Journal of Endocrinological Investigation (2021) 44:2601–2607
https://doi.org/10.1007/s40618-021-01566-9

ORIGINAL ARTICLE

Retrospective analysis of vitamin D status on ınflammatory markers and course of the disease in patients with COVID-19 infection

Y. A. Ünsal[1] · Ö. Ö. Gül[1] · S. Cander[1] · C. Ersoy[1] · E. Aydemir[1] · C. Ateş[1] · Z. Uzun[2] · E. Armağan[2] · O. Ünsal[3] · E. Ertürk[1]

Received: 28 December 2020 / Accepted: 29 March 2021 / Published online: 5 April 2021

Abstract

Purpose The aim of the study was to investigate the association between serum 25-hydroxyvitamin D status within the last 6 months prior to COVID-19 infection and parameters of immune function and clinical outcomes.

Methods Fifty-six patients, who were admitted to the emergency clinic and diagnosed with COVID–19 infection, were included in the study. Data on clinical characteristics, inflammatory parameters and vitamin D status were recorded for each patient. All the participants had data on 25-hydroxyvitamin D status within the last 6 months prior to COVID-19 infection.

Results The patients were stratified as those with vitamin D status less than 20 ng/mL and higher than 20 ng/mL. A group with vitamin D status less than 20 ng/mL had lower lymphocyte counts and lower haemoglobin levels that was statistically significant (respectively; $p=0.021$, $p=0.035$). Higher C-reactive protein (CRP) levels were seen in the vitamin D–deficient group ($p=0.013$). It was observed that vitamin D status of the patients who required oxygen therapy were lower than those who did not require oxygen therapy, not statistically significant ($p=0.05$). Patients who did not use vitamin D supplementation within 6 months prior to COVID-19 infection had more likely to be diagnosed with pneumonia ($p=0.004$).

Conclusion Cases with lower vitamin D status had increased inflammatory markers and worse clinical outcomes than patients with higher vitamin D status. This study suggests that vitamin D status can be used as a prognostic factor in COVID-19 patients, and vitamin D supplementation can be recommended to improve the clinical outcomes in COVID-19 infection.

Keywords Vitamin D · COVID-19 · Immunity · Anti-inflammatory · Pneumonia

✉ Y. A. Ünsal
yaseminunsalay@gmail.com

Ö. Ö. Gül
drozenoz@gmail.com

S. Cander
drcander@gmail.com

C. Ersoy
ecanan@uludag.edu.tr

E. Aydemir
ensaraydemir@gmail.com

C. Ateş
drcsknates@gmail.com

Z. Uzun
drziyauzun61@gmail.com

E. Armağan
earmagan9999@yahoo.com

O. Ünsal
oktayunsal@uludag.edu.tr

E. Ertürk
erturkerdinc@gmail.com

[1] Faculty of Medicine, Department of Endocrinology and Diseases of Metabolism, Bursa Uludag University, Bursa, Turkey

[2] Faculty of Medicine, Emergency Department, Bursa Uludag University, Bursa, Turkey

[3] Faculty of Medicine, Oncology Department, Ankara Gazi University, Ankara, Turkey

Introduction

A novel coronavirus, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), as a cause of pneumonia cases that has affected the healthcare systems across the world in late 2019 [1]. As the SARS-CoV-2 virus has high levels of transmissibility, and the disease spread quickly to all over world, World Health Organisation (WHO) declared the outbreak as the public health emergency [2].

The spectrum of infection is highly heterogeneous, from asymptomatic cases to cases with multiple organ dysfunctions have been seen and fewer than 15% of the cases develop severe disease [3–5]. People older than 60 years, males, Black, Hispanic and South Asian and with pre-existing comorbidities such as cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer, chronic kidney disease, obesity and smoking are more vulnerable to severe form of the disease [6–10].

Vitamin D is one of the factors that may be linked to the severity of COVID-19. Vitamin D deficiency is pandemic like COVID-19, and it has become a global problem. The best laboratory indicator of vitamin D deficiency is serum 25-hydroxyvitamin D [25(OH) vitamin D] concentration [11]. The Institute of Medicine suggests that serum 25 (OH) vitamin D concentration of 20 ng/mL is sufficient for most individuals, but Endocrine Society and National Osteoporosis Foundation say that a minimum level of 30 ng/mL is necessary to minimise the risk of falls and fracture [12, 13].

Vitamin D is important for bone health and calcium–phosphorus metabolism. It plays a role in the modulation of the immune response in autoimmune diseases [14, 15]. Many tissues in the skeletal system and intestine and cells in the bone marrow, brain, colon, breast, malignant cells and also immune cells express vitamin D receptor [16]; this suggests that vitamin D plays a role in the immune system. In one study that includes 19,000 subjects between 1988 and 1994, it was revealed that individuals with lower vitamin D status (< 30 ng/mL) had been more likely to have a recent upper respiratory tract infection than others [17]. Many studies reported an association between vitamin D status and infections such as influenza, bacterial vaginosis and human immunodeficiency virus. These studies reported an association of lower vitamin D status and increased rates of infection [16, 18, 19].

Vitamin D plays a role in both innate and adaptive immunity [20]. The innate immune system is the defence against invading pathogens, such as SARS-CoV-2 virus. Active vitamin D [1,25$(OH)_2$D] induces antimicrobial peptides such as cathelicidin that leads to viral destruction, killing and clearance of these pathogens by neutrophils, monocytes/macrophages and dendritic cells, and then the adaptive immune response is initiated [21, 22]. Chronic activation of the innate immune response can result in a cytokine storm. Active vitamin D can downregulate chronic innate immune response via downregulation of toll-like receptors and direction inhibition of tumour necrosis factor/nuclear factor-kappa B (TNF/NF-κB) and interferon-gamma (IFN-γ) signalling pathways. Also, 1,25$(OH)_2$D regulates adaptive immunity by limiting the maturation of dendritic cells and reduces their ability to present antigen to T cells. It causes shifting the T-cell profile from the pro-inflammatory T helper cell type 1 (Th1) and Th17 subsets to Th2 and T regulatory cell (Treg) subsets and so that the expression of anti-inflammatory cytokines such as interleukin-1alpha (IL-1α) and TNF-α are reduced [23]. Furthermore, SARS-CoV-2 enters into pneumocytes and enterocytes by binding with angiotensin-converting enzyme 2 (ACE-2) on the surface of the cells. Vitamin D downregulates ACE-2 so that it inhibits the action of the virus [24, 25]. Recent studies on COVID-19 and vitamin D indicates an association between low 25 (OH) vitamin D status and clinical outcomes of the infection [26, 27].

This study evaluated the association between 25 (OH) vitamin D status and inflammatory markers, clinical outcomes, mortality in cases with positive result for COVID-19 infection and data on 25 (OH) vitamin D status within the last 6 months.

Materials and methods

Patients and data source

Fifty-six patients, who had admitted to the emergency clinic of Uludag University Faculty of Medicine Hospital and diagnosed with COVID-19 infection between March 2020 and October 2020, were included in the study. All the participants had data on 25 (OH) vitamin D within the last 6 months prior to COVID-19 infection. Time frame of the measurement of 25(OH) vitamin D was 3 (1–6) months. Patients diagnosed with COVID-19 infection between March 2020 and October 2020 were included in this study to minimise the sunlight effect that can change status. This study did not include patients who had measured 25 (OH) vitamin D status at any time. The study protocol was approved by ethics committee of Uludag University Faculty of Medicine (2020-20/10).

Data collection and laboratory analysis

Data such as age, gender, weight, height, smoking status, prior vitamin D supplementation, symptoms of infection,

comorbidities and reports of chest X-ray and chest computed tomography were provided from the hospital database.

Biochemical and haematological laboratory parameters on hospital admission were recorded. Data on 25 (OH) vitamin D, which was measured in the last 6 months, were obtained from the same hospital database (Uludag University Faculty of Medicine) with the same assay by chemiluminescence immunoassay method. SARS-CoV-2 infection was confirmed in all patients of COVID-19 by reverse transcription-polymerase chain reaction (RT-PCR) on nasopharyngeal swabs.

Statistical analysis

Statistical analyses were performed using the SPSS software version 15. The variables were investigated using visual (histograms) and analytical methods (Kolmogorov–Smirnov/Shapiro–Wilk test) to determine the normal distribution. Descriptive analyses were performed using medians for non–normally distributed and ordinal variables. The categorical data were shown in counts and percentages. Non-parametric tests were conducted to compare these parameters and the ordinal variables. The chi-squared test or Fisher's exact test (when chi-squared test assumptions do not hold because of low expected cell counts), where appropriate, was used the compare the proportions in different groups. A p value of less than 0.05 was considered to show a statistically significant result.

Results

A total of fifty-six patients were included in this study. Median age of patients was 44 years (26–76 years). Approximately 67.9% of patients were female and 26.8% of the cases were evaluated as obese [body mass index (BMI) ≥ 30 kg/m^2]. It was learned from the anamnesis that 78.5% of the patients had never smoked. These patients had a history of chronic disorder; 21.4% had hypertension, 19.6% had diabetes, 17.9% had depressive disorder, 16.1% had asthma, 16.1% had hypothyroidism, 12.5% had malignancy, 8.9% had coronary artery disease, 8.9% had hyperlipidaemia and 5.4% had chronic kidney disease. Also, 3.6% of patients had chronic obstructive lung disease, and 3.6% of patients were followed-up with a diagnosis of chronic liver disease. The baseline characteristics of patients are presented in Table 1.

Only one person had no symptoms of infection at the time of admission. He was admitted to emergency outpatient clinic because of the family history of COVID-19 PCR positivity. Cough was found to be the most common symptom, as described by the COVID-19 patients. Malaise (44.6%), myalgia (44.6%), fever (39.3%), anosmia (39.3%), ageusia (35.7%), shortness of breath (30.4%), sore throat (28.6%), diarrhoea (21.4%), nausea/vomiting (19.6%), headache (17.9%) and arthralgia (17.9%) were the other common symptoms, as described by the patients.

Table 1 Demographics, comorbities of COVID–19 patients

Characteristic	Results
Age, median (year)	44 (26–76)
Sex (*n*)/(%)	
Female	38 (67.9)
Male	18 (32.1)
Body mass index (kg/m^2)	
≥ 30 (*n*) (%)	15 (26.8)
< *30* (*n*) (%)	36 (64.3)
Smokers (*n*)/(%)	
Never smoke	44 (78.6)
Current or former smoker	12 (21.4)
Comorbidity (*n*)/(%)	
Hypertension	12 (21.4)
Diabetes mellitus	11 (19.6)
Depressive disorder	10 (17.9)
Asthma	9 (16.1)
Hypothyroidism	9 (16.1)
Malignancy	7 (12.5)
Coronary artery disease	5 (8.9)
Hyperlipidemia	5 (8.9)
Chronic kidney disease	3 (5.4)
Chronic obstructive lung disease	2 (3.6)
Chronic liver disease	2 (3.6)
25 (OH) vitamin D (ng/mL)	
< 20 ng/ml (*n*) (%)	27 (48.2)
≥ 20 ng/ml (*n*) (%)	29 (51.8)

Numerical variables were expressed as median and categorical variables were presented as percentages

25 (OH) vitamin D 25 hydroxyvitamin D

Median status of 25 (OH) vitamin D was 21.5 ng/mL (6.6–51 ng/mL). Twenty-seven patients (48.2%) had 25 (OH) vitamin D status less than 20 ng/mL, 51.8% of patients (29 patients) had 25 (OH) vitamin D status higher than or equal to 20 ng/mL. Patients were stratified as vitamin D normal (≥ 20 ng/mL) and deficient (< 20 ng/mL) groups. When inflammatory markers were compared between the two groups, higher C-reactive protein (CRP) levels were seen in the vitamin D–deficient group ($p = 0.013$). Procalcitonin levels were also found to be higher in the vitamin D–deficient group that was not statistically significant ($p = 0.074$) (Table 2). Although D-dimer levels of the two groups were not different, these were found to be significantly higher ($p = 0.025$) in patients with vitamin D status less than or equal to 10 ng/mL.

No patients were followed-up in the intensive care unit (ICU), 51.8% of patients were admitted to inpatient clinic.

Table 2 Some laboratory parameters of COVID-19 patients in relation to vitamin D status

Parameter	Vitamin D status		*p* value
	< 20 ng/ml	≥ 20 ng/ml	
White blood cell (C/ml)	5665 (2960–17,810)	5590 (1370–10,530)	*0.769*
Neutrophils (C/ml)	3520 (1303–4666)	3320 (940–8603)	0.315
Lymphocyte (C/ml)	1140 (370–2481)	1550 (290–3254)	0.021
Neutrophil/lymphocyte ratio	3.8 (0.73–13.81)	2.53 (0.81–12.06)	0.018
C-reactive protein (CRP) (mg/L)	18.4 (2–294.4)	4. 45 (2–67.9)	0.013
Erythrocyte sedimentation ratio (mm/saat)	37 (2–87)	20 (1.09–47)	0.440
Procalcitonin(μg/L)	0.04 (0–0.97)	0.02 (0–1.09)	0.074
Ferritin (mg/dL)	67.6 (4.2–6167)	62.5 (4.1–309)	0.779
Albumin (g/L)	33 (4–46)	41 (4.4–49)	0.413
Fibrinojen (mg/dL)	483.9 (242.6–697.4)	306 (121.1–564)	0.361
D-dimer (mg/L)	0.45 (0.17–16.27)	0.35 (0.17–1.9)	0.111

Table 3 Outcomes analysis of the patients

Parameters	Patient number/(%)
Respiratory support (number)	
No requirement	47 (83.9)
Low-flow nasal oxygen therapy	5 (8.9)
High-flow nasal oxygen therapy	3 (5.4)
Invasive mechanical ventilation	1 (1.8)
Pneumonia	18 (32.1)
Hospitalization status	
Hospitalized	29 (51.8)
Outpatient clinic management	27 (48.2)
Treatments	
Favipravir	40 (71.4)
Hydroxychloroquine	35 (62.5)
Antimicrobial therapies	24 (42.9)
Heparin	22 (39.3)
Glucocorticoids	11 (19.6)
Plasmapheresis	6 (10.7)
Oseltamivir	5 (5)
Tocilizumab	2 (3.6)
Mortality	2 (3.6)

Numerical variables were expressed as median and categorical variables were presented as percentages

Table 4 Requirement of respiratory support according to vitamin D status

25 (OH) vitamin D levels	Requirement of respiratory support	
	No need (*n*) (%)	Need to support (*n*) (%)
< 20 ng/ml	20 (42.6)	7 (77.8)
≥ 20 ng/ml	27 (57.4)	2 (22.2)

Table 5 Usage of vitamin D supplementation and diagnosis of pneumonia

Usage of vitamin D supplementation	Diagnosis of pneumonia	
	Yes (*n*) (%)	No (*n*) (%)
Yes	4 (22.2)	24 (63.2)
No	14 (77.8)	14 (36.8)

Vitamin D supplementation Average 800–1000 IU/day with cholecalciferol

Median time of hospital stay was 10 days (2–35 days) and there was no difference in the median time of hospital stay between vitamin D subgroups. Outcomes analysis of the patients are presented in Table 3. Although 47% of all patients did not need any respiratory support, 1.8% of cases need invasive mechanical ventilation. Vitamin D status of the cases who need oxygen therapy was found to be lower than those who did not need oxygen but not significant ($p = 0.05$) (Table 4).

Many of the vitamin D–deficient patients (50% of the cases) were on vitamin D supplementation average 800–1000 IU/day with cholecalciferol and were likely to be repleted. The patients with supplementation were found to be higher 25 (OH) vitamin D status than others, which was statistically significant [$p = 0.03$; 25.5 (6–51) ng/mL, 16.9 (6–40.4) ng/mL, respectively]. Pneumonia was observed in 22.2% of the patients who used vitamin D supplementation; 77.8% of the patients who did not use vitamin D supplementation were diagnosed with pneumonia ($p = 0.004$) (Table 5).

Two patients (3.6%) died because of COVID-19 infection; these patients were not followed up in the ICU because they were ineligible to ICU, but during the follow-up severity of lung involvement rapidly increased. Because of the rapid deterioration of the patients, they died before being taken to ICU. 25 (OH) vitamin D status of these cases were found to be less than 20 ng/mL.

Discussion

COVID-19 infection is an increasing global health problem, and many studies have been done to evaluate the modifiable risk factors. Many retrospective studies had determined the correlation between vitamin D status and COVID-19 [28]. Vitamin D is a steroid hormone and plays an important role in bone-mineral metabolism and immunity. Many studies have emphasised a correlation between vitamin D deficiency and various diseases, including systemic infections [29–31]. Vitamin D stimulates secretion of antiviral peptides, which improves physical barrier to viruses. It also stimulates cellular immunity by decreasing the cytokine storm with influence on IFN-γ and TNF-α and regulates adaptive immunity through inhibiting Th1 responses [32, 33].

Cao and his colleagues have reported high incidence of lymphopenia in COVID-19 patients [34]. Lymphocyte percentage in the patients of this study with vitamin D status less than 20 ng/mL was found to be lower than others that is considered as immunomodulatory effect of vitamin D. Lymphopenia can be seen in COVID-19 patients because of many reasons: increased expression of the coronavirus receptor ACE-2 by lymphocytes makes them target for COVID infection. Also, TNF-α, IL-6 and other pro-inflammatory cytokines and elevated lactic acid levels interfere with proliferation of lymphocytes. Liu et al. noticed that the neutrophil-to-lymphocyte ratio (NLR) could be an independent risk factor for critical illness in patients with COVID-19 infection. In that prospective study, 61 COVID-19 cases were evaluated, and the NLR values were found to be higher in the severe or critical group on admission [35]. Median neutrophil/lymphocyte ratio in this study was found to be significantly lower in the group with vitamin D status higher than or equal to 20 ng/mL that can be because of higher lymphocyte counts in this group ($p = 0.018$).

Studies demonstrated that a lower haemoglobin level was associated with more severe COVID-19 disease course. This situation can be attributed to inflammation associated with COVID-19. In acute inflammation, cytokines-induced iron metabolism dysregulation, inhibition of erythropoietin formation, bleeding because of iatrogenic anticoagulation or disseminated intravascular coagulation can contribute to decreased haemoglobin levels [36]. Since ICU patients have a deeper decline in haemoglobin levels, data suggest that the drop is related to the severity of inflammation associated with SARS-CoV-2 infection. In a cross-sectional study including 601 COVID-19 patients it was found that lower haemoglobin levels at presentation were associated with poorer prognosis [37]. In our study, lower haemoglobin levels were found in a group with 25 (OH) vitamin D status less than 20 ng/mL. This finding can support the hypothesis of the correlation between vitamin D deficiency and poorer prognosis.

A prospective observational study with 372 COVID-19 patients demonstrated that vitamin D deficiency was more prevalent in COVID-19 patients with severe clinical picture and serum level of inflammatory markers was found to be higher in patients with vitamin D deficiency [38]. Similarly, Adami et al. found that patients with arterial partial oxygen pressure (PaO_2) < 60 mmHg had significantly lower mean vitamin D status compared to patients with $PaO_2 \geq 60$ mmHg. Also, in the study it was seen that vitamin D deficiency was associated with increased levels of CRP, increased risk of severe systemic inflammatory response and respiratory failure in COVID-19 patients [39]. In our study higher CRP levels were seen in vitamin D–deficient cases ($p = 0.013$). Procalcitonin levels were also found to be higher in the vitamin D–deficient groups that was not statistically significant.

D-dimer levels may increase for many reasons in the majority of patients with COVID-19. Increased pro-inflammatory cells can induce the dysfunction of endothelial cells, resulting in excess thrombin generation [40]. Hypoxia may stimulate thrombosis. Patients with more severe clinical picture of COVID-19 are usually elderly and have many comorbidities; thrombosis risk is higher in these patients. Disseminated intravascular coagulation can be seen in COVID-19 patients [41]. Zhang et al. demonstrated that D-dimer levels greater than 2.0 µg/mL (fourfold increase) on admission could effectively predict in-hospital mortality in patients with COVID-19. In other studies, markedly elevated D-dimer levels were observed in those non-survivors [42, 43].

Some clinical reports demonstrated that deficiency of vitamin D leads to increased thrombosis, however, the exact mechanism is not known [44, 45]. In our study patients with markedly lower vitamin D status (≤ 10 ng/mL) had shown higher D-dimer levels ($p = 0.025$). This suggests that severe vitamin D deficiency can promote thrombosis in COVID-19 patients.

In a retrospective study with 212 COVID-19 patients in South Asian countries, it is demonstrated that there was a significant difference in the mean status of vitamin D within the mild, ordinary, severe and critical cases of COVID-19 [46]. Maghbooli et al. noticed that vitamin D sufficiency was associated with significant lower risk of hypoxia [47]. In a small cohort study it was observed that fewer COVID-19 patients who received oral doses of vitamin D had required subsequent oxygen therapy compared to controls [48]. However, Murai et al. demonstrated that a single dose of 200 000 IU of cholecalciferol did not result in any clinically relevant effects or did not lead to reduce length of hospital stay among hospitalized patients with

moderate-to-severe COVID-19 in the multicenter, double-blind, randomized, placebo-controlled trial. But this finding can be attributed to the heterogeneity of the sample and geographic differences. Also, in this study, the patients were given a dose of cholecalciferol after a relatively long time from symptom onset to randomization [49]. Vitamin D status of the cases who needed oxygen therapy in our study were lower than those who did not need oxygen, which is not statistically significant ($p = 0.05$). Moreover, pneumonia was observed more frequently in patients who did not take vitamin D supplementation than patients who took vitamin D supplementation ($p = 0.004$).

Our study is a real-world study but has retrospective design. Vitamin D status evaluated in this study was measured within the last 6 months prior to the COVID-19 infection to minimise the influence of sunlight exposure or other factors that could affect 25 (OH) vitamin D status. Studies with more recent vitamin D measures, such as taken at the time of hospital admission with symptoms of COVID-19 infection, should be done.

Some potential factors associated with COVID-19 severity and mortality are age, sex, body mass index, comorbidities and co-infection. This study did not assess the impact of comorbidities and co-infection on COVID-19 patients. Risk factors such as socioeconomic status and behavioural factors that can have an impact on the clinical parameters of COVID-19 infections were not recorded. Our study had a single-centre design and had small sample size. Thus, larger studies should be done for more robust conclusions.

Conclusion

Increased inflammatory markers and adverse clinical outcomes of COVID-19 infection in vitamin D–deficient cases can be interpreted as increased risk of mortality and morbidity in COVID-19 patients is associated with lower vitamin D status. Vitamin D status may be a useful prognostic factor. Patients with prior vitamin D supplementation had shown lower incidence of pneumonia in this study. Patient with lower vitamin D status required more ventilation support. Like randomised trials and meta-analysis, our study had shown that vitamin D supplementation had positive effects against COVID infection. Therefore, administration of vitamin D supplementation can be recommended in cases with risk of COVID-19 infection or to COVID-19 patients.

Acknowledgements English language revision of this article has been supported by the Society of Endocrinology and Metabolism of Turkey

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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