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Orijinal Araştırma / Original Article

The Effect of Vitamin B12 Levels on Prognosis in COVID-19 Patients

COVID-19 Hastalarında Vitamin B12 Düzeyinin Prognoz Üzerine Etkisi

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Abstract

Objectives: It is known that vitamins have some effects such as suppressing viral replication, developing anti-inflammatory responses and that they increase immunity in COVID-19. This study aimed to investigate the correlation between the vitamin B12 (Vit B12) serum levels and the prognosis of the disease in patients with COVID-19.

Material and Method: A total of 408 participants were included in the study. Sociodemographic information such as age, educational status, serum vitamin B12 levels, hemogram parameters, and clinical findings of the patients who were admitted for follow-up after the end of COVID-19 infection was evaluated retrospectively. Serum vitamin B12 level between 150-200 pg/mL was assessed as mild deficiency, the value between 100-150 pg/mL as severe deficiency and the value under 100 pg/mL as extremely severe deficiency.

Results: It was determined that the clinical progression of COVID-19 patients with vitamin B12 deficiency was worse than those without vitamin B12 deficiency. Therefore, we think that Vit B12 supplementation may have a positive effect in COVID-19 patients. However, longer-term and more comprehensive studies with more patients are needed on this subject.

Conclusion: The clinical progression was worse in COVID-19 patients with Vit B12 deficiency than those who had no Vit B12 deficiency. Therefore, it has been concluded that Vitamin B12 supplement can have positive effects on COVID-19 patients; however, more comprehensive further studies with longer duration and higher number of patients are needed.

Keywords: COVID-19, vitamin B12, inflammation, prognosis

Öz

Amaç: Vitaminlerin, Koronavirüs Hastalığında (COVID-19) viral replikasyonu bozma, anti-inflamatuar yanıt geliştirme gibi etkileri olduğu ve immüniteyi artırdıkları bilinmektedir. Bu çalışmada, COVID-19 hastalarında Vitamin B12 (Vit B12) serum seviyeleri ve hastalığın prognozu arasındaki ilişkiyi görmeyi amaçladık.

Gereç ve Yöntem: Çalışmaya COVID-19 enfeksiyonu geçiren 408 katılımcı dâhil edildi. Hastaların yaş, eğitim durumu gibi sosyodemografik bilgileri, serum Vit B12 düzeyleri, hemogram parametreleri, klinik bulguları retrospektif olarak incelendi. Serum B12 vitamini düzeyi 200-2000 normal, 150-200 pg/mL arası hafif eksiklik, 100-150 pg/mL arası ağır eksiklik 100 pg/mL'nıın altı ise çok ağır eksiklik olarak gruplandırıldı.

Bulgular: Katılımcıların yaş ortancası 44.51(18-88), Vit B12 düzeyi ortancası ise 179.50 ng/L (75-641) idi. Hastaların 248 (%60.78)'inde Vit B12 eksikliği vardı. Ağır Vit B12 eksikliği olan hastalarda ve çok ağır Vit B12 eksikliği olanlarda ateş, diğer gruplardan daha fazlaydı. Benzer şekilde öksürük, tat ve koku kaybı, baş ağrısı, pnömöni ve hospitalizasyon oranı daha yüksekti (P<0.01). Gruplar arasında platelet ve nötrofil sayıları açısından anlamlı farklılık vardı. Vit B12 düzeyi normal oranlara göre hafif ve ağır olan hastaların platetet sayısından daha yüksekti (p<0.01).

Sonuç: Vit B12 düzeyi eksikliği olan COVID-19 hastalarının klinik progresyonunun Vit B12 eksikliği olmayanlardan daha kötü olduğu belirlendi. Bu nedenle COVID-19 hastalarında Vit B12 takviyesinin olumlu etkisi olabileceğini düşünmekteyiz. Fakat bu konuda daha uzun süreli ve daha fazla hasta ile kapsamlı çalışmaların yapılması gerekmektedir.

Anahtar Kelimeler: COVID-19, vitamin B12, inflamasyon, prognoz

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INTRODUCTION

COVID-19 causes a wide clinical spectrum of diseases such as asymptomatic infection, mild upper respiratory tract infection and severe lower respiratory tract infection with respiratory failure.[1]

Vit B12 is an important immunomodulator that has a supportive function for hematopoietic, nerve and immune systems.[2] It can suppress viral replication in the host cell.[3] In Vit B12 deficiency, lymphopenia, decrease in the number of CD8 cells and dysfunction of natural killer cells can be observed.[4] In addition, Vit B12 deficiency increases oxidative stress by increasing methylmalonic acid and homocysteine, which results in endothelial dysfunction, thrombocyte activation, elevated tissue factor expression, and activation of the coagulation cascade.[5,6]

Nutritional deficiencies such as vitamin D, Vit B12 and selenium deficiency are seen in patients with COVID-19 and it is known that these deficiencies can affect the host immune responses against viral infections and inflammatory activity. Moreover, nutritional deficiencies can be effective in the onset of COVID-19 infection and the clinical severity of the disease.[7,8] Optimal levels of vitamins and trace elements known as immunomodulators and stimulators for the immune system to function in optimal conditions are important in the struggle against COVID-19.[9] Vit B12 is predicted to increase immunity with the effects of suppressing viral replication, developing anti-inflammatory responses and decreasing proinflammatory responses in COVID-19.[10] However, according to the authors' knowledge the correlation between serum Vit B12 levels and clinical results of Vit B12 deficiency in patients with COVID-19 has not been clarified yet.

This study aimed to reveal the effect of Vit B12 level and Vit B12 deficiency on the clinic and symptoms in patients with COVID-19.

MATERIAL AND METHOD

This is a retrospective study performed on patients who were diagnosed with COVID-19 by a PCR test and admitted to the Pandemic Outpatient Clinic of XXXX State Hospital between February-June 2020 for follow-up examination within the 14 days after the end of quarantine. The study sample was obtained from the files of all patients who were Turkish citizens diagnosed with COVID-19 and admitted to XXXX State Hospital Internal Diseases Outpatient Clinic for post-COVID follow-up and who were tested for serum Vit B12 level. A total of 408 patients were included in the study. Sociodemographic characteristics such as age and educational status, serum Vit B12 levels, laboratory parameters, neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were accepted as inflammatory markers, and clinical results of the patients diagnosed with COVID-19 were obtained with file scanning. The data obtained were recorded in a form prepared by the researchers. Demographic characteristics and comorbidities of the patients were assessed between those with and without Vit B12 deficiency. The patients were classified according to their Vit B12 levels in order to determine the differences between clinical and laboratory results. For Vit B12 levels, the values between 200-2000 ng/L as normal, 150-200 ng/L were accepted as a mild deficiency, values between 100-150 ng/L as severe deficiency and values under 100 ng/L as very severe deficiency.[11]

Setting and sampling

A total of 425 patients admitted between June 2020 and November 2020 were included in the study. Seventeen patients who did not meet the inclusion criteria were excluded from the study. The study was completed with 408 patients. The exclusion criteria were as follows; being under the age of 18, pregnancy or lactation, having a significant liver, renal or hematologic dysfunction during screening, and having heart failure or psychiatric disease.

Statistical analysis

The study's statistical evaluation was made using the SPSS version 22.0 (IBM Corp., Armonk, NY, USA) computer package program. Mean, standard deviation, median, minimum and maximum values as descriptive statistics were calculated for continuous variables among the emphasized features and categorical variables were expressed as numbers and percentiles. Whether the numerical data of the variables were normally distributed or not was determined with one sample Kolmogorov Smirnov test. The chi-square test was used to determine between the groups and categorical variables. The intergroup differences were assessed with ANOVA. Tukey test was used in values with difference. Statistical significance level was accepted as $p<0.05$.

RESULTS

A total of 408 participants were included in the study. The median Vit B12 level of all the patients was 179.50 (75-641). The median age of the participants was 44.51 years (18-88) Of the patients, 69 (16.92%) had at least one chronic disease. Fifty patients (12.25%) had hypertension; 38 (9.31%) had diabetes mellitus; 29 (7.10%) had pulmonary disorder; 12 (2.94%) had heart failure; 2 (0.50%) had neurological disorder; and 2 (0.50%) had malignancy. Of the patients, 248 (60.78%) had Vit B12 deficiency. When those with deficiency were categorized very severe deficiency was recorded in 16 (3.92%), severe deficiency in 105 (25.73%) and deficiency in 127 (31.12%) (**Table 1**). The groups with and without Vit B12 deficiency were similar in terms of age, gender and presence of at least one comorbid disease (p: 0.057, p: 0.168 and p: 0.426 respectively) (**Table 2**). The symptoms and their distributions were presented in the **Table 3** in detail. The rate of fever was higher in patients with severe Vit B12 deficiency and those with extremely severe

Vit B12 deficiency. Similarly pneumonia, cough, rate of hospitalization, loss of taste and smell (p<0.01), headache, sore throat and dyspnea were higher (p<0.05). The groups were different in terms of platelet and neutrophil counts. Platelet count was higher in the patients with mild and severe Vit B12 deficiency than in those with normal Vit B12 levels (p<0.01). Neutrophil levels were higher in the patients with severe Vit B12 deficiency than in those with normal Vit B12 levels (p<0.01) (**Table 4**).

Table 1. Vitamin B12 Levels of Study Group

Vitamin B12 Levels (Median, min-max)	
179.50 (75-641) ng/L	
Variables	**n (%)**
Normal Vitamin B12 (200-2000 ng/L)	160 (39.21)
Vitamin B12 Deficiency (<200 ng/L)	248 (60.78)
Mild (150-200 ng/L)	127 (31.12)
Severe (100-150 ng/L)	105 (25.73)
Very Severe (<100 ng/L)	16 (3.92)

Table 2. Socio-Demographic Information of Patients According to Their Vitamin B12 Status

Variables	Normal n (%)	Vitamin B12 Deficiency n (%)	p
Gender			0.168
Male	65 (40.62)	118 (47.58)	
Female	95 (59.37)	130 (52.41)	
Age	47.2±15.2	44.1±16.1	0.057
Marital Status			0.019
Single	25 (15.62)	63 (25.40)	
Married	135 (84.37)	185(74.60)	
Educational Status			0.135
Illiterate	20 (12.50)	18 (7.25)	
Primary / Secondary School	76 (47.50)	112 (45.16)	
High School	35 (21.87)	53 (21.37)	
Associate's/Bachelor's Degree	21 (13.12)	54 (21.77)	
Postgraduate	8 (5.00)	11 (4.43)	
Presence of Chronic Disease			0.426
Yes	30 (18.75)	39 (15.72)	
No	130 (81.25)	209 (84.27)	

*Pearson chi-square tests were used in the analysis of the data, and corrections were made with Fisher's exact test in the cells with small numbers (p<0.05)

DISCUSSION

This study was conducted with the aim of revealing the effect of Vit B12 level and deficiency on the clinics and symptoms in COVID-19 patients, it was found that pulmonary involvement and hospitalization rates were higher and the difference between the clinics and severity of the deficiency increased in the patients with Vit B12 deficiency. Vit B12 is a vitamin with an immunomodulation effect and plays an important role in our immune system. Vit B12 can decrease the severity of COVID-19 by suppressing viral replication.[12] As far as we reviewed literature we could not find many studies assessing Vit B12 level in COVID-19 patients and its relationship with clinical progression. Shakeri et al. found the serum Vit B12 levels of the hospitalized COVID-19 patients as 465.4±35.70 ng/L in their third day of hospital stays and Im et al. found Vit B12 levels of the COVID-19 adult patients admitted to Inha University Hospital in North Korea as 727 (535.5-962.8) ng/L in the seventh day. In the current study, Vit B12 level of the participants was 179.50 (75-641) ng/L, which was lower than those in the previous studies.[6,13] This may be due to race, gender and sociocultural differences.

Table 3. Comparison of Symptoms and Clinics of Patients According to the Status and Severity of Vitamin B12 Deficiency

	Normal n (%)	Mild n (%)	Severe n (%)	Very severe n (%)	p
Symptoms					
Fever	42 (26.25)	29 (22.83)	37 (35.24)	13 (81.25)	<0.001
Cough	56 (35.00)	39 (30.71)	42 (40.00)	15 (93.75)	<0.001
Sore Throat	48 (30.00)	27 (21.25)	23 (21.90)	9 (56.25)	0.010
Dyspnea	25 (15.62)	17 (13.38)	25 (23.81)	3 (18.75)	0.0184
Muscle and joint pain	80 (50.00)	62 (48.81)	61 (58.09)	10 (62.50)	0.386
Loss of taste/smell	82 (51.25)	71 (55.90)	73 (69.52)	15 (93.75)	<0.001
Lack of appetite	68 (42.50)	38 (29.92)	32 (30.47)	3 (18.75)	0.641
Backache	62 (38.75)	55 (43.30)	42 (40.00)	8 (50.00)	0.880
Fatigue	89 (55.62)	62 (48.81)	64 (60.95)	13 (81.25)	0.056
Headache	42 (26.25)	43 (33.85)	30 (28.57)	10 (62.50)	0.042
Clinics					
Hospitalization	9 (5.62)	9 (7.08)	15 (14.28)	7 (43.75)	<0.001
Pneumonia	8 (5.00)	7 (5.51)	15 (14.28)	7 (43.75)	<0.001

*Pearson chi-square tests were used in the analysis of the data, and corrections were made with Fisher's exact test in the cells with small numbers (p<0.05)

Table 4. Comparison of Laboratory Findings Data of Patients According to According to The Status and Severity of Vitamin B12 Deficiency

Laboratory Findings	Normal X±SS	Mild X±SS	Severe X±SS	Very Severe X±SS	p
Platelet, $\times10^9$/L	250.46±59.00	287.57±103.08	280.64±78.33	253.68±32.78	<0.001
Neutrophil, $\times10^9$/L	3.76±1.42	3.97±1.29	4.16±1.31	3.34±1.37	0.039
Lymphocyte, $\times10^9$/L	3.49±2.08	3.42±2.07	3.37±2.10	2.43±1.07	0.274
MPV f/L	8.39±2.64	8.43±2.86	8.76±2.51	9.08±2.37	0.555
PDW %	11.64±7.11	12.01±4.48	13.25±10.65	15.39±9.67	0.136
NLR	1.37±0.72	1.50±0.72	1.59±0.81	1.48±0.50	0.113
PLR	95.73±54.15	113.28±79.36	103.91±46.81	115.67±29.99	0.093

MPV: mean platelet volüme, PDW: platelet distribution width, NLR: neutrophil-to-lymphocyte ratio, PLR platelet-to-lymphocyte ratio, *ANOVA test was used to examine the differences in quantitative data between groups (p<0.05). The significant difference in PLT values is due to the differences between normal – severe (p=0.014) and normal - mild (p<0.001) groups. The significant difference in neutrophil values is due to the difference between the normal and very severe groups (p=0.047).

It can be assumed that Vit B12 supplement in the patients infected with COVID-19 will provide faster recovery, decrease oxidative stress, improve clinical progression and minimize the conditions caused by the disease such as lung infection, multiple organ dysfunction and mortality by acting as an anti-inflammatory and analgesic agent.[5,6] In a study assessing the levels of the hospitalized COVID-19 patients during admission and their clinical results (length of hospital stay, intensive care unit stay and mortality), Vit B12 levels of the death COVID-19 patients were lower than those of the patients staying in the intensive care unit and wards and Vit B12 levels did not affect the need for intubation or length of hospital stay.[13] However, it was reported in another study that Vit B12 supplement for COVID-19 patients reduced the length of hospital stay.[14] When we consider that Vit B12 supplement provides faster recovery and can decrease pulmonary involvement it is possible to expect higher rates of hospitalization and lung infection in COVID-19 patients with Vit B12 deficiency like in our study. In addition, our study had similar results with the other studies in terms of the increasing clinical deterioration with the increasing severity of the deficiency of Vit B12.

It is known that COVID-19 causes severe disruptions in the quality of life.[15] Although clinical findings of COVID-19 are various the most common symptoms are fever and cough. Sore throat and fatigue can accompany these symptoms.[16] In addition, loss of smell has a very high rate and it has been reported in some studies that its incidence ranges from 5% to 68%.[17] Loss of taste and smell tends to happen together. The mechanism under the loss of smell in COVID-19 patients is not clearly known. However, it is considered to be due to neurological damage.[18] Additionally, Vit B12 deficiency can cause disruptions in respiratory, gastrointestinal and central nervous systems as well.[19] In our study, those with extremely severe Vit B12 deficiency had a higher rate of loss of taste. Further studies are needed to understand whether Vit B12 deficiency has an effect on loss of taste in COVID-19 patients.

The information about between the severity of Vit B12 deficiency and COVID-19 symptoms is insufficient in the literature. It has been revealed in studies that Vit B12 supplements have the potential to decrease the symptoms associated with COVID-19.[8,10] In our study, the rates of fever, cough, and loss of taste/smell were higher, which suggests that the symptoms and quality of life can be affected by the increasing Vit B12 deficiency.

Lymphopenia is one of the common hematologic changes in COVID-19.[20] A significant systemic increase occurs in inflammatory mediators and cytokines about 7-14 days after the onset of the symptoms and lymphopenia becomes significant.[21] The increased NLR and PLR levels, markers of inflammation, are associated with the clinical severity of COVID-19.[22,23] There is no study assessing the hematologic parameters in Vit B12 deficiency in COVID-19 patients. Therefore, it is one of the rare studies revealing the correlation between Vit B12 deficiency and clinics and laboratory results in COVID-19 patients, which is the strength of our study. Vit B12 deficiency can cause hematologic changes as well.[19] The group with Vit B12 deficiency had a higher rate of lymphopenia and high NLR and PLR, which may be caused by the disease process and Vit B12 deficiency which is an immunomodulator. Moreover, when it is considered that Vit B12 supplement decreases inflammation it can be expected that the inflammation markers increase in case of its deficiency.

The limitations of the present study were being retrospectively performed and the analyses could not be performed during the quarantine period when the disease was active.

CONCLUSION

The clinical progression of COVID-19 patients with Vit B12 deficiency is worse. The specific symptoms such as fever, loss of taste/smell and cough were more common in patients with Vit B12 deficiency. In addition, the inflammation markers of the patients with Vit B12 deficiency were higher. Therefore, it is considered that Vit B12 has effects on the prognosis and symptoms in COVID-19 patients. Moreover, Vit B12 supplements in COVID-19 patients can have a positive effect on the clinics during the infection period. More comprehensive basic and clinical studies on the effect of Vit B12 deficiency on the pathology and Vit B12 supplement in COVID-19 patients should be performed..

ETHICAL DECLARATIONS

Ethics Committee Approval: The institutional consent to perform the study was obtained from Kayseri Provincial Directorate of Health and the study was approved by the Ethics committee of Nuh Naci Yazgan University (Decision number: 1/711 and Date: 19.02.2021).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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