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Research article

The Association Between the Level of Serum 25(OH) Vitamin D, Obesity, and underlying Diseases with the risk of Developing COVID-19 Infection: A case-control study of hospitalized patients in Tehran, Iran

Running head: Vitamin D, Obesity and COVID-19 Infection

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Abstract:

Background and objectives: The outbreak of COVID-19 has created a global public health crisis. Little is known about the predisposing factors of this infection. The aim of the current study was to explore an association between the serum vitamin D level, obesity and underlying health conditions, and the vulnerability to COVID-19 in the Iranian population.

Methods: We conducted a case-control study of 201 patients with coronavirus infection and 201 controls. Cases and controls were matched for age and gender. The study was carried out for 2 months (February 2020 to April 2020) at Imam Khomeini Hospital Complex, Tehran, Iran. Serum 25(OH) vitamin D was measured using enzyme-linked immunosorbent assay method. Information containing age, gender, clinical symptoms, body mass index (BMI), CT scan findings, and underlying health conditions related to each participant were elicited from health records.

Results: A significant negative correlation (p = 0.02) was observed between the serum vitamin D level and developing coronavirus infection. Also, the results showed that the COVID-19 cases were more likely to be overweight than the controls (p=0.023). Diabetes mellitus, hypertension, and respiratory infections were found in 20.89%, 9.65%, and 6.96 % of cases, respectively. These underlying health conditions were not significantly different between cases and controls (p= 0.8111).

Conclusions: Vitamin D deficiency and obesity are two main predisposing factors associated with the vulnerability to coronavirus infection in Iranian population.

Keywords: Vitamin D, Abdominal obesity, Body mass index, COVID-19, Iran

Background:

The world is now experiencing a major epidemic of coronavirus (CoV) infection which began in Wuhan, Hubei province, China, in late 2019. Coronavirus disease 2019 (COVID-19) is the name for this disease, and the virus that causes it is known as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)[1]. As the Covid-19 pandemic continues to spread, the need to understand which populations are most at risk of developing this infection grows. Recent studies have found an association between vitamin D level and Covid-19 severity and mortality.[2, 3] There are considerable experimental data showing that vitamin D may protect individuals from viral infection.[4, 5] Vitamin D has been associated with a reduced risk of getting common cold.[6] It also enhances cellular immunity and modulates adaptive immunity.[7, 8] Vitamin D reduces the angiotensin-converting enzyme 2 (ACE2) that is believed to serve as the binding site and gateway for SARS-CoV-2 to become infectious. [9-11]. Vitamin D deficiency is one of the most prevalent conditions worldwide, this is particularly true in Iran, because the main source of vitamin D for humans is the exposure of skin to sunlight, and due to the types of clothing and the population's limited exposure to natural sunlight, vitamin D deficiency is prevalent in this country.[12, 13] Furthermore, the connection between obesity and COVID_19 infection severity

has been established in earlier studies.[14] Furthermore, it has been demonstrated that countries with a higher ratio of obesity, also have significantly higher numbers of COVID-19 deaths.[15] According to reports, nearly half of the Iranian adult population is obese or overweight.[16] Obesity is usually associated with a dysregulated renin–angiotensin–aldosterone system (RAAS) axis.[17] RAAS has been observed to be involved in patients with acute lung injuries and myocardial injuries, and as such, has been noted as a potential regulator of COVID-19 severity. ACE2 (the binding site of SARS-CoV-2) is a protective component of the RAAS axis and its downregulation observed following SARS-CoV-2 infection .[18] The RAAS axis could thus be a link between obesity and COVID-19 severity.[19] Several studies have examined patients with an increased risk of developing severe forms of COVID-19 infection. These include older patients, individuals with obesity, cardiovascular and respiratory diseases, chronic kidney disease, diabetes, and a range of other chronic conditions.[20-22] So far, most of the evidence in Iran comes from observational studies with no proven results.

Objectives:

The aim of this study was to determine whether an association exists between the serum vitamin D level, obesity and underlying health conditions, and the vulnerability to COVID-19 in the Iranian population, and to demonstrate the general clinical and radiological picture of COVID-19 in Iranian individuals.

Materials and methods:

Study design and participants

This was a matched case–control study involving adult hospitalized patients at Imam Khomeini Hospital Complex, Tehran, Iran. During a period of two months from Thursday, 20 February 2020 to Monday, 20 April 2020 a total of 201 hospitalized patients with positive real-time PCR test result for COVID-19 were matched with 201 controls with negative real-time PCR test result. Within each pair, participants were matched for age (±5 years) and gender. Information regarding age, gender, clinical symptoms, body mass index (BMI), CT scan

findings, and underlying health conditions related to each participant were extracted from health records.

Measurement of plasma 25(OH) vitamin D

Five-milliliter blood samples were taken from all participants. Blood samples were collected in K_2EDTA tubes (Becton-Dickinson, Franklin Lakes, NJ, USA), centrifuged at 1200 x g for 10 min at 4°C, and plasma aliquots were stored at -80°C until assayed. Serum 25(OH) vitamin D was measured by an enzyme-linked immunosorbent assay method using IDS 25(OH) vitamin D kits, code AC 57F1 (Tecan Group Ltd., Männedorf, Switzerland). Serum 25(OH) vitamin D has 4 categories including deficient (<10 ng/ml), insufficient (10-30 ng/ml), sufficient (>30-100 ng/ml), and toxicity (>100 ng/ml), as indicated by the manufacturer.

Statistical analysis

The data were entered in and analyzed by SPSS software (IBM SPSS Statistics for Windows, Version 21.0, IBM Corp, Armonk, NY, USA). We used mean (standard deviation[SD]) as a numerical measure for normally distributed quantitative data and median (interquartile range [IQR]) for non-normally distributed variables. The Kolmogorove-Smirnov test for normality was used to check whether continuous variables are normally distributed. Parametric two-sample *t*-test or non-parametric Mann-Whitney U test was used where appropriate.

Categorical variables were presented as frequencies (percent) and compared using chi-square test. A *P*-value of less than 0.05 was accepted as statistically significant.

Ethical statement

The study was approved by the ethics committee of Tehran University of medical sciences (code: IR.TUMS.MEDICINE.REC.1399.022), Tehran, Iran. Written informed consent was obtained from all individuals, both cases and controls, before inclusion in the study.

Results:

In total, 201 (66 males, 135 females) cases and 201 (66 males, 135 females) controls were enrolled. The mean (SD) age of cases and controls were 48 (16.95) and 46.34 (13.5) years, respectively. The median (IQR) serum 25 (OH) vitamin D level in cases and controls were 24 (19-29) and 26 (21-35) ng/ml, respectively. Cases and controls were matched according to their age and gender. In comparison with the control group, the level of serum 25(OH) vitamin D in cases was significantly lower (p = 0.02) and the results demonstrated that there was a significant relationship between the levels of serum 25(OH) vitamin D and the vulnerability to COVID-19 (table 1). Furthermore, after categorizing patients in vitamin D sufficient and not sufficient groups and comparing as categorical variables the relationship remained significant (p = 0.001).

The results of our study showed that the COVID-19 cases were significantly more likely to be overweight than the controls (p = 0.023).

Table 1 presents the distribution of clinical symptoms, BMI, CT scan findings, and underlying diseases in case and control groups.

Myalgia (n=199, 99%), dry cough (n=140, 69.65%), dyspnea (n= 124, 61.69%) and sore throat (n=108, 53.73%) were the most common symptoms in the case group (Table 1). Statistical analysis showed that there was a significant difference between cases and controls with regards clinical symptoms (p < 0.001).

Bilateral lung involvement was observed in 112 cases (55.72%) and unilateral lung involvement was observed in 89 cases (44.27%) and there was a significant difference between cases and controls with regards to CT scan findings (p< 0.001).

Diabetes mellitus, heart failure and hypertension, and respiratory infections were found in 20.89%, 9.65%, and 6.96 % of cases, respectively (Table 1). These predisposing factors were not significantly different between cases and controls (p = 0.81).

Discussion:

We reported here a hospitalized case-control study including 201 cases (hospitalized patients with laboratory-confirmed COVID-19 infections) and 201 controls (hospitalized patients with negative laboratory results for COVID-19 infection). In the current study, we checked the associations of serum levels of vitamin D, obesity, and underlying diseases with the vulnerability to SARS-CoV-2 infection in the Iranian population. The results of the current study demonstrated that in comparison with the control group, the level of serum 25(OH) vitamin D in the cases was significantly lower. Our results demonstrated that individuals with higher serum levels of 25(OH) vitamin D are less susceptible to COVID-19 infection and there is a connection between vitamin D deficiency and testing positive for COVID-19. In agreement with our results, results of studies conducted by Ilie et al in the United Kingdom, and Kara et al in Turkey showed that the population with low serum vitamin D levels was the most vulnerable group to COVID-19.[2, 3] Evidence suggests that vitamin D may have an important supportive role for the immune system, particularly in regulating cytokine response to COVID-19.[23] Other studies have demonstrated the relationship between serum vitamin D level and COVID-19 infection.[9, 24, 25] Some studies have resulted in a different set of findings. For instance, Claire. E et al., by using UK biobank data, have conducted a study on 348,598 participants among which 449 individuals were confirmed COVID-19 cases. In their survey, serum vitamin D level was universally associated with COVID-19 infection but not after adjusting for the confounders. Consistent with our findings, whenever participants were grouped into vitamin D deficient versus not deficient, the significant association was detected, as well as results obtained from analysis on serum vitamin D level as a continuous variable.[26]

It has been a long time since the vitamin D was recognized as a immune response modulator that enhances human defense system.[27] *In vitro* studies have demonstrated that vitamin D plays an important role in antiviral innate immunity by reducing pro-inflammatory cytokines and boosting antiviral protein synthesis.[28] A recent study has identified the active form of Vitamin D,

calcitriol, as a potent agent against SARS-CoV-2.[29] The fact that these effects were brought about by regulation of the renin-angiotensin system (RAS) in an animal model is of particular significance in the context of a severe COVID-19 infection where overactivation of RAS is linked to poor prognoses.[30]

Also, myalgia (99%), cough (69.65%), dyspnea (61.69%), and sore throat (53.73%) were the most common symptoms in COVID-19 patients in the present study. Another study in Iran performed by Rastad H et al., showed that the most common symptoms at the time of admission were cough, shortness of breath, while myalgia was identified as the most prevalent symptom at the time of admission according to our findings .[31]

The study of Guan and colleagues in China showed that the most common symptoms in COVID-19 patients were fever (43.8% on admission and 88.7% during hospitalization) and cough (67.8%).[32] Also, in another study conducted by Huang et al. in China common symptoms at the onset of the illness were fever (98%), cough (76%), and myalgia or fatigue (44%).[33] Additional evidence about common symptoms in COVID-19 patients is needed with longer observation periods and larger population sizes in a more diverse demographic.

In the current study, it was clarified that the COVID-19 cases were more likely to be overweight than the controls. Obesity has been established as a predisposing factor for developing more severe forms of COVID-19 infection in other studies.[34, 35]

The results of a study conducted by Simonnet et al. in France showed a high frequency of obesity among patients admitted to intensive care units due to COVID-19.[36] The reason for this observation is the fact that abdominal obesity is associated with impaired ventilation of the base of the lungs, resulting in reduced oxygen saturation of blood.[37] Furthermore, the abnormal secretion of adipokines and cytokines such as tumor necrosis factor-alpha and interferon characterize a chronic low-grade inflammation that is characteristic of abdominal obesity, which may impair immune response and have effects on the lung parenchyma and bronchi.[38, 39]

Studies demonstrated that patients at risk for developing COVID-19 infection have been characterized as having pre-existing diseases, such as hypertension, cardiovascular disease, diabetes, chronic respiratory infections, and cancer.[37-44] In the current study, diabetes mellitus, heart failure and hypertension, and respiratory infections were the most common underlying diseases in COVID-19 patients. Risk factors of cardiac events include older age, pre-existing cardiovascular diseases, and greater severity of pneumonia at presentation.[45] Coronary heart disease has also been found to be associated with acute cardiac events and poor outcomes in influenza and other respiratory viral infections.[46, 47] Also, diabetes patients have an immune system with a lower ability to respond to and deal with diseases of any type. This means they are more prone to illness than the general population. Diabetes can contribute to the development of fungal/bacterial/viral pneumonia, tuberculosis, and chronic obstructive pulmonary disease (COPD).[48] Furthermore, when patients have previous respiratory diseases such as COPD, their lung function is damaged. They have lower resistance to the virus and are prone to developing COVID-19. Thus, underlying diseases such as diabetes, hypertension, cardiovascular disease, or respiratory disease are risk factors for disease progression in the Iranian population.

In the present study, all 201 COVID-19 patients had abnormal findings on chest CT scans. Bilateral lung involvement was observed in 112 COVID-19 cases (55.72%) and unilateral lung involvement was observed in 89 COVID-19 cases (44.27%). Similarly, in a study conducted by Wu et al. in China, among 130 COVID-19 patients, 14 (10.7%) cases with unilateral lung involvement and 116 (89.3%) cases with bilateral involvement were reported.[49] While in a study conducted by Huang et al. in China, it was demonstrated that all COVID-19 patients (100%) had abnormal findings on chest CT scans, with preliminary reports indicating bilateral abnormal lung opacities in each patient.[33] Also, most patients (79%) in a cohort study conducted by Shi et al. in China showed bilateral lung involvement.[50]

Among limitations to be noted in the current study, is that adjusting for confounders in a regression model was not possible due to the unavailability of

the relevant data about other potential confounders. Data on inflammatory markers and their relation to serum vitamin D levels in COVID-19 cases was not collected; a shortcoming that can be alleviated in future studies to broaden their scope.

Conclusion:

The findings of the current study indicate that individuals with lower levels of serum vitamin D are more vulnerable to COVID-19 infection. Therefore, improving an individual's vitamin D status could have a protective role against the infection. Individuals with COVID-19 were more likely to be overweight or obese in our study. Despite some diversity in initial symptoms, most COVID-19 patients in our study presented with myalgia and respiratory symptoms. Finally, the predominant pattern of abnormality in CT scan findings was bilateral lung involvement.

Footnotes

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Conflict of interest

The authors have no conflicts of interest to declare for this study.

Ethical Considerations: The study was approved by the Ethical Committee of Tehran University of Medical Sciences, Tehran, Iran (code: IR.TUMS.MEDICINE.REC.1399.022). All patients signed consent form before participation in the study.

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Data Availability Statement:

The data analyzed in the present study have not been made available.

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Table

Table 1. The demographic, clinical, paraclinical, and imaging findings in COVID-19 cases and controls.

			Cases (n=201)		Controls (n=201)		P-value
Age, mean (SD) (years)			48 (16.95)		46.34 (13.5)		0.28
Serum 25(OH) vitamin D, median (IQR) (ng/mL)			24 (19-29)		26 (21-35)		0.001
Serum 25(OH) vitamin D, Number (%)	**Deficient**	**Not sufficient**	1 (0.49%)	162 (80.5%)	1 (0.49%)	132 (65.67%)	0.001*[a]
	Insufficient		161 (80%)		131 (65.17%)		
	Sufficient		39 (19.4%)		69 (34.32%)		
Clinical symptoms, Number (%)	Sleep disorders		28 (13.93%)		18 (8.95%)		<0.001*[b]
	Gastrointestinal symptoms		64 (31.84%)		23 (11.44%)		
	Dry cough		140 (69.65%)		7 (3.48%)		
	Dyspnea		124 (61.69%)		9 (4.41%)		
	Anosmia		24 (11.94%)		0 (0%)		
	Sore throat		108 (53.73%)		3 (1.49%)		
	Myalgia		199 (99%)		7 (3.48%)		
	Eye involvement						

			4 (2%)		0 (0%)	
BMI [c], Number (%)	Normal (18.5-24.9 kg/m2) Overweight (25-29.9 kg/m2) Obese-Class 1 (30-34.9 kg/ m2) Obese-Class 2 (35-39.9 kg/m2) Obese-Class 3 (≥ 40 kg/m2)		22 (10.94%) 78 (38.80%) 25 (12.43%) 28 (13.93%) 48 (23.89%)		128 (63.68%) 40 (19.9%) 12 (5.97%) 15 (7.46%) 6 (3%)	0.023*[d]
CT [e] scan of the lung, Number (%)	Unilateral involvement Bilateral involvement		89 (44.27%) 112 (55.72%)		1 (0.49%) 0 (0%)	<0.001*
Underlying diseases, Number (%)	Hypothyroidism		12 (5.97%)		27 (13.43%)	0.81
	Diabetes mellitus		42 (20.89%)		19 (9.45%)	
	Splenectomy		1 (0.49%)		0 (0%)	
	Heart failure and hypertension		20 (9.95%)		15 (7.46%)	
	Respiratory infections		14 (6.96%)		8 (39.80%)	
	Autoimmune diseases	Rheumatoid arthritis	11 (5.47%)	3 (1.49%)	14 (6.96%)	4 (2%)
		Multiple Sclerosis		2 (1%)		4 (2%)

		Ankylosing spondylitis		5 (2.46%)		0 (0%)
		Pemphigus vulgaris		1 (0.49%)		6 (3%)
	AIDS [f]		4		1 (0.49%)	

[*] Statistically significant difference between groups (P-value less than 0.05),[a] Chi-square test obtained for 2x2 table (sufficient vs not sufficient), [b] Comparing symptomatic to asymptomatic individuals, [c] BMI: body mass index, [d] Comparing overweight/obese to normal, [e] CT scan: computerized tomography scan, [f] AIDS, Acquired immunodeficiency syndrome