RESEARCH ARTICLE / *Araştırma Makalesi*

An Assessment of 25-hydroxyvitamin D Levels and Inflammation Markers in Diabetic Patients with Mild COVID-19

Hafif COVID-19'lu Diyabetik Hastalarda 25-hidroksivitamin D Düzeylerinin ve İnflamasyon Belirteçlerinin Değerlendirilmesi

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Abstract

Introduction	The effects of 25-hydroxyvitamin D (25(OH) D) on inflammation are gaining attention, particularly for diabetic individuals with COVID-19. Therefore, we examined 25(OH) D and inflammation-related markers in diabetic subjects with mild COVID-19.
Materials and Methods	This investigation was intended to be retrospective. The present study covered the medical records of patients who applied to the our hospital between March 2020 and November 2022. All patients suffer from COVID-19. The control group (n = 30) had no diabetes, while the study group (n = 36) had diabetes. Inflammatory markers such as ferritin, C-reactive protein and erythrocyte sedimentation rate were measured in addition to 25 (OH) D levels in each subject. Also, the results of the complete blood count were obtained from the hospital database.
Results	Our participants were matched in terms of gender and age between study groups. ESR, CRP, ferritin, and 25 (OH) D levels, among other variables, did not significantly differ between the non-DM and DM groups (p>0.05). Also, we evaluated all participants according to deficiency of 25 (OH) D, and inflammatory markers were not evaluated in diabetic subjects with COVID-19. However, our findings showed that ferritin levels and Hba1c levels in diabetic individuals significantly correlated positively.
Conclusion	Diabetes mellitus and deficiency of 25 (OH) D are known as risk factors for COVID-19. But as compared to non-diabetic participants with COVID-19, our findings did not reveal any considerable elevation neither inflammatory markers nor changes 25 (OH) D in the diabetics.
Keywords	25-hydroxyvitamin D, COVID-19, Diabetes Mellitus, Inflammation

Öz

Amaç	*25-hidroksi vitamin D'nin (25(OH) D) enflamasyon üzerindeki etkisi özellkle COVID-19 tanısı olan diyabetik hastalarda giderek daha çok dikkat çekmektedir. Bu nedenle, bu çalışmada, hafif COVID-19 geçiren diyabetik hastalarda 25(OH) D ve enflamasyon belirteçlerini değerlendirmeyi amaçladık.*
Yöntem ve Gereçler	*Retrospektif olarak planlanan bu çalışma Mart 2020 ile Kasım 2022 tarihleri arasında hastanemize başvuran hasta kayıtlarını kapsamaktadır. Hastaların hepsi COVID-19 tanısı almıştı. Kontrol grubu (n = 30) diyabet hastalığına sahip değilken, çalışma grubu ise (n=36) önceden Diabetes Mellitus tanısı almıştı. Ferritin, C-reaktif protein ve eritrosit sedimentasyon hızı gibi enflamasyon belirteçleri ve 25 (OH) D sonuçları her hastada mevcuttu. Ayrıca, tam kan sayımının sonuçları hastane veritabanından alınmıştır.*
Bulgular	*Katılımcılarımız çalışma grupları arasında cinsiyet ve yaş açısından eşleştirilmiştir. ESR, CRP, ferritin ve 25(OH)D düzeyleri DM ve DM olmayan gruplar arasında anlamlı farklılık göstermedi (p>0.05). Ayrıca tüm katılımcıları 25 (OH) D eksikliğine göre değerlendirdik ve COVID-19'lu diyabetik olgularda inflamatuar belirteçler gruplar arasında farklı değildi. Ancak bulgularımız, diyabetik bireylerde ferritin düzeyleri ile Hba1c düzeylerinin anlamlı derecede pozitif korelasyon gösterdiğini ortaya koymuştur.*
Sonuç	*Diabetes mellitus ve 25 (OH) D eksikliği COVID-19 için risk faktörleri olarak bilinmektedir. Ancak COVID-19'lu diyabetik olmayan katılımcılarla karşılaştırıldığında, diyabetik hastaların inflamatuar belirteçlerinde ve 25 (OH) D düzeylerinde önemli bir değişim gözlenmedi.*
Anahtar Kelimeler	*25-hidroksi vitamin D, COVID-19, Diabetes Mellitus, İnflamasyon*

INTRODUCTION

Coronaviruses are responsible for a range of respiratory tract infections in humans, encompassing both mild and severe clinical presentations. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the illness it causes, coronavirus disease 2019 (COVID-19), are both names given to the novel coronavirus that emerged as a major worldwide health problem.[1] The most prevalent clinical symptoms of COVID-19 infection include fever, fatigue, dry cough, headache, hemoptysis (coughing up blood), diarrhea, anorexia (loss of appetite), sore throat, chest pain, chills, nausea, and vomiting.[2,3] Additionally, there have been reports documenting olfactory and taste disorders as a consequence of coronavirus infection.[4] COVID-19 infection leads to tissue damage and the excessive release of pro-inflammatory cytokines, which in turn promotes the accumulation of granulocytes and macrophages, collectively referred to as pro-inflammatory cells. This process triggers an elevation in cytokine secretion and the aggregation of leukocytes, ultimately giving rise to a systemic inflammatory response known as macrophage activation syndrome (MAS) or secondary hemophagocytic lymphohistiocytosis (sHLH). This phenomenon is commonly referred to as a cytokine storm.[5]

Diabetes mellitus (DM), a well-recognized metabolic disorder, represents a significant global health concern affecting a large population worldwide. Inflammation has been recognized as both a risk factor and an etiological factor in the development and progression of type 2 diabetes. It serves a crucial role in determining the disease's clinical course.[6,7] The association between DM and inflammation has been established through epidemiological studies conducted over the years. Adipose tissue is considered a primary source of inflammation, where infiltration of macrophages and other immune cells leads to an upregulation of inflammatory markers.[8] Markers of inflammation generated from whole blood count such as the neutrophil/lymphocyte ratio (NLR), platelet/lymphocyte ratio (PLR), and lymphocyte/monocyte ratio (LMR), have been extensively studied in the context of diabetes and diabetic complications, including diabetic retinopathy, cardiovascular disorders, and peripheral artery disease. The findings from these studies consistently demonstrate a close association between diabetes and its related disorders with inflammation. Moreover, these markers are found to be elevated in these pathologies.[9-11]

The potential effect of 25-hydroxy vitamin D (25(OH) D) in modulating inflammation has attracted a growing amount of attention. Insufficient levels of 25(OH) D have been implicated in various infectious diseases, ranging from Crohn's disease and rheumatoid arthritis to DM. The influence of 25(OH)D levels on inflammation has been recognized as a potential factor in the pathogenesis and progression of these diseases.[12] 25(OH) D has been observed to possess anti-inflammatory properties. It contributes to the maintenance of a balanced inflammatory response by modifying the levels of cytokines that trigger inflammation.[13] 25(OH)D deficiency and DM are recognized as prevalent risk factors for coronavirus infection, as they contribute to cytokine elevation and a robust inflammatory response. Inflammation is linked to both DM and COVID-19; therefore, the aim of this study was to examine the association between inflammatory markers and 25(OH)D levels in diabetic individuals with COVID-19.

MATERIAL and METHOD

Patients Selection

Participants at Taksim Training and Research Hospital between March 2020 and November 2022 had their medical records reviewed for this retrospective study. The study encompassed a total of 66 patient records, which were categorized into two main groups: non-diabetic (n=30) and diabetic (n=36) individuals. Reverse transcription polymerase chain reaction (RT-PCR) and computed tomography (CT) diagnostic techniques were used to confirm COVID-19 infection in each patient included in the study. Patients who matched the following qualifications for the study were included: (i) age ranging from 18 to 85 years,

(ii) pre-existing diagnosis of DM) and no hospitalization specifically for coronavirus infection, and (iii) availability of 25(OH)D, inflammatory markers, and whole blood count results. The patients who had fasting blood glucose ≥ 126 mg/dL or HbA1c ≥ 6.5 % were enrolled the study as diabetic patients.

The following were the study's exclusion criteria: patients with a diagnosis of oncologic diseases and undergoing treatment for it, patients with rheumatic or autoimmune diseases, patients with advanced liver or heart failure diseases, being pregnant, and patients who had undergone surgical operations within the last month.

The institutional and/or national research committee's ethical guidelines were followed in all the methods used in this study that included people. The study adhered to the principles outlined in the 1964 Helsinki Declaration and its subsequent amendments, or comparable ethical standards. Ethical approval for this study was obtained from the local research committee at Gaziosmanpasa Training and Research Hospital. [Approval No:2023-12].

Laboratory Measurements

All laboratory results of the subjects were obtained from the laboratory database. The biochemistry tests, including creatinine, glucose, aspartate transaminase (AST), albumin, and C-reactive protein (CRP) measurements, were conducted using commercial kits on the Roche Cobas c501 autoanalyzer. The levels of 25(OH)D and ferritin were determined using the Roche Cobas e601 immunoassay autoanalyzer (Roche Diagnostics, Mannheim, Germany). Glycated hemoglobin (HbA1c) levels were analyzed using the Adams HA-8380V instrument by reverse phase cation exchange chromatography. The erythrocyte sedimentation rate (ESR) was measured using the Alifax analyzer. Lastly, the complete blood count was performed using the Mindray BC6800 analyzer.

The hemogram-derived indices were calculated as follows:

- NLR (Neutrophil/Lymphocyte Ratio)
- PLR (Platelet/Lymphocyte Ratio)

Statistical Analysis

Statistical Package for the Social Sciences (SPSS) software, version 20.0 (SPSS Inc., Chicago, IL), was used to conduct the statistical analyses. The normality of variables was assessed using the Kolmogorov-Smirnov test. Normally distributed parameters were expressed as mean ± standard deviation (SD), while non-normally distributed variables were presented as medians with interquartile range (25th-75th percentile). Categorical variables were reported as absolute and relative frequencies (n and %). To assess differences between groups, the independent samples t-test and Mann-Whitney U test were employed, depending on the parametric assumptions. For categorical variables, the Fisher's Exact test or the Pearson Chi-square test were applied. Spearman's correlation analysis was used to perform correlation analyses. P-values less than 0.05 were regarded as statistically significant for all two-tailed comparisons.

RESULTS

Table 1 provides an overview of each of the research groups' demographic details and laboratory results. The gender distribution between the non-DM and DM groups did not differ significantly ($p>0.05$). The proportion of female patients was higher than that of male subjects in both groups, with 70% and 64% females in the non-DM and DM groups, respectively. Additionally, there was no statistically significant difference in the two groups' median ages ($p>0.05$).

It found that the groups' medians for glucose and HbA1c differed statistically ($p<0.001$ for both). As expected, the DM group exhibited higher levels of glucose and HbA1c compared to the non-DM group ($p<0.001$ for both variables). However, the values of 25(OH)D and ferritin were similar between the two groups ($p>0.05$).

ESR, CRP, and white blood cell (WBC) levels for the in-

flammatory indicators did not differ considerably between the DM and non-DM groups. However, the absolute lymphocyte and neutrophil counts were found to be higher in the DM group compared to the non-DM group (p=0.017 and p=0.023, respectively). Furthermore, there were no significant differences in the neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) between the two groups (p>0.05).

Table 1: Summary of demographic features and laboratory results of all patients with COVID-19

	Non-DM (n=30)	DM (n=36)	p
Gender			
Female %	21 (70)	25 (64)	0.235
Male %	9 (30)	14 (36)	
Age, year	57 (48-66)	58 (54-63)	0.789
Creatinine, mg/dL	0.91 ± 0.16	0.81 ± 0.17	**0.037**
eGFR, mL/min.1.73 m^2	76.8 ± 11.6	88.3 ± 17.4	**0.004**
Glucose, mg/dL	93 (87-99.5)	133 (121-179)	**<0.001**
AST, U/L	19.2 ± 3.58	26.5 ± 13.1	**0.006**
Albumin, mg/dL	45 (43.7-47)	46.6(40-47.7)	0.802
25(OH)D, µg/L	18.3 (13.7-27.4)	16 (11.1-24.9)	0.434
HbA1c, %	5.4 (5.3-5.5)	7.1 (6.8-8.3)	**<0.001**
Ferritin, µg/L	66 (47.8-98)	79.4 (36-144)	0.705
ESR, mm/h	8 (4.5-16.5)	12 (5.75-19.5)	0.285
CRP, mg/dL	2.85 (1.16-5.96)	3.88 (1.46-7.35)	0.442
WBC, 10^3/µL	7.00 ± 2.23	8.07 ± 2.72	0.096
Lymphocyte, 10^3/µL	2.05 ± 0.62	2.62 ± 1.09	**0.017**
Neutrophile, 10^3/µL	3.98 (2.83-4.77)	4.71 (3.95-5.75)	**0.023**
Platelet, 10^3/µL	258 ± 53	273±100	0.466
Hemoglobin, g/L	133 ± 11	133 ± 16.4	0.929
NLR	1.84 (1.34-2.51)	1.79 (1.48-2.48)	0.850
PLR	137 ± 47.4	116 ± 48.3	0.086

DM: diabetes mellitus, eGFR: estimated glomerular filtration rate, AST: aspartate transaminase, HbA1C: hemoglobin A1c, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, WBC: white blood cell, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

Table 2 presents the demographic, clinical, and laboratory results of the participants categorized according to 25(OH)D deficiency. The prevalence of DM cases in the 25(OH)D deficiency group was higher than the normal 25(OH)D group, but this difference was not statistically significant (p>0.05). Similarly, there were no significant differences observed between the study groups in terms of inflammatory markers, including CRP, ESR, WBC, NLR, and PLR (p>0.05).

The direct relationship between inflammatory markers and 25 (OH)D and HbA1c were analyzed and it was found a significant positive correlation between ferritin and HbA1c in the patients diagnosed with DM (r=0.335, p=0.006).

Table 2: Summary of inflammatory markers of patients in terms of vitamin D levels

	25(OH)D < 20 µg/L (n=36)	25(OH)D > 20 µg/L (n=30)	p
Gender			
Female %	27 (75)	12 (40)	0.178
Male %	9 (25)	18 (60)	
Age, year	57 (50.5 - 61.5)	58 (54 - 67.5)	0.438
Diabetes Mellitus, %	24 (67)	17 (57)	0.374
Creatinine, mg/dL	0.83 ± 0.19	0.88 ± 0.15	0.246
eGFR, mL/min.1.73 m^2	85.1 ± 18.4	81.6 ± 13.1	0.388
Glucose, mg/dL	110 (87.5-133)	122 (96-175)	0.112
AST, U/L	21 (17.5-27)	20 (16.5-25.1)	0.887
Albumin, mg/dL	45 (41-47)	45.2 (41.5-48)	0.660
HbA1c, %	6.8 (5.45-7.3)	6.6 (5.35-7.55)	0.530
Ferritin, µg/L	66 (39.5-136)	69 (37.5-118)	0.995
ESR, mm/h	10 (4.5-20)	8.5 (6-17.5)	0.872
CRP, mg/dL	3.58 (1.35-7.70)	2.85 (1.43-7.29)	0.722
WBC, 10^3/µL	8.05 ± 2.79	7.10 ± 2.18	0.139
Lymphocyte, 10^3/µL	2.54 ± 1.11	2.19 ± 0.71	0.139
Neutrophile, 10^3/µL	4.81 ± 2.10	4.52 ± 1.26	0.520
Platelet, 10^3/µL	269 ± 105	265 ± 46	0.240
Hemoglobin, g/L	129 ± 13.9	137 ± 13.5	0.017
NLR	2.27 ± 1.82	2.27 ± 1.00	0.998
PLR	119 ± 51.0	133 ± 45.4	0.240

eGFR: estimated glomerular filtration rate, AST: aspartate transaminase, HbA1C: hemoglobin A1c, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, WBC: white blood cell, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

DISCUSSION

The purpose of the research was to examine the relationship between 25(OH)D levels and inflammatory marker levels in patients diagnosed with DM, as well as those currently diagnosed with COVID-19 infection. The study included all participants who were outpatient. According to the study's findings, there were no statistical differences between the non-DM and DM participants in terms of 25(OH)D, ferritin, CRP, or ESR levels. Furthermore, The NLR and PLR, which are derived ratios from the total blood count, did not show any differences comparing the two groups. However, there were significant differences observed in the absolute counts of neutrophils and lymphocytes between the non-DM and DM study groups. DM groups had higher levels of neutrophils and lymphocytes than the non-DM group. In addition to comparing the non-DM and DM study groups, the subjects were also analyzed based on 25(OH)D deficiency. However, the results did not show any significant differences among the subjects with regards to deficiency of 25(OH)D. Moreover, the analysis revealed a strong positive correlation between ferritin and HbA1c in diabetic patients.

Since the COVID-19 pandemic, accumulating evidence has highlighted the association between DM and COVID-19 infection. Reports have shown that individuals with COVID-19, even those without a prior diagnosis of diabe-

Table 3: Correlation of inflammatory markers with vitamin D levels and hba1c

		CRP	ESR	Ferritin	NLR	PLR
Non-DM group	**HbA1c**	r=0.075	r=0.113	r=-0.125	r=0.001	r=-0.232
		p=0.547	p=0.393	p=0.316	p=0.999	p=0.061
	25(OH)D	r=-0.058	r=-0.076	r=0.039	r=0.082	r=0.063
		p=0.646	p=0.565	p=0.755	p=0.513	p=0.613
DM	**HbA1c**	r=-0.023	r=0.012	**r=0.335**	r=-0.094	r=-0.183
		group	p=0.928	**p=0.006**	p=0.450	p=0.141
	25(OH)D	r=-0.083	r=0.011	r=0.094	r=0.029	r=0.051
		p=0.506	p=0.936	p=0452	p=0.816	p=0.685

DM: diabetes mellitus, HbA1C: hemoglobin A1c, ESR: erythrocyte sedimentation rate, CRP: C reactive protein, WBC: white blood cell, NLR: neutrophil lymphocyte ratio, PLR: platelet lymphocyte ratio

tes, often exhibit significant hyperglycemia.[14] In line with these reports, several case-control studies have consistently demonstrated that patients with pre-existing DM are more likely to experience severe clinical outcomes following COVID-19 infection. These outcomes include a higher risk of developing severe respiratory symptoms, requiring intensive care unit (ICU) admission, and experiencing an increased mortality rate.[15] The exact processes underlying the association between coronavirus infection and DM are still unclear. However, it is evident that individuals with comorbidities, particularly DM, are at a higher risk of experiencing severe and even fatal cases of COVID-19.[16,17] The outcomes of COVID-19 infection in diabetic patients were strongly related to get mechanical ventilation and in-hospital mortality.[17,18] Rajpal et al proposed a possible mechanism for the severity of coronavirus infection in diabetic patients. The researchers suggest that DM is closely associated with low-grade chronic inflammation, and hyperglycemia leads to increased expression of angiotensin-converting enzyme 2 (ACE2) in the lungs and other tissues, which serves as the viral entry pathway. The combination of pre-existing DM and COVID-19 infection results in powerful inflammatory responses known as cytokine storms, leading to more severe cases of coronavirus infection and a higher mortality rate among diabetic patients.[19]

A recent study has emphasized that 25(OH)D decreases the risk of COVID-19 mortality through various mechanisms. These include maintaining physical barriers by preserving cell junctions and gap junctions, elevating cellular immunity, decreasing cytokine storm by affecting interferons and tumor necrosis factor, and promoting balanced adaptive immunity via T cells.[20] In parallel with these finding, reports from different countries have been state that the status of 25 (OH) D is very essential to get coronavirus infection. studies have emphasized that 25 (OH) D deficiency could be a risk factor for COVID-19.[21,22]

Pre-existing DM and a deficiency of 25 (OH)D are both important risk factors for COVID-19 infection. The present results revealed that the patients with diabetes had a lower state of 25(OH) D than the non-DM group, but not statistical significance. Similarly, the percentage of DM cases in 25(OH) D deficiency group was higher than 25 (OH) D >20 μg/L groups without statistical significance. Singh et al have reported that the relationship between diabetic subjects with COVID-19 and 25(OH) D was proven by growing studies, and this relationship was clearer when the level of 25 (OH)D was below 10 μg/L.[23] In concordance with this report, Wang et al have suggested that the level of 25(OH)D may be a significantly prognostic indicator and may be a preventive therapy option for diabetic patients with COVID-19.[24] It has been stated that the patients with deficiency 25(OH) D and hyperglycemic state were higher risk at severe coronavirus infection, higher inflammatory response and worse outcomes of infection in recent report of Di Filippo et al.[25] On the other hand, a study from India reports that 25 (OH) D levels were statistically higher in the non-COVID-19 group compared to the COVID-19 patients with pre-existing Type 2 DM. In contrast to our results, this report revealed that serum CRP, ferritin, and IL-6 levels were increased in diabetic patients with COVID-19 who had a fatigue score above 4.[26] It is well documented that 25(OH) D suppresses Th1 and Th17 production as well as the expression of IFN-, TNF-, IL-1, IL-2, IL12, IL-23, IL-17, and IL-21. 25 (OH) D regulates the development of th2 and their anti-inflammatory secretion, including IL-4 and IL-10, in addition to minimizing the pro-inflammatory response.[27]

We also investigated inflammatory markers in COVID-19 patients with pre-existing DM. The newly hemogram-derived parameters, such as NLR and PLR were not statistically different between the study groups. We found increased absolute lymphocyte and neutrophil counts in the DM group compared to the non-DM group. There are conflicting results in the literature about vitamin D and its effect on inflammatory markers. A meta-analysis recently published a summary of the reports related to the link be-

tween 25 (OH) D and inflammation in diabetic patients with COVID-19. The researchers concluded that vitamin D supplementation is beneficial for managing both diabetes and coronavirus infections. Also, it has been shown that 25 (OH) D reduces CRP levels.[28] However, some reports published contradictory results, like that supplementation of 25 (OH) D had no healthful effect on pro-inflammatory cytokines and TNF-α levels.[29]

In patients with diabetes and COVID-19, we found an important relationship between ferritin and HbA1c. In parallel with our results, a study comparing blood parameters in diabetic patients diagnosed with COVID-19 showed an increased level of ferritin in COVID-19 positive diabetic patients compared to COVID-19 negative patients.[30] Wang et al has supported our results with their report, which showed elevated ferritin levels in diabetic patients diagnosed with COVID-19 compared to non-diabetic patients.[31]

There are some limitations to the current study. Our data did not involve detailed clinical and demographic characteristics of participants since it was planned as a retrospective study. In parallel with this, our study has limited number of participants. Additionally, some important inflammatory parameters associated with COVID-19 were missing, such as IL-6 and TNF-α.

In conclusion, we investigated 25 (OH) D and inflammatory markers in diabetic individuals with COVID-19. Given that our participants had no severe symptoms of COVID-19 and all of them were outpatients, we did not find any significant elevation in inflammatory indicators in diabetic patients with COVID-19, and 25(OH)D status was almost similar in the DM group compared to the non-DM group. However, it should be stated that ferritin and Hba1c levels were positively correlated in the DM group.

Conflict of interest statement

The authors declared that there was no conflict of interest.

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Ethics Approval

The research followed the ethical guidelines established by the Helsinki Declaration and its later revisions, or those of an equivalent kind. The study was approved by the ethics board of Gaziosmanpasa Training and Research Hospital. Acceptance No. 2023-12.

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