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ORIGINAL ARTICLE

INVESTIGATION OF THE RELATIONSHIP BETWEEN VITAMIN D LEVELS AND SYSTEMIC IMMUNE INFLAMMATION INDEX PARAMETERS IN PEOPLE OVER 65 YEARS OF AGE

Abstract

Introduction: Vitamin D exerts anti-inflammatory effects. This study investigated the relationship between vitamin D levels and inflammatory parameters in older adults.

Materials and Method: This retrospective study included healthy older individuals aged >65 years treated at the Geriatrics Clinic of Ankara Bilkent City Hospital between January 1 and December 31, 2023. Based on the exclusion criteria and simultaneous measurements of vitamin D levels, complete blood count, and C-reactive protein levels, 654 patients were included in the study. Systemic immune inflammatory parameters were calculated from complete blood counts. First, the correlations among vitamin D, C-reactive protein, and systemic immune inflammation parameters were investigated. Individuals were classified according to their vitamin D levels in deficient, insufficient, or normal groups. The groups were then compared for systemic immune inflammation and C-reactive protein levels.

Results: C-reactive protein levels were negatively correlated with vitamin D levels and positively correlated with systemic immune inflammation parameters.Furthermore, a weak correlation was observed between systemic immune inflammation parameters and vitamin D. C-reactive protein levels were significantly higher in the deficient group than in the insufficient and normal groups. Systemic immune inflammatory parameters were significantly higher in the deficient and insufficiency groups than in the control group.

Conclusion: Low vitamin D levels are associated with increased inflammation. Incorporating systemic immune inflammatory parameters into routine complete blood count reports will facilitate their clinical use. In the future, we plan to investigate the molecular mechanisms underlying the relationship between vitamin D and inflammation.

Keywords: Vitamin D; Inflammation; Aged.

INTRODUCTION

Inflammation is a simple but complex physiological phenomenon, defined as a unique response of the body to tissue damage or inflammatory stimuli (1). Long-term inflammation can lead to insulin resistance, diabetes, heart disease, atherosclerosis, obesity, and metabolic syndromes. Inflammation may also play a role in the pathogenesis of many neurological diseases, including Alzheimer's disease (2). Systemic immune inflammation index parameters (SIP) are typically calculated using parameters measured during routine complete blood counts (leukocytes, lymphocytes, neutrophils platelets, and monocytes). Recently, SIP parameters have emerged as a noninvasive marker to determine the severity, prognosis, and activation of any disease, as well as to assess the degree of inflammation. Notably, in patients with high SIP values, the inflammatory response is high and disease prognosis is poor (3).

Anti-inflammatory drugs and dietary interventions are frequently used to treat chronic inflammation. Vitamin D has recently been recognized as an anti-inflammatory agent. It exhibits antiapoptotic, anti-inflammatory, and immune-regulatory properties. Owing to its pleiotropic effects, vitamin D deficiency is associated with cardiovascular and other diseases (diabetes and cancer), low resistance to infectious diseases, and the emergence of autoimmune diseases (4). Many factors, including ages, seasons, environmental factors, genetic factors, and various diseases, negatively affect vitamin D synthesis, commonly leading to deficiencies and insufficiencies.But structural changes in the dermis that occur with ageing have been reported to significantly decrease vitamin D synthesis in the skin. Consequently, a 70-year-old produces 75% less vitamin D through skin synthesis than a 20-year-old (5). According to the study by Nowak et al., vitamin D deficiency is observed in all geriatric patients, regardless of the season (6). Elderly individuals are also susceptible to vitamin D deficiency when they are not absorbing dietary supplements or animal foods adequately (7). Consequently, vitamin D insufficiency or deficiency, especially in older individuals is a global public health concern.

Vitamin D has immunomodulatory and anti-inflammatory properties (4). However, whether vitamin D deficiency occurs due to inflammation or inflammation occurs due to vitamin D deficiency remains unclear. This study aimed to investigate the correlation between vitamin D levels and SIP while excluding clinical conditions that may cause inflammation. In addition, we examined whether SIP parameters vary according to vitamin D levels categorized as deficient, insufficient, and normal.

MATERIALS AND METHOD

This study was approved by Ankara Yıldırım Beyazıt University Health Sciences Ethics Committee on 14.03.2024 under the number 02-580. This retrospective study analyzed the data of patients who visited the Geriatrics Clinic of Ankara Bilkent City Hospital between January 1 and December 31, 2023, without any sex discrimination. Demographic information, including age, sex, educational status, chronic diseases, and simultaneous vitamin D levels, CRP,and complete blood results, was collected from the files.In hospitals, CRP levels are routinely measured in patient files, but high-sensitivity CRP (hs-CRP) is not routinely measured. Therefore, hs-CRP data were not collected because of insufficient number of hs-CRPs. As in previous studies (5, 6) the seasonal cycle was not considered when collecting data on vitamin D levels. Patients with deficiencies in blood tests, infections detected in blood and urine cultures, age <65 years, neurological diseases (Alzheimer's disease, dementia, Parkinson's disease), malignancy, inflammatory rheumatic diseases, fractures in the extremities, neuropathy, those receiving anti-inflammatory treatments, or those using antibiotics were excluded.

According to the reference ranges, vitamin D levels were classified as normal (75–375 nmol/L), insufficient (50–75 nmol/L), and deficient (<50 nmol/L). Vitamin D levels >375 nmol/L were considered toxic. We first performed correlation analysis between vitamin D and CRP levels and inflammation parameters for all data and classified the patients into three groups according to the vitamin D levels: deficient vitamin D group (DG), insufficient vitamin D group (IG), and normal vitamin D group (NG). Similarly, according to the reference ranges, normal values were defined as follows: 0–5 mg/L for CRP, 3.6–10.5 × 10^9/L for leukocytes, 1.5–7.7 × 10^9/L for neutrophils, 1.1–4 × 10^9/L for lymphocytes, 0.1–0.9 × 10^9/L for monocytes, and 160–400 ×10^9/L for platelets.

After manually entering the data of older adults suitable for the study into an Excel file, SIP-related calculations were performed according to the formulas below:

SII: (Platelet×Neutrophil/Lymphocyte Ratio) Platelet×Neutrophil/Lymphocyte

NLR: Neutrophil/Lymphocyte

dNLR: (derived NLR) Neutrophil/(Leukocyte-Lymphocyte)

PLR: (Platelet Lymphocyte Ratio) Platelet/Lymphocyte

MLR: (Monocyte Lymphocyte Ratio) Monocyte/Lymphocyte

NLPR: (Neutrophil Lymphocyte Platelet Ratio) Neutrophil/Lymphocyte×Platelet

SIR-I: Neutrophil × Monocyte/Lymphocyte)

Kolmogorov–Smirnov analysis was performed to assess the normality of the data distribution. Notably, the data were not normally distributed ($p<0.05$). Furthermore, as our sample size exceeded 50, skewness and kurtosis analyseswere performed, which also confirmed that the data were not normally distributed. Therefore, nonparametric tests were used for analysis. Spearman rank correlation analysis was used to determine the relationship between the parameters in our data. As significant correlation was observed, the data were divided into three aforementioned groups. The Kruskal–Wallis H test was used to analyze differences among three or more groups. For variables showing significant differences, the Mann–Whitney U test was conducted to identify which specific groups differed significantly. All statistical analyses were performed using the IBM SPSS Statistics version 22. Significance level was set at $p<0.05$.

RESULTS

In this retrospective study, we obtained the records of 2,713 patients. Approximately 1,000 patients who were in follow-up and underwent examinations at defined intervals were excluded. Finally, 654 participants were included. Among the older adults included in the study, 215 were men and 439 were women. The mean age of participants was 76.9 years. Among the older adults, 9.4% were followed up with a diagnosis of hypertension (HT), were using antihypertensive drugs, and had regulated blood pressure. Furthermore, 60.1% of the older adults were followed up with a diagnosis of diabetes mellitus (DM) + HT, and 5% were followed up only with a diagnosis of DM. Based on the HbA1c levels of individuals diagnosed with DM, only those with regulated blood sugar levels (HbA1c level <47) were included in the study. Additionally, 25.5% of older adults did not have chronic diseases during the follow-up (Table 1).

We examined the correlation between vitamin D, CRP, and SIP parameters. We observed a negative correlation between vitamin D and CRP ($r(654)= -0.184$; $p<0.001$) and a weakly significant negative correlation between vitamin D and SIP parameters (SII [$r(654)= -0.268$; $p<0.001$], NLR [$r(654)= -0.287$; $p<0.001$], dNLR [$r(654)= -0.264$; $p<0.001$], PLR [$r(654)= -0.162$; $p<0.001$], MLR [$r(654)= -0.250$; $p<0.001$], NLRP [$r(654)= -0.211$; $p<0.001$], and SIR-I [$r(654)= -0.291$; $p<0.001$]). CRP exhibited varying

Table 1. Demographic information of older adults. DM, diabetes mellitus; HT, hypertension

Variables		n (%)
Sex	Women	439 (67.1)
	Men	215 (33.9)
Education	Uneducated	97 (14.6)
	Less educated	67 (10.1)
	Primary school	227 (34.6)
	Secondary school	86 (13.1)
	High school	113 (17.1)
	University	64 (9.8)
Vitamin D levels	Deficient	245 (37.2)
	Insufficient	189 (29.4)
	Normal	220 (33.4)
Chronic diseases	Regulated hypertension	62 (9.4)
	Regulated DM + HT	395 (60.1)
	Regulated DM	32 (5)
	No chronic disease	165 (25.5)
Total patients		654 (100)

degrees of positive correlation with SII, NLR, dNLR, PLR, MLR, NLPR, and SIR-I (Table 2).

The data were grouped according to vitamin D levels, and the groups were compared based on CRP levels. CRP levels of the DG group were statistically higher than in the ID and ND groups (mean±standard deviation [SD] values 9.193±13.05 mg/L, 6.635±11.47 mg/L, and 6.184±14.63 mg/L, respectively, $p<0.001$) (Table 3).

The SII values, were significantly higher in the DG (736.782±380.70) and ID groups (656.578±264.23) than in the ND group (527.145 ± 256.97) ($p<0.001$) (Table 3).

In the analyses for NLR and dNLR parameters, the values in DG, IG, and NG groups for both parameters gradually decreased, and the difference between all groups was statistically significant (NLR: 2.989 ± 1.39, 2.612 ± 0.95, and 2.170 ± 0.99, respectively, $p<0.05$), (dNLR: 1.984 ± 0.73, 1.759 ± 0.57, and 1.553 ± 0.62, respectively, $p<0.001$) (Table 3).

In PLR analysis, the lowest PLR value was observed in the NG group, and this decrease was

Table 2. Correlation results and significance levels between vitamin D, C-reactive protein, and systemic immune inflammation parameters.

	Mean±SD	Vitamin D	CRP	SII	NLR	dNLR	PLR	MLR	NLPR	SIR-I
Vitamin D	63.980± 33.94	1								
CRP	7.442±13.24	-0.184*	1							
SII	643.083±322.90	-0.268*	0.263*	1						
NLR	2.605±1.20	-0.287*	0.224*	0.772*	1					
dNLR	1.774±0.67	-0.264*	0.195*	0.754*	0.952*	1				
PLR	149.877±60.90	-0.162*	0.129*	0.726*	0.511*	0.460*	1			
MLR	0.295±0.71	-0.250*	0.210*	0.517*	0.682*	0.531*	0.453*	1		
NLPR	0.011±0.01	-0.211*	0.128*	0.358*	0.845*	0.805*	0.192*	0.615*	1	
SIR-I	1.313±3.27	-0.291*	0.295*	0.685*	0.766*	0.674*	0.274*	0.836*	0.593*	1

* $p<0.001$. CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; dNLR, derived neutrophil lymphocyte ratio; PLR,platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio; NLPR, neutrophil lymphocyte platelet ratio; SIR-I, systemic inflammation response index; SII, systemic immune inflammation index. Results are presented as themean± standard deviation.

significant compared with that in the DG and IG groups (Table 3).

For MLR values, the mean ± SD in the NG group (0.263 ± 0.75) was lower than that in the ID and NG groups (p<0.001).

A significant difference was found between all groups for the NLRP level. The NLRP mean ± SD values were 0.013±0.01, 0.011±0.010, and 0.010±0.01 in the DG, IG, and NG groups, respectively (p<0.001) (Table 3).

SIR-I was 1.618 ± 4.59 in the DG group, 1.233±1.27 in the ID group, and 1.043±2.60 in the NG group, and the difference between all groups was statistically significant (p<0.001) (Table 3).

Examination of the SIR-I parameter revealed a significant difference between the groups (p<0.001). The average of individuals with normal vitamin D levels (1.043±2.60) was found to be significantly lower than that of the other groups (p<0.001). Furthermore, the average of individuals with insufficient vitamin D levels (1.233 ± 1.27) was significantly lower than the average of individuals with deficient vitamin D levels (1.618 ± 4.59) (p<0.010) (Table 3).

DISCUSSION

This study investigated the correlation between SIPand vitamin D in older adults. SIP has recently been reported as an indicator of inflammation (8).

Table 3. Comparison of systemic immune inflammation index (SII) parameters and significance levels among groups.

Variables	Deficient group (DG) (n=245)	Insufficient group (IG) (n=189)	Normal group (NG) (n=220)	Significant difference*
	Mean±SD	Mean±SD	Mean±SD	
CRP (mg/L)	9.193±13.05	6.635±11.47	6.184±14.63	DG>IG DG>NG
SII	736.782±380.70	656.578±264.23	527.145±256.97	DG>NG IG>NG
NLR	2.989±1.39	2.612±0.95	2.170±0.99	DG>IG DG>NG IG>NG
dNLR	1.984±0.73	1.759±0.57	1.553±0.62	DG>IG DG>NG IG>NG
PLR	160.103±66.76	155.036±58.05	134.058±53.02	DG>NG IG>NG
MLR	0.336±0.89	0.279±0.23	0.263±0.75	DG>NG IG>NG
NLPR	0.013±0.01	0.011±0.01	0.010±0.01	DG>IG DG>NG IG>NG
SIR-I	1.618±4.59	1.233±1.27	1.043±2.60	DG>IG DG>NG IG>NG

*p<0.05, Mann–Whitney U

* p<0.001. CRP, C-reactive protein; NLR, neutrophil lymphocyte ratio; dNLR, derived neutrophil lymphocyte ratio; PLR,platelet lymphocyte ratio; MLR, monocyte lymphocyte ratio; NLPR, neutrophil lymphocyte platelet ratio; SIR-I, systemic inflammation response index; SII, systemic immune inflammation index. Results are presented as the mean±standarddeviation

First, we examined the relationship between vitamin D and CRP levels. CRP level is a potent marker of inflammation (9). Studies on CRP and vitamin D levels have indicated their possible correlation with inflammation (10). Statistical analyses revealed a weak inverse correlation between vitamin D and CRP levels in individuals aged >65 years. Therefore, we confirmed the correlation between vitamin D levels and inflammation. However, high SIP levels were observed at high CRP levels, indicating a positive correlation. These results also support the notion that SIP levels can be considered as the marker of inflammation.

Further analysis revealed a similarly weak negative correlation between vitamin D levels and SIP, and as vitamin D levels decreased, SIP levels increased. Our results are consistent with those reported by Dziedzic et al. (11). In this study, a negative correlation was observed between vitamin D levels and the SII and SIR-I levels in 699 adult patients with ischemic heart disease and acute coronary syndrome. A retrospective study by Bayramoğlu et al. involving 103 patients, which investigated the correlation between vitamin D levels and inflammatory markers (CRP, fibrinogen) in young individuals diagnosed with COVID-19, reported a strong negative correlation between vitamin D levels and inflammatory markers (12). Furthermore, adult patients with acute coronary syndrome exhibited a strong negative correlation between vitamin D, SII, and SIR-I levels (11). A study by Vurgun in 2022 involving adults aged ≥18 years revealed weak negative correlations between vitamin D levels and CRP, erythrocyte sedimentation rate, leukocyte count, and NLR parameters (13). Our findings show that variations in SIP values are associated with vitamin D levels, as reported in individuals aged ≥65 years (6), an age group in which vitamin deficiency is common. Meanwhile, in our study, inflammation was confirmed based on the CRP levels and seven different SIP markers. The consistent negative correlations observed across all parameters further strengthened our findings.

The physiological changes in the older adults result in low levels of vitamin D (5, 6). The results of the study by Nowak et al. showed that there was no significant difference in median vitamin D concentration between patients hospitalised during the four seasons. Therefore, appropriate vitamin D supplementation is recommended in the older adult regardless of the season (6).In a study that was performed in Brazil, a very sunny country, vitamin D levels were found to be significantly lower at the end of summer and at the end of winter, but there was no significant difference between the results at the end of the season. Vitamin D levels were also compared with the levels measured in a study conducted in very sunny Islamic countries. Although clothing style was emphasised in these countries, the low levels in Brazil excluded clothing style (14). It is emphasised that inadequate absorption of dietary animal foods or inadequate absorption of supplements in elderly individuals causes vitamin D deficiency regardless of the season (14). In our study, diseases that may cause inflammation were excluded and therefore, according to the results, vitamin D deficiency or insufficiency seems to trigger inflammation. In the study conducted by Konuksever et al., involving 16,312 healthy young individuals aged <18 years, classified all patient data into two groups based on vitamin D deficiency and examined the correlation between inflammatory parameters (NLR, PLR, and CRP) and vitamin D. Statistically significant correlations were observed between inflammatory markers and vitamin D (15). Consistently, our study also demonstrated a negative correlation between vitamin D levels and NLR and PLR. A cross-sectional study by Sharifan et al. assessed a correlation between depression, anxiety, stress, dietary inflammation index, healthy nutrition index, and some inflammation indices (cytokines, CRP, NLR, and PLR) in 309 adult patients. They classified

patients into two groups based on vitamin D levels and reported higher PLR, NLR, and CPR levels in the vitamin D-deficient group (16). Another cross-sectional study of patients on hemodialysis assessed the correlation between vitamin D levels and inflammatory markers (CRP, NLR, and PLR). Notably, these parameters were significantly higher in the vitamin D-deficient group (17). The results of our study are consistent with those of the aforementioned studies.

Vitamin D plays an important role as a regulator of the immune system by reducing the incidence and severity of bacterial and viral infections. Specifically, vitamin D supplementation in cases of vitamin D deficiency reduces the risk of acute respiratory tract infections (18). In a study by Başaran et al., 204 patients diagnosed with COVID-19 could be divided into three groups according to their vitamin D levels (deficient, insufficient, and normal). Inflammation may be more severe in patients with vitamin D deficiency, and CRP levels are significantly higher in the deficient vitamin D group than in the insufficient and normal groups (19), consistent with our findings.

Vitamin D exerts a direct effect on immune cells, which are critical in the pathogenesis of autoimmune diseases. Clinical studies have demonstrated a correlation between vitamin D deficiency and an increased risk of morbidity in cases of infectious diseases, as well as the onset or progression of autoimmune diseases (RA, SLE, and MS) (4).

Maintaining a balance between the pro- and anti-inflammatory components of the immune system is vital. The NLR and NLPR reflect the balance between innate and acquired immunity (20). A study by Shi et al. (21)involving 108 patients reported that high NLPR levels on day 5 in patients hospitalized in the intensive care unit, along with the sequential organ failure assessment score and patient age, could serve as predictive markers for patients with sepsis. A retrospective study by Ghobadi et al. involving 1,792 patients with COVID-19, including 710 older adults, reported similar findings. The study highlighted the utility of parameters such as NLR, PLR, MLR, dNLR, NLPR, aggregate index of systemic inflammation, SIR-I, and SII (22). Although NLPR and other SIP markers offer valuable insights into severe conditions, the relationship between vitamin D levels and SIP in geriatric populations remains unclear.

Although this was a single-center study, our data were derived from one of two geriatric polyclinics in Ankara, representing a substantial proportion of the population in the city. In the present study, we observed increased inflammation at low vitamin D levels, even in the absence of inflammatory triggers. This was determined by examining the SIP levels calculated from routine complete blood count without any additional examinations. We believe that our research will raise awareness among researchers and clinicians that vitamin D levels can be low even in the presence of inflammation. Furthermore, as only NLR values are included in our routine complete blood count reports, adding other SIP markers to the laboratory panels would facilitate their clinical utility. In future studies, we plan to investigate the molecular mechanisms underlying the relationship between vitamin D and inflammation.

Conflict of İnterest: The authors declare that they have no conflicts of interest.

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