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Vitamin D deficiency and clinical severity of Covid-19 infection

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Abstract

Aim: COVID-19 infection which emerged at Wuhan, China in 2019 has been continuing to cause major morbidity and mortality. Vaccination, targeted drug therapy, protective measures and immune system modulation with supportive treatment are desperately needed against this viral pathogen caused international pandemic. Vitamin D is a secosteroid which has immunomodulator, anti-inflammatory, antifibrotic and antioxidant properties. At this study we aimed to investigate correlation between Vitamin D deficiency and disease severity.
Materials and Methods: 225 patients who needed hospitalization has been inducted to the study. Vitamin D levels were measured at the acute period of disease. Patients were divided to two groups; service (n:163) and intensive care (n:62) and mean vitamin D levels between these two groups were compared. Vitamin D levels were classified as follows; severe deficiency: Vitamin$\leq$30 and normal level: vitamin D 30-80 nmol/L. Correlation between Vitamin D level and acute phase reactants which shows infection severity such as Complete blood count, sedimentation, C reactive protein, fibrinogen, ferritin, D-Dimer were investigated.
Results: There was a severe vitamin D deficiency at both service and intensive care groups. Intensive care group had statistically significant lower vitamin D level compared to service group. There was a negative correlation between vitamin D and white blood cell, neutrophil count.
Conclusion: There is a correlation between vitamin D deficiency and COVID 19 clinical severity. This is a modifiable risk factor and vitamin D treatment should be given at both acute disease and preventive treatment. Vitamin D levels should be brought to optimal levels.

Introduction

The new coronavirus disease "COVID-19", caused by the severe acute respiratory syndrome virus (SARS-COV-2), has become a serious public health problem threatening the lives of many people around the world. Preventive measures such as mask usage, hand hygiene, avoiding close contact, early case detection and quarantine application are suggested methods for reducing transmission of disease (1). Clinical features of this viral pathogen mediated disease can be seen as from spectrum of asymptomatic disease, mild upper respiratory tract symptoms to severe acute lung injury, systemic inflammation, multiple organ failure and death (2, 3). Unfortunately, there is not a targeted drug which proven to provide full recovery from disease up to today (4). Vaccination, protective measures and supportive treatment are desperately needed. Complication risk is higher at immunosuppressed patients which suggests the importance of immune system modulation for protection from COVID 19 outbreak (5) . Male gender, age, presence of comorbidity are non-modifiable risk factors for COVID 19 infection severity (6). Smoking, stress, hygiene, physical activity, nutrition status, vitamin and mineral deficiency are among the modifiable risk factors (7, 8). Positive changes of these modifiable risk factors can result improvement of immunomodulation and treatment of disease. Vitamin D deficiency is also a modifiable risk factor, and evidence suggests that vitamin D and its active metabolites have different roles at various systems. Vitamin D is not only a hormone tasked at bone mineral metabolism, but also a secosteroid with immunomodulator, anti-inflammatory, anti-fibrotic and antioxidant properties. Immune system effects of vitamin D are modulated by elevation anti-inflammatory cytokine levels ,Interleukin-4 (IL-4), Interleukin-5(IL-5), Interleukin-10 (IL-10), Transforming Growth Factor Beta (TGF-β) ,via stimulation of T helper 2 (Th 2) cells and it is also regulated by down regulation of pro inflammatory cytokines , Interleukin-2(IL-2), Interleukin-3(IL-3), Interferon gamma (IFN-γ), Tumor Necrosis Factor-alpha (TNF-α), via inhibition of T helper-1 (Th 1) and T helper-17(Th 17) cells (9). Vitamin D also inhibits the maturation of

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dendritic cells by preventing the differentiation of B cell precursors into plasma cells. Cluster of differentiation 4 (CD4) + T cells can transform into regulatory (Treg) and suppressor T cells as well as Th1 and Th2 cells. The active form of vitamin D is 1, 25 dihydroxy vitamin D3, called calcitriol [1, 25 (OH) 2 D3]. It has receptors in almost all tissues in the body. 1, 25 dihydroxy vitamin D3 increases the conversion of CD4 + T cells to Treg cells (10). Studies have shown that vitamin D deficiency has a potential link with systemic infections (11, 12). Vitamin D Increases natural immunity by enhancing mucosal defense against anti-viral peptides . In addition, according to the meta-analysis results of recent randomized studies, it has been shown that vitamin D can reduce the risk of acute respiratory tract infection (13, 14) . Moreover, it has been stated that vitamin D, together with the expression of Vitamin D receptors (VDR), has a suppressive effect on angiotensin converting enzyme 2 (ACE2), blocking the renin-angiotensin system and preventing lung damage caused by SARS-CoV-2 (15). In COVID-19 infection, the innate immune system compensatory increases the release of both proinflammatory and anti-inflammatory cytokines. Pro inflammatory cytokines are responsible for cytokine storm and increase of inflammation severity. Vitamin D, on the other hand, reduces tissue damage caused by SARS-CoV-2 by decreasing the release of proinflammatory cytokines such as TNF-α, INF-γ, and increasing the expression of anti-inflammatory cytokines by macrophages. Vitamin D also reduces the risk of microbial infection and mortality through physical barrier, cellular innate immunity (release of antimicrobials such as cathelicidin and defensins) and adaptive immune mechanisms. Many observational studies and a review of clinical studies showed that vitamin D supplementation reduced the risk of influenza infection, while its deficiency induced acute respiratory distress syndrome. Among the evidence supporting the role of vitamin D in reducing the risk of COVID-19 outbreaks, it was emphasized that the outbreak occurred during a winter when 25-hydroxyvitamin D concentrations were lowest. It has also been hypothesized that vitamin D deficiency may compromise respiratory immune function and increase the risk of COVID-19 severity and death (16, 17).Our aim in the study is to investigate the association between the clinical severity of COVID-19 infection and Vitamin D deficiency in hospitalized patients due to SARS-COV 2.

Material and Method

The study was designed as a retrospective study. Therefore, no randomization, blinding, or masking method was applied. Informed consent form was not required. The study was carried out on the records obtained from the database in the hospital automation system of the patients who applied to the emergency pandemic outpatient clinic of Kırşehir Training and Research Hospital. All of the patients in the study were diagnosed with COVID-19 infection with clinical, laboratory and radiological pulmonary findings and all of them were hospitalized. Data obtained from 225 patients between 1 July 2020 and 31 December 2020. Patients were divided to two groups as COVID service and COVID intensive care. Data were obtained from 163 patients hospitalized in the Covid service and 62 patients hospitalized in the covid intensive care unit. It was found that the patients were evaluated according to the indications for admission to the covid service and intensive care unit, clinical, physical examination and general condition of the patients. It was found that those who were hemodynamically unstable, whose saturation did not increase (spo2 <90) despite the administration of mask O2 at 4-10 liters / minute, and those who needed non-invasive or invasive mechanical ventilation were admitted to intensive care, and those whose clinical situation were more stable were admitted to the service. Age, gender and chronic diseases of the patients were recorded. Comlete blood count(CBC),white blood cell (wbc), neutrophil (neu), lymphocyte (ly), hemoglobin(hgb), hematocrit (HCT), C-Reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen, D-Dimer(DD) ferritin and Vit D levels, which are examined during hospitalization, were examined.
As the inclusion criteria for the study;

- Patients with Polymerase Chain Reaction (PCR) positive, with involvement in Thorax Computed Tomography (CT) findings, who were admitted to the covid service and whose Vit-D level was tested during acute illness
- PCR positive, with thorax CT involvement, hospitalized in the covid intensive care unit and Vit-D levels tested during acute illness As exclusion criteria;
- PCR positive patients with involvement in thorax CT but not requiring hospitalization
- Patients who did not diagnosed with COVID-19, PCR negative and patients with atypical thorax CT findings

First of all, the age, gender distribution, and chronic diseases (Hypertension (HT), Diabetes Mellitus (DM), Chronic Obstructive Pulmonary Disease (COPD), Chronic Renal Failure (CKD), Alzheimer) and mean vitamin D levels of the patients hospitalized in the service and intensive care unit were compared. The first measure of clinical severity in the study was the association of patients admitted to the service and intensive care unit according to their mean Vit-D levels. Later, both groups were classified based on total vitamin D levels. This classification was carried out according to national guidelines and laboratory standards. Vitamin D deficiency were classified as Vitamin D level $\leq$30 nanomoles per Litre (nmol/L) and normal Vitamin D level was classified as 30-80 nmol/L (18). This classification is correlated with acute phase reactants, exitus and cure ratios which are the indicators of the clinical severity of COVID-19 infection during hospitalization. Significant results obtained from this association were considered as a secondary criterion of clinical severity.

Ethics Committee

Our study was ethically approved by the Kırsehir Ahi Evran University Faculty of Medicine Local and Central Ethics committees on 09.03.2021 in accordance with the decision number of 2021-05/53.

Statistical Analysis

Before statistical analyses, the data set was examined in terms of missing data and outliers, and it was determined that there was no missing data in any variable in the data set. In addition, the presence of outliers was investigated with the help of box-line graphs obtained for each variable, and in the variables with outliers, the outliers were assumed to be informative for the research and nonparametric hypothesis tests, which are robust statistical methods to outliers, were applied in the comparison of these variables. Mean ± standard deviation(SD) and

median, minimum and maximum values were given for quantitative variables, while frequencies (n) with percentages (%) were reported for categorical ones.. Normality assumption was tested via Kolmogorov-Smirnov Test. The assumption of homogeneity of variance was examined with Levene's test, for quantitative data in group comparisons t-test or Mann-Whitney U-Test were used while Chi-Square Analysis was used for qualitative data. R Programming Language (version 4.0.4) (R Foundation for Statistical Computing, Vienna, Austria) was used for all analysis. Significance level was taken as 0.05.

Results

Results suggest that no statistically significant difference was found in terms of age of the patients in service (65.681 ± 15.335) and in Intensive Care groups (69.508 ± 12.645) (p = 0.089). Moreover, no statistically significant difference was detected between gender and service – Intensive Care groups (p = 0.07). On the other hand, there is statistically significant difference between service and Intensive Care groups in terms of Vitamin D values, that is; patients in Intensive Care groups (12.4 ± 7.151) were found to have significantly lower Vitamin-D values compared to patients in service (15.64 ± 13.121) (p = 0.019) (Table 1).

An association was found between service –Intensive Care groups and COVID patients with chronic diseases – without chronic diseases. It's observed that COVID patients without any chronic diseases were significantly more hospitalized in service (p = 0.013). On the other hand, proportion of patients diagnosed with CAD (p = 0.004), COPD (p = 0.006) and Alzheimer (p = 0.009) were observed to be significantly higher in Intensive Care groups; while propotion of patients diagnosed with CRF (p = 0.007) was significantly higher in service group. However, proportion of DM (p = 0.461) and HT(p = 0.095) were found to be similar in these groups. There were no statistically significant difference between Vit-D levels (Vit-D $\leq$ 30 and Vit-D > 30) in terms of age (p = 0.893) and gender (p = 0.485). On the other hand, WBC (p = 0.012) and Neu (p = 0.031) values were observed to be significantly higher in Vit-D$\leq$30 group. However, the other acute-phase reactant biomarker values were observed to be similar across Vit-D levels (p>0.05 for all). Furthermore, there is no statistically significant association between Vit-D levels and mortality-cure groups (p = 0.115) (Table 2).

Discussion

Our study was carried out on fully inpatients. Severe vitamin D deficiency was detected in 200 of 225 patients. It was found that patients with the indication for admission to intensive care had more severe clinical severity and their vitamin D levels were significantly lower (p <0.05) (Table 1).In a study conducted by Radojkovic et al., Vitamin D levels were shown to be lower in hospitalized patients (19) . Thus, it is revealed that as vitamin D levels decrease, hospitalization and clinical severity of COVID-19 increases. Katz et al also showed that vitamin D deficient patients is 4.6 times more likely to become infected with COVID-19 (20) . In our study, the primary point of the clinical severity of the patients is the need for intensive care. As vitamin D levels decreased, the rate of hospitalization in intensive care increased. However, we are aware that some chronic diseases (CAD, COPD and Alzheimer's) are higher in patients (Table 1). Of course, this is an important factor that determines the clinical severity. However, it should not be ignored that vitamin D deficiency contributes to this situation. Because in a retrospective cohort study conducted in Indonesia, 780 cases were examined, and mortality was found to be high in elderly and male patients with chronic diseases and Vitamin D deficiency. This study revealed that, after adjusting for confounding factors (age, gender, and comorbidity), vitamin D deficiency was strongly associated with COVID-19 mortality (21).However ,number of studies have shown that vitamin D deficiency is potentially linked to systemic infections (11, 12) . In a study by Verdoia et al., vitamin D deficiency was shown to be significantly associated with Coronary Artery Disease (CAD) severity (22)A negative correlation was found between vitamin D deficiency and type-2 DM, HT and Alzheimer's diseases (23, 24) .While the presence of chronic diseases poses a significant risk for morbidity and mortality in COVID-19 infection, the presence of vitamin D deficiency both negatively affects the prognosis of chronic diseases and increases the severity of COVID-19. For these reasons, vitamin D deficiency should not be ignored. The second important point is the negative correlation between Vitamin D levels and WBC and NEU levels (Table 2). As the vitamin D levels decreased, the severity of the infection increased. However, no correlation was found between ex and healing rates. It was observed that the rate of recovery was higher in the group with vitamin D deficiency (Table 2). However, this situation may be attributed to the fact that in the whole sample (225 persons) those with low vitamin D level (n: 200, 90.9%) are significantly higher in number than those with high vitamin D level (n: 25, 9.1%). Because when the treatment conditions of both groups were examined, different conservative treatments such as high-dose steroid or tocilizumab were not applied, especially for cytokine storm. Also, in a study conducted with large participants in a European population, it was found that there is a negative correlation between vitamin D deficiency and morbidity and mortality (25). It is also interesting that Italy and Spain are the European countries most severely affected by COVID-19 and have the lowest hypovitaminosis D (26). In a retrospective study of 186 positive cases and 2717 negative cases in Belgium, significant Vit-D deficiency was reported in COVID-19 patients compared to control subjects (27).We are aware that our study has some limitations due to its retrospective nature. The effects of vitamin D deficiency on mortality could be observed by giving controlled treatment in the initial period of COVID-19. Controlled vitamin D supplements should be performed by public health institutions within the scope of preventive treatment. Because there are studies showing that replacement of vitamin D deficiency reduces the frequency and severity of acute respiratory infections (28, 29). In addition, its immunomodulatory and anti-oxidant effects can be achieved with preventive and controlled treatments. The host defense barrier against the disease can be created earlier and stronger with vitamin D. Optimal vitamin D levels both activate the innate immune system and induce the long-term adaptive immune system (30, 31) . Thus, positive effects can be observed not only in case of acute illness, when there is extensive damage in the organism, but also in preventing this damage. In addition, studies have shown that it strengthens the innate immune response, reduces viral replication, inhibits viral entry into cells, and shows anti-bacterial activity by induction of cathelicidin and defensins (32). The results of the study of Katz et al. confirm this situation. This is because as vitamin D levels decrease, the risk of infection increases (20). In the stud-

Table 1. Vitamin D levels, age and gender distribution and comorbidities of service and intensive care patients

Variable	Covid Service (n:163)		Covid Intensive Care (n:62)		p-value
	Mean ± SD	Median [Min, Max]	Mean ± SD	Median [Min , Max]	
Age	65.681 ± 15.335	66 [19 - 104]	69.508 ± 12.645	70 [37 - 89]	0.089
Vit-D (nmol / L)	15.64 ± 13.121	12 [0 - 91]	12.4 ± 7.151	11 [0 - 34]	0.019
Female/Male (%)	(%46)/(%54)		(%33)/(%67)		0.07
Healthy	37 (%22.7)		6 (%9.7)		0.013
DM	59 (%36.2)		22 (%35.48)		0.461
HT	84 (%51.5)		38 (%61.29)		0.095
CAD	35 (%21.5)		24 (%38.71)		0.004
CRF	15 (%9.2)		0 (%0)		0.007
COPD	16 (%9.8)		14 (%22.58)		0.006
Alzheimer	4 (%2.45)		6 (%9.7)		0.009

CAD(Coronary Artery Disease), COPD (Chronic Obstructive Pulmonary Disease (COPD), CRF (Chronic Renal Failure), DM (Diabetes Mellitus), HT (Hypertension), Vit-D(Vitamin D)

Table 2. Relationship between vitamin D levels, acute phase reactants, mortality / healing and comorbidity distribution

Acute-phase	Vit-D $\leq$ 30nmol/L n:205		Vit-D :30-80 nmol/L n:20		p-value
	Mean ± SD	Median [Min , Max]	Mean ± SD	Median [Min , Max]	
Age	66.765 ± 14.780	67 [19 - 104]	66.3 ± 14.495	64.5 [32- 90]	0.893
Female/Male	85(%42)/120(%58)		10(%50)/10(%50)		0.485
WBC(10^3/µL)	8.304 ± 5.879	6.655 [2.07 - 43.65]	5.412 ± 2.377	4.55 [2.23 - 11.46]	0.012
Hb(g/dl)	12.89 ± 2.309	13.3 [4.1 - 17.4]	12.58 ± 2.544	12.4 [8.5 - 16.9]	0.599
HCT(%)	38.855 ± 6.593	39.35 [12.8 - 56.6]	37.975 ± 7.083	38.55 [24.4 - 51.2]	0.625
Neu(10^3/µL)	6.508 ± 4.884	5.02 [0.84 - 30.92]	4.439 ± 2.963	3.5 [1.21 - 12.2]	0.031
Ly(10^3/µL)	1.248 ± 2.386	0.87 [0.25 - 32.96]	1.051 ± 0.706	0.93 [0.07 - 3.19]	0.983
Plt(10^3/µL)	227.23 ± 98.744	211.5 [1 - 610]	204.75 ± 80.31	176 [65 - 364]	0.409
CRP(mg/L)	113.33 ± 78.873	104 [2 - 464]	116.05 ± 102.521	99 [4 - 433]	0.803
ESR(mm/h)	44.31 ± 24.603	44 [1 - 156]	45.88 ± 29.895	47 [5 - 88]	0.815
Ferritine(ng/mL)	549.944 ± 802.298	376.5 [7 - 7500]	550.444 ± 686.642	224.5 [28 - 2205]	0.547
DD(mg/L)	5.416 ± 29.918	0.728 [0.2 - 341]	1.885 ± 3.962	0.798 [0.2 - 15]	0.988
Fibrinogen(mg/dL)	534.450 ± 155.054	536 [3.73 - 896]	559.444 ± 160.014	561 [281 - 977]	0.641
Mortality	53 (26.5)		9 (45)		0.115
Healing	147 (73.5)		11 (55)		

CRP (C-Reactive protein),DD(D-DIMER), ESR(erythrocyte sedimentation rate), Hematocrit(HCT), Hb(Hemoglobin), Ly(Lymphocyte), Neu(Neutrophil), Plt(Platelet), Vit-D(Vitamin-D), WBC(WhiteBloodCell)

ies by Greiller and Grant et al., vitamin D has been shown to reduce proinflammatory cytokines, including TNF-6 and IL-6 (16, 33). Thus, the severity of inflammation decreases depending on the cytokine storm. In a small cohort observational study at an academic hospital in Singapore, 43 COVID-19 patients were treated with combined oral doses of vitamin D (1000 IU), Mg (150 mg), and vitamin B12 (500 µg) and it was reported that patients receiving vitamin D and B12 required less oxygen therapy compared to controls. (34)In addition, vitamin D supplementation was found to increase anti-oxidant gene expression. The optimal level of anti-oxidant capacity is extremely important in the fight against infection (35). In our study, there were no extremes or outliers in acute phase reactants. Because, depending on the clinical severity of the acute infection, severe low or high (leukopenia-leukocytosis, neutropenia-neutrophil, thrombocytosis-thrombocytopenia, etc.) may develop. When study is examined in terms of vitamin D levels; one patient with 90 nmol/l and with 0 nmol/l were detected respectively (table 2). 0 nmol/l value already fits the deficiency classification. There are some studies suggesting that optimal vit-D should be 50-125 nmol/L for skeletal health. Therefore, we did not see any drawbacks in including this extreme value in the study. Vitamin D deficiency is seen in more than one billion people around the world. Unfortunately, this deficiency has not yet been given enough importance. It can be used as a preventive and supportive method in the treatment management of COVID-19 infection. It is a very important risk factor which is easily modifiable. Vitamin D levels should be brought to the optimal level of 50-125 nmol / L(36). Preventive doses to be used should be 100 microgram (µg) vit-D3 / day. Otherwise, undesirable side effects such as hypercalcemia, hypercalciuria and renal stones may develop (37).

Conclusion

Serious vitamin D deficiency has been detected in patients requiring hospitalization due to COVID-19 infection. On the other hand, patients with severe clinical severity and in need of intensive care were observed to have significantly lower vi-

tamin D levels compared to patients hospitalized in the normal ward. There is an important association between vitamin D deficiency and clinical severity of COVID-19.

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