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CLINICAL STUDY

The relationship between vitamin D and the severity of COVID-19

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ABSTRACT

AIM: Vitamin D, which has immunomodulatory effect, can reduce risk of infections and concentrations of pro-inflammatory cytokines. The aim of this study was to investigate the relationship between the levels of vitamin D and severity of COVID-19.

METHODS: A total of 204 patients with COVID-19 disease were enrolled in the study. All patients had viral pneumonia, which was confirmed with chest computer tomography. All cases were divided in two groups- mild (outpatients); and serious (inpatients)- according to their clinical and laboratory data. Serum vitamin D levels were measured by chemiluminescence method.

RESULTS: Vitamin D deficiency was found in 41.7 % (n = 85) of cases and insufficiency was found in 46.0 % (n = 94), while in 12.3 % (n = 25) of cases normal vitamin D levels were found. The odds of having a serious clinical outcome were increased for vitamin D insufficiency patients 5.604 times (%95 CI:0.633–49.584) and for vitamin D deficiency patients 38.095 times (%95 CI:2.965–489.50) for each standard deviation decrease in serum 25(OH)D.

CONCLUSION: Adequate levels of vitamin D could suppress inflammation and reduce the severity of COVID-19. Vitamin D supplementation may have an important role in decreasing the impact of the pandemic *(Tab. 5, Fig. 2, Ref. 27)*. Text in PDF *www.elis.sk*

KEY WORDS: COVID-19, CRP, d-dimer, ferritin, vitamin D.

Introduction

Corona virus disease (COVID-19), first seen in the Wuhan region of China in December 2019, is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) (1). Coronaviruses are enveloped viruses with a single stranded RNA genome. COVID-19, which is transmitted from person to person, shows serious progression from simple symptoms of upper respiratory tract infections such as fever and cough to viral pneumonia and acute respiratory distress syndrome (ARDS). The binding of SARS-CoV-2 in the respiratory tracts of infected patients in order to enter their host cells is through angiotensin converting enzyme 2 (ACE2) receptors, which play an important role in the pathogenesis of infection (2).

The fact that there is a significant difference in COVID-19 mortality among countries, particularly countries in the southern hemisphere which have a relatively low mortality rate, brought with it a new debate. When mortality per million is evaluated by latitudes, it is seen that all countries below 35 degrees have relatively low mortality (3). People who live north of the 35th degree are less exposed to sunlight and do not receive sufficient sunlight to retain adequate vitamin D levels during winter season when the pandemic occurs (3). This makes the possible role of vitamin D prominent in determining the clinical status of patients in COVID-19.

Vitamin D is a secosteroid that has classical effects on calcium and bone homeostasis as well as plays an important role in the immune system and has a wide spectrum of immunomodulatory, anti-inflammatory, antifibrotic, and antioxidant actions (2,4). It has been reported that vitamin D helps to increase the production of anti-inflammatory molecules and reduce the production of pro-inflammatory molecules (5). Studies have also shown that vitamin D may alter the immune system response through its effect on the production of immune molecules known as cytokines (5). There is important experimental data showing that vitamin D has a significant role in regulating and suppressing the inflammatory cytokines response to various pathogens, including respiratory viruses (3). In an experimental study, vitamin D, which has immunomodulatory properties, has been shown to reduce the effects of the angiopietin(Ang)-2-Tie-2 signal pathway and renin-angiotensin pathway, thereby reducing acute lung damage due to lipopolysaccharide in mice (6). Nevertheless, there is little evidence that vitamin D can protect against infection, and it is assumed that vitamin D will not be able to protect against SARS-CoV-2 infection, but may be very important in the prevention of cytokine storm and ARDS, which is the cause of mortality (3).

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The aim of this study was to investigate the relationship between vitamin D levels and severity of COVID-19 disease.

Materials and methods

Subjects

This study was carried out in patients treated at the Prof.Dr. Cemil Tascioglu City Hospital. A total of 204 patients with the COVID-19 were included in the current study. According to the treatment protocol of our hospital COVID-19 patients who are diagnosed as critical or serious are treated in the hospital while others are treated at home. All included cases were divided in two groups -Group A, mild (outpatients); and Group B, serious patients (inpatients)-according to their clinical and laboratory data. Although all patients underwent PCR test, only 22 patients were confirmed with PCR test. All patients had viral pneumonia, which was confirmed with chest computer tomography, with fever and other respiratory symptoms and were treated as a covid-19 patient.

Vitamin D status of the patients was classified according to their serum 25(OH)D level. 25(OH)D of < 10 µgr/L was considered vitamin D deficiency; 25(OH)D of 10–20µg/L was considered insufficient; and, 25(OH)D of> 20µg/L was considered normal (7).

Patients who were starting vitamin D drugs at the hospital were excluded from the study.

Sample collection and preparation

Blood samples were collected in anticoagulant-free tubes. Immediate centrifugation (3500 rpm) was performed for 10 minutes and then the serum was analysed. Serum vitamin D levels were measured by chemiluminescence method with an autoanalyzer (Beckman Coulter in DXI 800). Other biochemical parameters were determined with commercial kits and an autoanalyzer (Beckman Coulter in DXI 800).

Ethics

All the participants were informed about the survey and signed and dated the consent form of free will. The protocol was approved by the Ethics Committee of Prof. Dr. Cemil Tascioglu City Hospital and was conducted in accordance with the Declaration of Helsinki.

Statistics

In descriptive statistics, normally distributed parameters were given as mean ± standard deviation while non-normally distributed parameters were given as median (25th–75th percentile). Frequency and percentage were used for categorical variables. Student-t test or Mann-Whitney U test was used as appropriate for comparing quantitative data while Pearson's chi-squared test was used for the comparison of qualitative data. One-way Anova test was used in comparisons of three or more groups with normal distribution and Bonferroni test was used in binary comparisons; Kruskal-Wallis test was used for comparisons of three or more groups that did not show normal distribution and Bonferroni-Dunn test was used for binary comparisons. Multivariate logistic regression was used to explore the association between biochemical parameters and clinical outcomes of the cases. Spearman correlation test was used to evaluate the correlations between 25(OH)D and the other parameters. All statistical analyses were performed using NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah, USA) software program. A p value below 0.05 was considered statistically significant.

Tab. 1. Demographic values of patients.

		n	%
Age (year)	Min–Max (Median)	23–94 (59)	
	Mean±Sd	57.55±17.89	
Gender	Female	103	50.5
	Male	101	49.5
Clinical status	Inpatient	162	79.4
	Outpatient	42	20.6
25(OH)D	Min–Max (Median)	0.2–44.1 (10.8)	
	Mean±Sd	12.18±7.18	
	Deficient (<10 µg/L)	85	41.7
	Insufficient (10–20 µg/L)	94	46.0
	Normal (>20 µg/L)	25	12.3

Tab. 2. The relationship between patients clinical outcomes with demographic and biochemical parameters.

		Clinical Status		p
		Inpatient (n=162)	Outpatient (n=42)	
Age (year)	Min–Max (Median)	24–94 (63.5)	23–80 (42)	[a]0.001**
	Mean±Sd	61.51±16.80	42.29±13.22	
Gender; n (%)	Female	82 (50.6)	21 (50.0)	[b]0.943
	Male	80 (49.4)	21 (50.0)	
25(OH)D (µgr/L)	Min–Max (Median)	0.2–36.4 (10)	9–44.1 (15.5)	[c]0.001**
	Mean±Sd	10.71±6.10	17.84±8.24	
Vitamin D status; n (%)	Deficient	80 (49.4)	5 (11.9)	[b]0.001**
	Insufficient	72 (44.4)	22 (52.4)	
	Normal	10 (6.2)	15 (35.7)	
Ferritin (µgr/L)	Min–Max (Median)	2.2–4721 (150.8)	7.6–338.4 (68.6)	[c]0.001**
	Mean±Sd	335.16±580.7	94.06±88.51	
CRP (mg/L)	Min–Max (Median)	0.7–372.2 (67.5)	0.4–19.3 (2.4)	[c]0.001**
	Mean±Sd	87.54±80.23	3.83±4.05	
D-dimer (ug/L)	Min–Max (Median)	125–8840 (907.5)	80–805 (291.5)	[c]0.001**
	Mean±Sd	1352.55±1504.62	337.64±192.04	
ALT (U/L)	Min–Max (Median)	4–246 (20)	8–184 (23)	[c]0.282
	Mean±Sd	31.23±32.15	32.29±29.98	
AST (U/L)	Min–Max (Median)	7–157 (23.5)	14–74 (20.5)	[c]0.190
	Mean±Sd	30.82±21.02	25.02±12.09	
Leukocyte ($\times10^3/mm^3$)	Min–Max (Median)	2.4–76.5 (7.2)	3.9–13.8 (7.5)	[c]0.273
	Mean±Sd	8.01±6.33	7.83±2.19	
Lymphocyte ($\times10^3/mm^3$)	Min–Max (Median)	0.2–7.3 (1.3)	0.7–3.8 (2.1)	[c]0.001**
	Mean±Sd	1.48±0.83	2.18±0.72	
Platelet ($\times10^3/mm^3$)	Min–Max (Median)	4.7–925 (235)	153–421 (240)	[c]0.756
	Mean±Sd	252.16±113.23	250.67±68.83	

[a]Student t Test, [b] Pearson's chi-squared Test, [c]Mann–Whitney U Test, **p<0.01

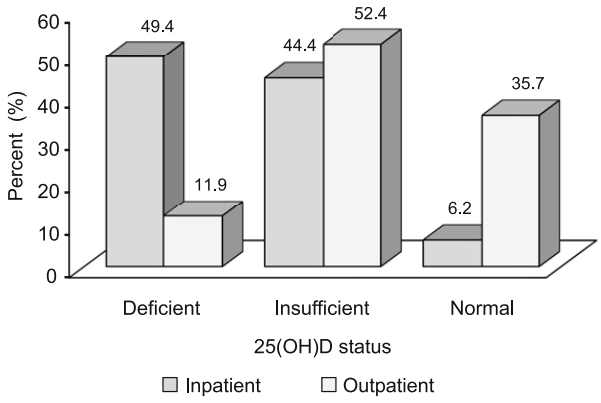

Fig. 1. Clinical status of patients according to vitamin D levels.

Data availability

The data associated with the paper are not publicly available but are available from the corresponding author on reasonable request.

Results

The demographic values of the patients are shown in Table 1. Of the 204 cases of COVID-19, 42 (20.6 %) were outpatients (mild cases), and 162 (79.4 %) were inpatients (serious cases). Mean serum 25(OH)D level was 12.18±7.18 µg/L. Vitamin D deficiency was found in 41.7 % (n = 85) of cases and insufficiency was found in 46.0 % (n = 94), while in 12.3 % (n = 25) of cases normal vitamin D levels were found.

The relationship between patients clinical outcomes with demographic and biochemical parameters are given Table 2. No significant differences were observed between the inpatient and the outpatient groups with regards to gender, ALT, AST, leukocyte, and platelet levels (p>0.05). There were significant differences between the two groups according to age, 25(OH)D, ferritin, CRP, d-dimer, and lymphocyte. The inpatients group had significantly lower levels of 25(OH)D (p=0.001) and lymphocyte (p=0.001), while had significantly higher ferritin (p=0.001), CRP (p=0.001), and d-dimer levels (p=0.001) than those in the outpatient group. According to the clinical status, vitamin D deficiency was higher in patients who were hospitalized, while vitamin D normal status was higher in the outpatient patients (Fig. 1).

The relationship between vitamin D status and other parameters are given Table 3. There was no significant difference in the age and gender according to vitamin D levels. According to the vitamin D status, ferritin and CRP levels of the patients were found statistically different (p=0.034, p=0.001, respectively). As a result of the binary comparisons made to determine the group that creates the difference, ferritin and CRP levels in the cases with vitamin D deficiency were higher than those with vitamin D insufficiency and normal vitamin D levels (p=0.048, p=0.023; p=0.013; p=0.001, respectively), while no significant difference was found for ferritin levels of cases with normal vitamin D levels (p>0.05). In terms of vitamin D status, the lymphocyte counts of the patients with vitamin D deficiency were lower than those with normal vitamin D levels (p=0.002) while there were no significant differences between the lymphocyte counts of other groups (p>0.05).

The correlations between the levels of vitamin D and other parameters in all patients are shown in Table 4. Vitamin D was negatively correlated with ferritin, CRP, and d-dimer (r = –0.236, p=0.001; r = –0.353, p=0.001; r = –0.185; p=0.008, respectively) (Figs 2 A,B,C). Positive correlations were observed between vitamin D levels and the lymphocyte and leukocyte counts (r = 0.294, p=0.001; r = 0.143,

Tab. 3. The relationship between vitamin D status and other parameters.

		Vitamin D status			p
		Deficient(n=85)	Insufficient (n=94)	Normal (n=25)	
Age (year)	Min–Max (Median)	24–88 (61)	23–94 (57)	28–82 (50)	[d]0.283
	Mean±Sd	59.18±16.32	57.37±19.46	52.72±16.51	
Gender; n (%)	Female	45 (52.9)	44 (46.8)	14 (56.0)	[b]0.601
	Male	40 (47.1)	50 (53.2)	11 (44.0)	
Ferritin (µgr/L)	Min–Max (Median)	8.4–4721 (174.9)	2.2–4260 (109.7)	9.1–811.7 (81.2)	[c]0.034*
	Mean±Sd	356.60±605.46	256.35±507.75	153.54±186.66	
CRP (mg/L)	Min–Max (Median)	0.4–372.2 (72.5)	0.4–355.7 (26.4)	0.8–193.5 (4.8)	[c]0.001**
	Mean±Sd	91.79±86.33	60.27±71.75	35.01±59.83	
D-dimer (ug/L)	Min–Max (Median)	111–8720 (745)	112–8840 (742)	80–2760 (630)	[c]0.054
	Mean±Sd	1375.94±1668.71	1061.88±1258.33	660.88±582.59	
ALT (U/L)	Min–Max (Median)	4–246 (19)	5–184 (25.5)	10–105 (20)	[c]0.099
	Mean±Sd	27.53±30.67	35.78±33.73	28.52±25.17	
AST (U/L)	Min–Max (Median)	7–157 (22)	9–112 (24)	12–47 (20)	[c]0.593
	Mean±Sd	30.05±21.43	30.77±19.95	23.92±8.43	
Leukocyte ($\times10^3/mm^3$)	Min–Max (Median)	2.4–22.7 (6.8)	2.6–76.5 (7.6)	3.7–16 (7.5)	[c]0.043*
	Mean±Sd	7.08±3.02	8.79±7.73	7.93±2.67	
Lymphocyte ($\times10^3/mm^3$)	Min–Max (Median)	0.3–3.3 (1.3)	0.2–7.3 (1.5)	0.7–3.5 (2)	[c]0.002**
	Mean±Sd	1.42±0.64	1.70±1.00	2.01±0.72	
Platelet ($\times10^3/mm^3$)	Min–Max (Median)	35–577 (223)	4.7–925 (242.5)	134–421 (261)	[c]0.158
	Mean±Sd	235.71±99.34	263.34±115.62	262.88±78.02	

[d]Oneway ANOVA Test, [c]Kruskal–Wallis Test, **p<0.01, *p<0.05

Tab. 4. Correlation analysis (r) between vitamin D and other laboratory parameters.

		Levels of vitamin D		
		Overall (n=204)	Inpatient (n=162)	Outpatient (n=42)
Ferritin (µgr/L)	r	–0.236	–0.156	–0.060
	p	0.001**	0.047*	0.706
CRP (mg/L)	r	–0.353	–0.180	–0.104
	p	0.001**	0.022*	0.513
D-dimer (ug/L)	r	–0.185	–0.032	0.259
	p	0.008**	0.683	0.098
ALT (U/L)	r	0.108	0.105	–0.050
	p	0.124	0.185	0.752
AST (U/L)	r	–0.025	0.020	–0.001
	p	0.722	0.804	0.997
Leukocyte ($\times 10^3/mm^3$)	r	0.143	0.149	–0.068
	p	0.042*	0.059	0.668
Lymphocyte ($\times 10^3/mm^3$)	r	0.294	0.162	0.065
	p	0.001**	0.041*	0.684
Platelet ($\times 10^3/mm^3$)	r	0.125	0.117	0.175
	p	0.075	0.140	0.269

R– Spearman's correlation coefficient, *p<0.05, **p<0.01

p=0.042, respectively) (Fig. 2 D). No correlations were observed between vitamin D and ALT, AST, and platelet levels in all patients.

A multivariate logistic regression analysis is given in Table 5. The effects of 25(OH)D, CRP, and D-Dimer levels on the severity of the disease were found statistically significant (p <0.05). A logistic regression analysis showed that the odds of having a serious clinical outcome (inpatient) rather than a mild outcome (outpatient) were increased for vitamin D insufficiency patients approximately 5.604 times (%95 CI:0.633–49.584) and for vitamin D deficiency patients 38.095 times (%95 CI:2.965–489.50) for each standard deviation decrease in serum 25(OH)D. For each standard deviation increase in serum CRP, the odds of having a serious clinical outcome rather than a mild outcome were increased approximately 1.256 times (%95 CI:1.065–1.481). The odds of having a serious clinical outcome were increased approximately 1.004 times (%95 CI: 1.001–1.008) for each standard deviation increase in d-dimer levels.

Ferritin and lymphocyte levels were effective factors influencing the severity of the disease in univariate analysis, whereas they were not found significant in multivariate logistic regression analysis (p>0.05). The age variable is included in the model to adjust other variables.

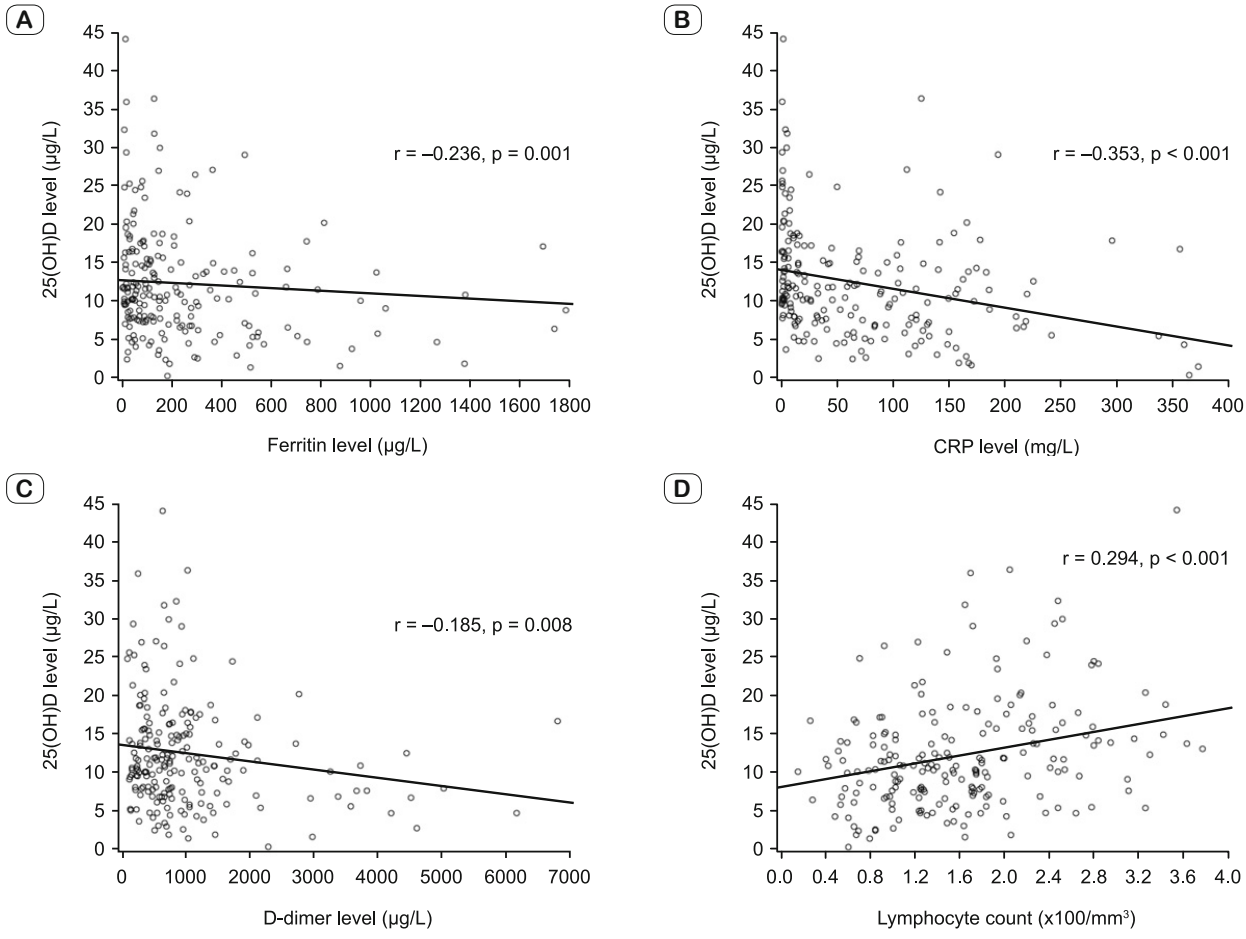

Fig. 2. The relationship between vitamin D with CRP levels (A), ferritin levels (B), d-dimer levels (C), and lymphocyte counts (D) in all patients.

Tab. 5. Logistic regression analysis of laboratory risk factors and severity of disease.

	p	ODDS	%95 CI	
			Lower	Lower
Age	0.951	1.001	0.955	1.051
25(OH)D (normal)	0.018*			
Insufficient (10–20 μg/L)	0.121	5.604	0.633	49.584
Deficient (<10 μg/L)	0.005**	38.095	2.965	489.508
Ferritin (μg/L)	0.368	0.997	0.991	1.003
CRP (mg/L)	0.007**	1.256	1.065	1.481
D-dimer (μg/L)	0.024*	1.004	1.001	1.008
Lymphocyte ($\times 10^3/mm^3$)	0.071	0.502	0.238	1.062

**p<0.01, *p<0.05

Discussion

Research focusing on the role of vitamin D, which can modulate the reaction against body infections, in the immune system have become increasingly important during the COVID-19 pandemic period.

The natural immune system stimulates pro-inflammatory and anti-inflammatory cytokines in response to viral and bacterial infections, as observed in COVID-19 patients (8). It is reported that vitamin D reduces the production of pro-inflammatory Th1 cytokines, such astumor necrosis factor and interferon-γ and increase the expression of anti-inflammatory cytokines by macrophages (8,9). It is known that COVID-19 infection is associated with the increased production of pro-inflammatory cytokines, C-reactive protein (CRP), and ferritin, increased risk of pneumonia, acute respiratory distress syndrome, and heart failure (10,11). Adequate levels of vitamin D can contribute to reduction of severity of the disease and the incidence of cytokine storm in COVID-19 patients.

In this study, we investigated the relationship between vitamin D levels and severity of disease in COVID-19 patients. In the present study, serum 25(OH)D levels in the outpatients of COVID-19 were determined to be significantly higher than in the inpatients of COVID-19 (p<0.001).

There are many studies that review the relationship between vitamin D and COVID-19 (12–14). Alipio (14) conducted a multinomial logistic regression to investigate the association between serum 25(OH)D level and clinical outcomes of 212 cases with laboratory-confirmed infection of SARS–CoV2. The author reported that a decrease in serum 25(OH)D level could worsen clinical outcomes of COVID-2019 patients (14). Ilie et al (12) searched the number of cases of COVID-19/1 million population in each of European countries and mortality caused by this disease/1 million population. They found significant relationships between vitamin D levels and the number COVID-19 cases and especially the mortality caused by this infection (12). Conversely, a study used UK Biobank data (2006–2010) for vitamin D status, and ethnicity and correlated it with COVID-19 cases (15). They reported that their findings do not support a potential link between vitamin D concentrations and risk of COVID-19 infection. On the other hand, recent studies have described the role of vitamin D in viral diseases such as respiratory syncytial virus (RSV) and rotavirus (16,17). Vitamin D regulates antimicrobial peptides (cathelicidin and β-defensin) which reduced other viruses' replication such as RSV and rotavirus (16,17). Our results showed that majority of the COVID-19 patients with higher vitamin D levels did not need hospitalization during their treatment. Although vitamin D level alone is not enough to prevent the infection, our results suggest that it may have a role to reduce replication of the SARS-CoV2 virus. We think that in vitro studies are required to confirm this result.

In our study, a logistic regression analyses indicated that the odds of having a serious clinical outcome increase when serum 25(OH)D level decreases. Alipio (14) has also found a similar result which is consistent with our findings. The one of the most notably findings in this study is that the odds of having a serious clinical outcome were increased approximately 38 times for each standard deviation decrease in serum 25(OH)D in the vitamin D deficiency patients. This suggests that vitamin D deficiency may play a role in the increase of the disease severity.

It has been determined that inflammatory factors such as IL-6, serum ferritin, and CRP are elevated in patients with COVID-19 (18). CRP and ferritin are extensively used in clinical practice as inflammatory plasma markers. In our study, CRP and serum ferritin were increased above normal levels in all patients. In this study, the serum ferritin and CRP levels in outpatients were found to be notably higher than the inpatients. Niet al (19) have found higher ferritin and CRP levels in severe COVID-19 patients and Zhou et al (20) have found results which are consistent with our study. In our study, vitamin D showed a negative correlation with ferritin and CRP. On the basis of vitamin D status, ferritin and CRP levels in the cases with vitamin D deficiency are higher than those with vitamin D insufficiency and normal vitamin D levels while no significant difference was found for ferritin levels of cases with normal vitamin D levels. Vitamin D has been demonstrated to downregulate the production of inflammatory cytokines, such as TNF alpha and IL-6, while increasing inhibitory cytokines (19). Adequate level of vitamin D can contribute to reduction of inflammation and cytokine production in severe COVID-19 disease. Our results support the hypothesis that vitamin D can have a possible role in the reduction of the level of inflammatory markers in serious COVID-19 disease.

Thrombotic complications are common in COVID-19 patients and over half of those patients have elevated D-dimer levels (21,22). The anti-thrombotic effects of vitamin D on the thrombogenic and anti-thrombogenic components of the coagulation system have been shown by several studies (23–25). In our study, we found that d-dimer levels of inpatients were significantly higher than those in outpatients. In addition, statistically significant negative correlation was found between vitamin D and d-dimer levels of all the cases. Our results were consistent with other studies as expected (10, 11). It is indicated that increased d-dimer levels have been related to poor prognosis in patients with the novel coronavirus (26). Our results have shown that vitamin D supplements can be effective in preventing poor prognosis of COVID-19.

Our other important finding was lymphocytopenia which is the general characteristic of viral pneumonia and reflects the deficiency of the adaptive immune response (19). Recent studies have reported that lymphocyte counts were reduced in patients with severe COVID-19 (19, 20, 27). In our study, the lymphocyte

counts in COVID-19 outpatients were found to be significantly higher than in the inpatients of COVID-19. In terms of vitamin D status, the lymphocyte counts of patients with vitamin D deficiency were lower than those with normal vitamin D levels. We also found a positive and statistically significant weak correlation between vitamin D and lymphocyte counts. Our results suggest that adequate vitamin D levels can be effective on the lymphocyte count and severity of COVID-19.

The current study has several limitations to consider. First, the group sizes and ages are not equal. Second, we did not have critical patients' results that were in the intensive care unit. Furthermore, we did not compare the groups according to their comorbidities.

Conclusion

Vitamin D is linked to the development of innate and adaptive immunity against various types of infections. Our results suggest that vitamin D deficiency may be one of the factors on the severity of COVID-19 disease. We think that adequate levels of vitamin D may suppress inflammation and cytokine storm with immunomodulatory effects and lead to better clinical outcomes. Thus, vitamin D supplementation may have a critical role in the COVID-19 pandemic period.

References

1. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020. DOI: 10.1016/j.jpha.2020.03.001.

2. Ebadi M, Montano-Loza AJ. Perspective: improving vitamin D status in the management of COVID-19. Eur J ClinNutr 2020. DOI:10.1038/s41430-020-0661-0.

3. Rhodes JM, Subramanian S, Laird E, Kenny RA. Editorial: low population mortality from COVID-19 in countries south of latitude 35 degrees North supports vitamin D as a factor determining severity. Aliment PharmacolTher 2020; 51 (12): 1434–1437. DOI:10.1111/apt. 15777.

4. Vanherwegen AS, Gysemans C, Mathieu C. Regulation of Immune Function by Vitamin D and Its Use in Diseases of Immunity. Endocrinol Metab Clin North Am 2017; 46:1061–1094. DOI:10.1016/j.ecl.2017.07.010.

5. Laird E, McNulty H, Ward M et al. Vitamin D deficiency is associated with inflammation in older Irish adults. J ClinEndocrinolMetab2014; 99 (5): 1807–1815. DOI: 10.1210/jc.2013-3507.

6. Kong J, Zhu X, Shi Y et al. VDR attenuates acute lung injury by blocking Ang-2-Tie-2 pathway and renin-angiotensin system. Mol Endocrinol 2013; 27 (12): 2116–2125. DOI:10.1210/me.2013-1146.

7. Bolland MJ, Avenell A, Grey A. Should adults take vitamin D supplements to prevent disease? BMJ 2016; 355:i6201. DOI:10.1136/bmj.i6201.

8. Grant WB, Lahore H, McDonnell SL et al. Evidence that Vitamin D Supplementation Could Reduce Risk of Influenza and COVID-19 Infections and Deaths. Nutrients 2020; 12 (4): 988. DOI:10.3390/nu12040988.

9. Gombart AF, Pierre A, Maggini S. A Review of Micronutrients and the Immune System-Working in Harmony to Reduce the Risk of Infection. Nutrients 2020; 12 (1): 236. DOI:10.3390/nu12010236.

10. Zhou F, Yu T, Du R et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort. Lancet 2020; 395 (10229): 1054–1062. DOI:10.1016/S0140-6736 (20)30566-3.

11. Huang C, Wang Y, Li X et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395 (10223): 497–506. DOI: 10.1016/S0140-6736 (20)30183-5.

12. Ilie PC, Stefanescu S, Smith L. The role of vitamin D in the prevention of coronavirus disease 2019 infection and mortality [published online ahead of print, 2020 May 6]. Aging ClinExp Res 2020; 1–4. DOI:10.1007/s40520-020-01570-8.

13. Weir EK, Thenappan T, Bhargava M, Chen Y. Does vitamin D deficiency increase the severity of COVID-19? [published online ahead of print, 2020 Jun 5]. Clin Med (Lond) 2020; clinmed.2020-0301. DOI:10.7861/clinmed.2020-0301.

14. Alipio M. Vitamin D Supplementation Could Possibly Improve Clinical Outcomes of Patients Infected with Coronavirus-2019 (COVID-19) (April 9, 2020). Available at SSRN: https://ssrn.com/abstract=3571484 or http://dx.DOI.org/10.2139/ssrn.3571484.

15. Hastie CE, Mackay DF, Ho F et al. Vitamin D concentrations and COVID-19 infection in UK Biobank. Diabetes MetabSyndr 2020; 14 (4): 561–565. DOI:10.1016/j.dsx.2020.04.050.

16. Barlow PG, Svoboda P, Mackellar A et al. Antiviralactivity and increased host defense against influenza infection elicited by the human cathelicidin LL-37.PLoS ONE 2011; 6: e25333. DOI:10.1371/journal.pone.0025333.

17. Zhao Y, Ran Z, Jiang Q et al. D Alleviates Rotavirus Infection through a Microrna-155-5p Mediated Regulation of the TBK1/IRF3 Signaling Pathway In Vivo and In Vitro. Int J Mol Sci 2019; 20 (14): 3562. DOI:10.3390/ijms20143562.

18. Chen N, Zhou M, Dong X et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395 (10223): 507–513. DOI:10.1016/S0140-6736 (20)30211-7.

19. Ni M, Tian FB, Xiang DD, Yu B. Characteristics of inflammatory factors and lymphocyte subsets in patients with severe COVID-19.J Med Virol 2020; 10.1002/jmv.26070. DOI:10.1002/jmv.26070.

20. Zhou B, She J, Wang Y, Ma X. Utility of Ferritin, Procalcitonin, and C-reactive Protein in Severe Patients with 2019 Novel Coronavirus Disease, 19 March 2020, PREPRINT (Version 1) available at Research Square [+https://DOI.org/10.21203/rs.3.rs-18079/v1+].

21. Giannis D, ZiogasIA, Gianni P. Coagulation disorders in coronavirus infected patients: COVID-19, SARS-CoV-1, MERS-CoV and lessons from the past. J Clin Virol 2020; 127:104362. DOI:10.1016/j.jcv.2020.104362.

22. Yormaz B, Ergun D, Tulek B et al. The evaluation of prognostic value of acute phase reactants in the COVID-19. Bratisl Med J 2020; 121 (9): 628–633. DOI: 10.4149/BLL_2020_103.

23. Mohammad S, Mishra A, Ashraf MZ. Emerging Role of Vitamin D and its Associated Molecules in Pathways Related to Pathogenesis of Thrombosis. Biomolecules 2019; 9 (11): 649. DOI:10.3390/biom9110649.

24. BlondonM,Rodabough RJ, Budrys N et al. The effect of calcium plus vitamin D supplementation on the risk of venous thromboembolism. From the Women's Health Initiative Randomized Controlled Trial. ThrombHaemost 2015; 113 (5): 999–1009. DOI:10.1160/TH14-05-0478.

25. Wu WX, He DR. Low Vitamin D Levels Are Associated with the Development of Deep Venous Thromboembolic Events in Patients With-Ischemic Stroke. Clin Appl ThrombHemost 2018; 24 (Suppl 9): 69S–75S. DOI:10.1177/1076029618786574.

26. Tang N, Li D, Wang X, Sun Z. Abnormal coagulation parameters are associated with poor prognosis in patients with novel coronavirus pneumonia. J ThrombHaemost 2020;18 (4): 844–847. DOI:10.1111/jth.14768.

27. El Hassoun O, Valaskova Z, Polak S, Hulin I. Few Insights on the problem of COVID-19. Bratisl Med J 2020; 121 (7): 471–474. DOI:10.4149/BLL_2020_078.

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