.

Ethics approval and consent to participate

This study had been approved by the ethics committee of Kerman University of Medical Sciences (Code: IR.KMU.REC.1399.010).

Consent for publication

Consent for publication was obtained from patients.

Conflict of interests

Authors declare that they have no conflict of interest.

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