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THE VARIATION OF THE SYSTEMIC IMMUNE-INFLAMMATION INDEX IN THE PATIENTS WITH VITAMIN D DEFICIENCY

D Vitamini Eksikliği Olan Hastalarda Sistemik İmmün İnflamasyon İndeksinin Değişkenliği

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ABSTRACT

In this study, the variability of the systemic immune inflammation index (SII), which is accepted as a new marker of inflammation, was researched in patients with vitamin D deficiency. The biochemistry and hemogram results of outpatients were scanned and recorded retrospectively from digital data. SII was calculated with whole blood parameters (neutrophil x platelet/lymphocyte) for each patient. The relationship between SII and vitamin D variation was investigated. The mean age of 113 patients included in the study was 38.58±12.37 years. Mean levels of vitamin D, B12, and folate were 13.68±6.57 ng/ml, 309.54±110.73 pg/ml and 7.13±2.77 ng/ml, respectively. The mean SII was 434.39±156.72. While vitamin D was below 10 ng/mL in 38 patients (33.6%), it was between 10-20 ng/mL in 56 patients (49.5%) and 20 ng/mL and above in 19 patients (16.8%). Vitamin B12 was lower in the primary group than in the second group ($p<0.05$). No significant correlation was found between SII and vitamin D values ($p>0.05$). Vitamin D deficiency is one of the most common health problems, and possible relationships between vitamin D deficiency and inflammation are still under investigation. In this study, we researched the SII variation in patients with vitamin D deficiency, but no relationship was observed.

Keywords: Inflammation, Inflammation mediators, Systemic immune-inflammation index, Vitamin D deficiency.

ÖZ

Bu çalışmada, D vitamini eksikliği olan hastalarda inflamasyonun yeni bir belirteci olarak kabul edilen sistemik immün inflamasyon indeksinin (SII) değişkenliği araştırıldı. Ayaktan tedavi olan hastaların biyokimyasal ve tam kan sayımı verileri dijital verilerden retrospektif olarak taranıp kaydedildi. SII, her hasta için tam kan parametreleri (nötrofil x trombosit/lenfosit) ile hesaplandı. SII ve D vitamini varyasyonu arasındaki ilişki araştırıldı. Çalışmaya alınan 113 hastanın yaş ortalaması 38.58±12.37 yıl idi. Ortalama D vitamini, B12 ve folat düzeyleri sırasıyla 13.68±6.57 ng/ml, 309.54±110.73 pg/ml ve 7.13±2.77 ng/ml idi. Ortalama SII 434.39±156.72 idi. D vitamini 38 hastada (%33.6) 10 ng/mL'nin altında iken, 56 hastada (%49.5) 10-20 ng/mL arasında, 19 hastada (%16.8) 20 ng/mL ve üzerindeydi. B12 vitamini birincil grupta ikincil gruba göre anlamlı derecede düşüktü ($p<0.05$). SII ile D vitamin değerleri arasında herhangi bir anlamlı ilişki bulunmadı ($p>0.05$). D vitamini eksikliği en yaygın sağlık sorunlarından biridir, D vitamini eksikliği ve inflamasyon arasındaki olası ilişkiler halen araştırılmaktadır. Bu çalışmada D vitamini eksikliği olan hastalarda SII varyasyonunu araştırıldı ancak herhangi bir ilişki bulunmadı.

Anahtar kelimeler: Enflamasyon, Enflamasyon belirteçleri, Sistemik immün-enflamasyon indeksi, Vitamin D eksikliği.

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INTRODUCTION

Vitamin D is a lipid-soluble vitamin with hormone action. Along with dietary resources, it's synthesized in cutaneous tissue with exposure to sunlight along with ultraviolet B radiation. In the intestinal system, it induces calcium and phosphate reabsorption and provides calcium balance in terms of bone mineralization, growth, and remodeling. Vitamin D has also an activity for regulation of cell growth and metabolism, modulation of immune function, and reduction of inflammation (Mosekilde, 2008). Prostate, colon, and breast tissue can convert 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, and this transformation partially modulates the genes involved in cell growth, differentiation, and apoptosis (Manson, Bassuk & Buring, 2017; Vanoirbeek et al., 2011) In the process of malignancies, the diversity of Vitamin D is one of the popular research subjects (Holick, 2007).

The level of 25 hydroxyvitamin D (25OH vitamin D) under 20 ng/mL is defined as deficiency and under 10-12 ng/mL as severe deficiency (Amrein et al., 2020). Along with the variation between countries, one-third of the worldwide population is deficient and approximately 7% is severely deficient (Hilger et al., 2014). Risk factors are; darkly pigmented skin, long winter seasons, skin coverages, and extreme use of sunscreens. The other related disorders are obesity, older age, renal diseases, malabsorption, genetics (Indo-Asians) and medication-related side effects as anticonvulsants, thiazide diuretics, corticosteroids, laxatives, cholestyramine, etc. (Medical Advisory Secretariat, 2010).

The treatment of vitamin D deficiency was associated with decreased infection risk, suppression of Crohn's disease activity, decreased type 1 diabetes incidence in early childhood, improved lung function, reduced central blood pressure, and age-related bone loss (Bouillon et al., 2019; A. R. Martineau et al., 2017). Lappe *et al.* reported decreased malignancy risk along with calcium and vitamin D replacement, but a certain relationship was not observed (Lappe et al., 2017). In a meta-analysis of randomized controlled studies, although no decline was presented for total malignancy incidence, reduced mortality rates were reported with vitamin D replacement (Keum, Lee, Greenwood, Manson & Giovannucci, 2019). 1,25(OH) vitamin D modulates the functions of antigen-presenting cells. It decreases interleukin-12 (IL-12) and increases IL-10. Also, it inhibits the expression of toll-like receptors and inflammatory cytokines such as IL-2, IL-6, and IL-17 (Dickie et al., 2010).

Inflammation is the major end-point for many disorders and the predictive markers are important subjects for research. The systemic immune-inflammation index (SII) is one of them, and it includes platelet, neutrophil, and lymphocyte counts. SII was approved as a

prognostic indicator in many disorders, including coronary artery disease, ischemic stroke, postmenopausal osteoporotic fracture, and malignancies along with unfavorable outcomes (Fest et al., 2020; Hou et al., 2021; Yang et al., 2020). Especially for patients with solitary malignancies, its' predictivity was presented an acceptable level (H. Li et al., 2019; Toyoda et al., 2022). It has been shown in many studies that SII, which is a proinflammatory marker, can be used to reveal the severity and activity of many infectious diseases and rheumatic diseases and to predict mortality (Karaaslan & Karaaslan, 2022; Wu, Yan & Chai, 2021). In this study, we researched the variation of this index in patients with vitamin D deficiency.

MATERIAL AND METHOD

This is a retrospective observational study and it was approved by the Local Ethics Committee number E-54022451-050.05.04-15200 / 05.03.2021. Between December 2020 to March 2021 -in the winter season- the files of the patients that were admitted to one internal medicine outpatient clinic were screened for inclusion. The only inclusion criteria was the diagnosis of vitamin D deficiency that was recorded along with The International Statistical Classification of Diseases and Related Health Problems (ICD) code.

The exclusion criteria are as follows; the patients with diabetes mellitus, ischemic heart disease, chronic kidney disease, chronic liver disease, autoimmune disorders, malignancy, increased acute phase, the hemoglobin that under 12.5 g/dL or up to 17.5 g/dL, the neutrophil count up to 7000/mm3, the lymphocyte count up to 4000/mm3, thrombocytopenia, and with vitamin replacement. Because of the retrospective properties, all medications of all patients could not be determined.

Finally, the results of 113 patients who meet the criteria were included in the study. 25OH vitamin D (ng/mL), vitamin B12 (pg/mL) and folate (ng/mL) levels, neutrophil (N), lymphocyte (L), and platelet (P) numbers were recorded (mm^3). Hemoglobin level (g/dl) and neutrophil to lymphocyte ratio were determined. SII was calculated using the equation, SII = P x N/L. According to deficiency levels, we categorized the patients into three groups; severely deficient (0-10 ng/mL), deficient (10-20 ng/mL), and normal (over 20 ng/mL) (Amrein et al., 2020). All analysis was performed by using IBM SPSS Statistics, v.20.0 (Armonk, NY: IBM Corp.). The data were normally distributed and presented as the mean ± standard deviation (SD) and percentages. Since the data were normally distributed the Pearson correlation coefficients were used for quantitative variables and One-way Anova and Pearson Chi-Square tests were used for categorized data. *p* values below 0.05 were considered statistically significant.

RESULTS

The data of the 113 patients (38 male, 75 female) were included in the analysis. The mean age was 38.58±12.37 years. The minimum, maximum, and mean results of all parameters were presented in table 1. Between male and female patients, there was no difference in vitamin D levels (p=0.172). In correlation co-efficient, the age of the patients was positively correlated with lymphocyte number and negatively with NLR and SII index (p<0.05). There was no correlation between plasma vitamin B12, folate, and SII index (p=0.687, p=0.337). The expected correlation was observed between NLR and SII (p<0,001).

Table 1. The Minimum, Maximum, and Mean Results of The Parameters

	Minimum	**Maximum**	**Mean±SD**
Age (years)	18.0	65.0	38.58±12.37
Neutrophil (mm^3)	2050.0	6390.0	4195.75±917.2
Lymphocyte (mm^3)	1450.0	3910.0	2554.78±558.8
Platelet ($x10^3$/mm3)	152.0	378.0	251.0±43.9
Hemoglobin (g/dL)	12.22	17.2	14.13±1.2
NLR	0.72	3.53	1.74±0.6
Vitamin B12 (pg/mL)	113.0	792.0	309.54±110.7
Folate (ng/mL)	2.8	17.4	7.13±2.8
Vitamin D (ng/mL)	2.90	41.30	13.68±6.6
SII	148.25	864.9	434.39±156.7

NLR: Neutrophil to lymphocyte ratio, SII:Systemic immune-inflammation index.

According to plasma vitamin D, the diversities of the parameters was presented in table 2. Vitamin B12 level was found to be significantly lower in the group with 0-10 ng/ml vitamin D (p<0.05). There was no significant correlation between plasma vitamin D level and SII index (p=0.787).

Table 2. The Variation of Parameters According to Plasma Vitamin D Levels

	Vitamin D n=38 (0-10 ng/mL)	**Vitamin D** n=56 (10-20 ng/mL)	**Vitamin D** n=19 (>20 ng/mL)	***p***
Age (years)	37.44 ±13.10	39.11±12.30	39.32±11.54	0.787
Neutrophil (mm^3)	4082.11±1072.66	4223.93±801.83	4340.00±923.47	0.579
Lymphocyte (mm^3)	2486.05 ±563.67	2627.32± 572.84	2478.42 ±504.44	0.395
Platelet ($x10^3$/mm3)	253.32 ±45.57	250.59 ±37.82	247.58± 57.48	0.895

Hemoglobin (g/dL)	14.13 ±1.11	14.29 ±1.18	13.64 ±1.32	0.121
NLR	1.78 ±0.64	1.69±0.52	1.80± 0.43	0.624
Vitamin B12 (pg/mL)	270.34 ±104.05	333.95± 114.54	317.26 ±94.16	<0.05*
Folate (ng/mL)	6.85±2.76	7.62±3.01	6.36±1.84	0.268
SII	442.63±182.13	424.17±138.38	448.04±159.55	0.787

NLR: Neutrophil to lymphocyte ratio, SII:Systemic immune-inflammation index

DISCUSSION

The worldwide prevalence of vitamin D deficiency is quite higher than 40% but routine screening except for risky patients is not recommended (Palacios & Gonzalez, 2014). The immunomodulatory role of vitamin D and Vitamin D deficiency-related disorders are recent subjects of research (Sassi, Tamone & D'Amelio, 2018).

83% of our patients had vitamin D deficiency. Pin and needle sensation in the hands and feet, fatigue, and dizziness were the main problems of our patients. When we consider the exclusion criteria, these patients had no severe comorbidities but accompanying Vitamin B12 and folate deficiency was remarkable. Insufficient sunlight and nutrition disorders look like major determinants from these results. For vitamin D deficiency-related proinflammation, we researched the SII index sensitivity in this study, but could not observe a relationship.

Immunmodulatory perspective of Vitamin D is among the other subjects of researches. Vitamin D deficiency was correlated with severe respiratory infections and tuberculosis along with the benificial role of replacement (Adrian R. Martineau et al., 2017). For patients with coronavirus disease 2019 (COVID-19), therapy with vitamin D had favorable effects in terms of viral replication (Gündüz & Karaaslan, 2020; Mitchell, 2020). For autoimmune disorders, vitamin D deficiency was associated with multiple sclerosis, type 1 diabetes, systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease (Bae & Lee, 2018; Duan et al., 2014). Although these studies were considerable, treatment with vitamin D has not been associated with favorable outcomes (Martens, Gysemans, Verstuyf & Mathieu, 2020). The other disorders associated with vitamin D deficiency are atherosclerosis, essential hypertension, peripheral arteriopathies, metabolic syndrome, and chronic liver disease. In patients with non-alcoholic fatty liver disease, decreased vitamin D was associated with fibrosis grade (Kim, Rotundo, Kothari, Kim & Pyrsopoulos, 2017). In observational studies, vitamin D replacement was demonstrated with favorable results in oncologic disorders, but the same benefit was not observed in randomized controlled trials (Goyal, Perisetti, Rahman, Levin & Lippi, 2019).

Erythrocyte sedimentation rate and C-reactive protein were exhibited as sensitive markers for vitamin D deficiency-related proinflammatory. Although increased sedimentation rate was associated with vitamin D deficiency, no relationship was observed with C-reactive protein (de la Torre Lossa, Moreno Álvarez, González Guzmán, López Martínez & Ríos Acosta, 2020; Kaya, Akçay, Ertürk, Ergenç & Tamer, 2018). More sensitive inflammatory markers are popular subjects for researchers in recent years. In 2014, the SII index was firstly published in patients with hepatocellular carcinoma (Hu et al., 2014). The increased score was associated with an unfavorable prognosis for lung, gastrointestinal, gynecological, breast cancers, and hepatocellular carcinoma (Ji & Wang, 2020; Wang et al., 2019). In a large prospective cohort study with 442,115 cases, this index was researched with neutrophil platelet ratio, platelet lymphocyte ratio, and lymphocyte monocyte ratio, and its' sensitivity were proven in good grade in the last year before clinical diagnosis (Nøst et al., 2021).

The other disorder associated with this index has been coronary artery disease, and increased SII was associated with cardiac death, nonfatal stroke, and nonfatal myocardial infarction (Yang et al., 2020). For patients with Parkinson's disease, this index was demonstrated as a predictor of motor performance along with vitamin B12 and folate (S. Li et al., 2021). In our study, the mean age of our patients was 38.58±12.37 years and the mean results of vitamin B12, folate, and vitamin D were at the lower limit. Because of retrospective properties, only vitamin B12 and folate were demonstrated with vitamin D. Vitamin D deficiency was detected in 83% of our patients. The variation of the SII index was researched between the patients with different vitamin D levels in our study. As far as in the literature, no similar study has been found on this subject. The limitations of our study were deficient data for nutrition, the absence of other vitamin and mineral status, and a relatively insufficient number of patients. The other inflammatory markers could be included and the variation of the SII index could be researched according to co-morbidities and medications.

CONCLUSIONS

Vitamin D deficiency-related pro-inflammation and disorders are one of the subjects of research in recent years. The SII index has been associated with unfavorable outcomes in many disorders, especially for patients with malignancy. In this study we could not observe a relationship between SII index and vitamin D deficiency, but we believe that this study, inspire novel research to determining the deficiency-related pro-inflammation.

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