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The relationship between vitamin D and inflammatory markers in maintenance hemodialysis patients

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Abstract

Purpose The aim of this study was to investigate the relationship between vitamin D and novel inflammatory markers in hemodialysis patients.

Methods In total, 129 eligible maintenance hemodialysis patients were enrolled in this cross-sectional study. Patients were divided into two groups according to their serum vitamin D levels. A serum 25-hydroxyvitamin D (25(OH)D) level <20 ng/ml was identified as vitamin D deficiency and a serum level ≥ 20 ng/ml was identified as normal. The neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were calculated from the complete blood cell count. Spearman correlation analysis and both logistic and linear regression analyses were used to define the relationships between the study parameters.

Results The two groups showed statistically significant differences for gender and for C-reactive protein (CRP) and NLR values ($p=0.017$, $p=0.010$, and $p=0.013$). Age and gender were independently associated with vitamin D deficiency ($p=0.003$ and $p=0.030$). Serum 25(OH)D levels showed significant but weak inverse correlations with CRP ($r=-0.205$, $p=0.020$) and with NLR ($r=-0.219$, $p=0.013$). Serum 25(OH)D levels also showed a significant but very weak correlation with PLR ($r=-0.182$, $p=0.039$). Serum 25(OH)D levels showed no correlation with mean platelet volume ($p=0.660$). Gender was the only variable significantly associated with serum vitamin D levels, as determined by linear regression analysis ($p=0.003$).

Conclusion CRP levels and NLR values were significantly higher in the vitamin D deficiency group. A significant inverse correlation was found between serum vitamin D levels and CRP levels, and NLR and PLR values.

Keywords Hemodialysis · Inflammation · Vitamin D · C-reactive protein · Neutrophil-to-lymphocyte ratio

Introduction

Chronic kidney disease (CKD) is a growing public health problem with an estimated worldwide prevalence of approximately 10% [1]. The prevalence of end-stage renal disease (ESRD) is also increasing, and current predictions are that nearly 5.5 million people will be treated with renal replacement therapy, mostly in the form of hemodialysis [2]. The mortality rate of hemodialysis patients has decreased in the last decade; however, it is still several times higher than the mortality rate in the normal population [3]. Cardiovascular disease, which is responsible nearly 50% of deaths, is the far more leading cause of death in the hemodialysis population, and inflammation is one of the major mechanisms underlying this condition [4]. The chronic inflammatory state observed in hemodialysis patients is also related to other mortality risk factors, such as anemia, bone-mineral disorders, and malnutrition [5, 6].

Inflammation in hemodialysis patients can be measured using several markers, such as C-reactive protein (CRP), high sensitive CRP, interleukin-6, tumor necrosis factor alpha, procalcitonin, albumin, ferritin, and cholesterol levels [7]. Of these inflammatory markers, CRP is the gold standard in hemodialysis due to its proven accuracy, low cost, and availability [8]. Recently, the use of these markers has been supplemented by inclusion of the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), and the mean platelet volume (MPV) as inflammatory markers in different disorders [9–12]. Current studies now indicate that

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the NLR and PLR, in particular, can be used as reliable and cost-effective inflammation markers in hemodialysis patients [13, 14].

Another potential inflammatory marker is vitamin D, a steroid hormone that plays a central role in bone-mineral metabolism. Vitamin D deficiency is related to cardiovascular disease, autoimmune disease, infections, renal disease, anemia, depression, cognitive dysfunction, and malignancies [15], which are all disorders associated with inflammation [16]. The effects of increasing vitamin D on inflammation—or, conversely, the effects of inflammation on vitamin D levels—remain controversial, although several studies have shown that vitamin D and its analogues have potential anti-inflammatory activities catalyzed by multiple mechanisms [17–19].

A chronic inflammatory state is an important problem in the hemodialysis population. Interestingly, the vast majority of hemodialysis patients also show vitamin D deficiency [20]. However, only a very few limited studies have explored the relationship between vitamin D and inflammation and inflammatory markers, and the results have been conflicting [21, 22]. The aim of the present study was to contribute to the current literature on this topic by investigating the relationship between vitamin D levels and novel inflammatory markers in hemodialysis patients.

Materials and methods

Study design

In this cross-sectional study, 148 patients with ESRD treated with conventional maintenance hemodialysis in our city were evaluated between 01/02/2019 and 10//02/2019. Inclusion criteria for the study were age ≥ 18 years and treatment with hemodialysis due to ESRD for at least 3 months. Exclusion criteria included active infection, unwillingness to participate in the study, history of malignancy, active inflammatory disease, and history of immunosuppressive drug usage. Overall, 11 patients were excluded due to active infection, 4 patients were excluded due to malignancy, 2 patients were excluded due to a history of immunosuppressive drug usage, and 2 patients were excluded due to active inflammatory disease. Ultimately, 129 out of 148 patients who met the criteria were enrolled in the study. The study was approved by the local ethics committee (12/2018; 35/3).

Data collection

All patients were assessed for age, gender, cigarette smoking, dialysis access, dialysis vintage, comorbidities (Charlson comorbidity index, CCI, was used), body mass index, Kt/v index, hemoglobin, albumin, C-reactive protein (CRP), ferritin, intact parathyroid hormone (iPTH), lipid parameters, and serum 25-hydroxyvitamin D (25(OH)D) as a marker for vitamin D status. Blood samples were taken from the patients just before the first midweek dialysis session of the month. Serum 25(OH)D levels were measured by liquid chromatography tandem mass spectroscopy (LC–MS, Agilent Technologies). Measurement of iPTH levels were made by a chemiluminescence method (ADVIA centaur XPT immunoassay, Siemens). Ferritin levels were measured by a ferritin immunoassay (ADVIA Centaur XPT immunoassay, Siemens). Hemoglobin, platelet, mean platelet volume (MPV), and white blood cells (WBCs), including leukocyte differentials, were measured as part of a complete blood cell count by fluorescence flow cytometry (Sysmex XN 2000). Albumin was measured by spectrophotometry (Beckman Coulter AU 2700), CRP was measured by an immunonephelometric method (NFL BN-II), and lipid parameters were measured by an enzymatic color test (Beckman Coulter AU 2700). The NLR and PLR values were calculated from the complete blood cell count as the ratio of neutrophils to lymphocytes (NLR) and the ratio of platelets to lymphocytes (PLR). Patients who had not smoked cigarettes for the last 6 months were evaluated as non-smokers. Although no consensus exists regarding the optimal serum levels of 25(OH)D, most experts define vitamin D deficiency as a serum 25(OH)D level < 20 ng/ml [23, 24]. Therefore, a serum 25(OH) D level of < 20 ng/ml was identified as vitamin D deficiency and a serum level of ≥ 20 ng/ml was identified as normal in our study.

Statistical analysis

The results for categorical variables were presented as numbers and percentages and the results for continuous variables as median (95% confidence interval). Data were analyzed using SPSS 19 for Windows (IBM Corp. Released 2010. IBM Statistics for Windows, Version 19.0. Armonk, NY: IBM Corp.). The Chi square test was used for categorical variables and the independent samples *t* test was used for continuous variables. Logistic regression analysis was performed to determine the effects of possible risk factors for vitamin D deficiency. The correlation between variables was identified using Spearman's rho correlation analysis (for variables that were not normally distributed). Results were given as correlation coefficient (*r*) and *p* values. Linear regression analysis was also used to define independent variables associated with serum vitamin D levels. Age and gender were included in the model as biological adjustment factors. Based on the results of univariate analysis, any variable with a result of $p < 0.25$ was drawn into both the logistic regression analysis and linear regression analysis [25]. A *p* value < 0.05 was considered statistically significant.

Results

A total of 129 maintenance hemodialysis patients were included in the study, based on the eligibility criteria. The mean age of the patients was 60.50 ± 14.79 years, and 55.2% ($n = 72$) of the patients were male. The patients were divided into two groups based on their serum 25(OH) D levels. Patients with serum 25(OH)D levels < 20 ng/ml were classified as having a vitamin D deficiency ($n = 83$) and those with serum 25(OH)D levels ≥ 20 ng/ml were classified as having normal vitamin D levels ($n = 46$). The mean serum 25(OH)D levels were 11.13 ± 3.60 ng/ml in the deficient group and 27.04 ± 7.20 ng/ml in the normal group. The demographics and the clinical and laboratory characteristics of the two groups are presented in Table 1.

Statistically significant differences were detected between the two groups for gender, CRP levels, and the NLR

Table 1 Demographics and clinical and laboratory parameters of hemodialysis patients with vitamin D deficiency and normal serum vitamin D levels

	Patients with vitamin D deficiency ($n = 83$)	Patients with normal vitamin D ($n = 46$)	p
Age (years)	67.0 (63.0–70.0)	59.5 (52–62.0)	**0.007**
Gender			**0.017**
Male	40 (48.2%)	32 (69.6%)	
Female	43 (51.8%)	14 (30.4%)	
Cigarette smoking			0.669
Smoking	17 (20.5%)	8 (17.4%)	
Non-smoking	66 (79.5%)	38 (82.6%)	
Dialysis access			0.234
Fistula or graft	57 (68.7%)	36 (78.3%)	
Catheter	26 (31.3%)	10 (21.7%)	
Conventional maintenance hemodialysis (4 h per session)			0.789
Thrice weekly	79 (95.2%)	44 (95.7%)	
Twice weekly	4 (4.8%)	2 (4.3%)	
Dialysis vintage (months)	36.0 (30.0–54.0)	48.0 (27.0–84.0)	0.219
Comorbidity index	7.0 (6.0–8.0)	6.0 (6.0–8.0)	0.665
Body mass index (kg/m^2)	24.5 (22.6–26.6)	25.6 (23.2–28.8)	0.263
Kt/v index	1.65 (1.58–1.72)	1.57 (1.48–1.69)	0.066
Hemoglobin (g/dl)	11.0 (10.8–11.4)	11.4 (10.8–11.9)	0.389
Albumin (g/dl)	3.8 (3.7–3.9)	3.9 (3.8–4.0)	0.330
CRP (mg/l)	8.9 (6.3–11.4)	6.3 (5.0–8.1)	**0.010**
NLR	2.7 (2.4–3.2)	2.4 (2.1–2.5)	**0.013**
PLR	129.0 (114.2–148.5)	118.7 (103.4–139.0)	0.086
MPV	10.2 (9.7–10.6)	10.0 (9.2–10.7)	0.628
Ferritin (ng/ml)	321.5 (303.6–391.9)	355.5 (320.7–425.0)	0.738
iPTH (pg/ml)	304.9 (235.2–394.0)	401.2 (204.5–561.5)	0.189
LDL-C (mg/dl)	72.0 (67.0–84.8)	79.8 (74.8–92.8)	0.297
HDL-C (mg/dl)	39.0 (36.0–41.0)	37.0 (33.0–40.0)	0.129
Triglyceride (mg/dl)	145.0 (121.0–169.0)	160.0 (130.0–200.0)	0.413
Medications		9.93 ± 1.47	0.368
ESA	64 (77.1%)	36 (78.2)	0.128
Vitamin D analogs	25 (30.12%)	19 (41.3%)	0.096
Antihypertensive	52 (62.6)	31 (67.3)	0.678
ESA dose (units/week)	4000.0 (3000.0–4000.0)	4000.0 (3000.0–4500.0)	0.107
Iron dose (mg/week)	100.0 (100.0–200.0)	100.0 (100.0–100.0)	0.065

Significant p values are indicated in bold

Results are presented as median (95% confidence interval) for continuous variables and n (%) for categorical variables

CRP C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *iPTH* intact parathyroid hormone, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *ESA* erythropoiesis-stimulating agent

($p=0.017$, $p=0.010$ and $p=0.013$, respectively). Logistic regression analysis was used to define the possible independent risk factors for vitamin D deficiency (Table 2). Age and gender were independently associated with vitamin D deficiency ($p=0.003$ and $p=0.030$, respectively). The risk of vitamin D deficiency was decreased 4.8-fold by male gender.

Correlation analysis between serum 25(OH)D levels and inflammatory markers showed that serum 25(OH)D levels had a significant but weak inverse correlation with CRP level ($r=-0.205$, $p=0.020$) and with the NLR ($r=-0.219$, $p=0.013$). Similarly, serum 25(OH)D levels showed a significant but very weak inverse correlation with the PLR ($r=-0.182$, $p=0.039$). No significant correlation was noted between serum 25(OH)D levels and the MPV ($p=0.660$). Scatter plot graphics of the correlations are shown in Fig. 1.

We also analyzed the independent risk factors for serum vitamin D levels by multiple linear regression analysis (Table 3). The only significantly associated variable with serum vitamin D levels was gender ($p=0.003$).

Discussion

A chronic inflammatory state is one of the major factors underlying the increased mortality observed in hemodialysis patients. An increasing number of studies now show that more than half of hemodialysis patients have elevated inflammatory markers and that these markers (especially CRP) are strongly associated with mortality and morbidity in this population [26]. In our study, we also found that more than half of our patients had increased levels of inflammatory markers. In recent years, the NLR, PLR, and MPV have been identified as novel and inexpensive inflammatory markers of systemic inflammation that can be used to estimate survival and adverse outcomes in a variety of diseases, including ESRD [9, 13, 27]. Hemodialysis patients also show an even higher prevalence of 25(OH)D deficiency than is seen in the normal population, in which deficiency of this vitamin already exists across the globe [20]. An association between vitamin D and inflammation has been described, although the direction of the relationship remains controversial. Some studies have claimed that inflammation reduces vitamin D levels, while others have claimed that increased vitamin D levels can suppress inflammation [28, 29].

Some researchers have examined the relationship between vitamin D levels and inflammatory markers but have reported controversial results. For example, the retrospective study by Akbas et al. of 4120 patients reported a significant association of the PLR and NLR with 25(OH)D levels [30]. A study examining > 17,000 asymptomatic adults indicated a statistically significant inverse relationship between 25(OH)D deficiency and CRP levels [31]. Conversely, a study of chronic urticaria patients found no significant relationship between vitamin D and CRP levels [32]. Liefaard et al. showed that higher levels of vitamin D were associated with lower levels of CRP, but they found no causal relationship [33].

In the hemodialysis population, very limited data are available regarding the relationship between vitamin D and inflammatory markers, although alterations in both are much more commonly seen than in the general population. Mirchi et al. investigated the relationship between 25(OH)D level and inflammatory markers in hemodialysis and peritoneal dialysis patients and found significantly higher NLR and hsCRP values in the low 25(OH)D group. A weak negative inverse correlation was also found between 25(OH)D and hsCRP [22]. A cross-sectional study of hemodialysis patients by Mohiuddin et al. analyzed the relationship between vitamin D level and inflammatory markers and reported no significant association between vitamin D levels and CRP levels [21]. In the present study, the 25(OH) deficiency rate in our patients was 64.3%, consistent with the literature [20]. We also found significantly higher CRP and NLR values in the 25(OH)D deficiency group, but neither value was an independent risk factor for vitamin D deficiency, according to our logistic regression analysis. Age and gender were independent risk factors for vitamin D deficiency, as in the general population.

Gender was the only significant risk factor for serum 25(OH)D levels. Our findings are compatible with the

Table 2 Factors associated with normal serum vitamin D levels in hemodialysis patients according to logistic regression analysis

	β	Odds ratio	95% confidence interval		p
			Lower	Upper	
Age (years)	−0.070	0.932	0.889	0.977	**0.003**
Gender (male)	1.565	4.781	1.166	19.607	**0.030**
Kt/v	−1.467	0.231	0.026	2.041	0.187
CRP (mg/l)	−0.025	0.975	0.886	1.073	0.606
NLR	−0.208	0.812	0.405	1.627	0.558
PLR	0.001	1.001	0.985	1.016	0.943
MPV (fl)	0.103	1.109	0.773	1.589	0.575
HDL (mg/dl)	0.037	1.037	0.964	1.116	0.330
iPTH (pg/ml)	−0.001	0.999	0.997	1.001	0.578
ESA	0.032	1.032	0.195	5.463	0.970
Vitamin D analogs	−0.992	0.371	0.070	1.962	0.243
Iron dose (mg/week)	−0.008	0.992	0.982	1.003	0.162
ESA dose (units/week)	0.000	1.000	1.000	1.000	0.988

Significant p values are indicated in bold

CRP C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MPV* mean platelet volume, *HDL-C* high-density lipoprotein cholesterol, *iPTH* intact parathyroid hormone, *ESA* erythropoiesis-stimulating agent

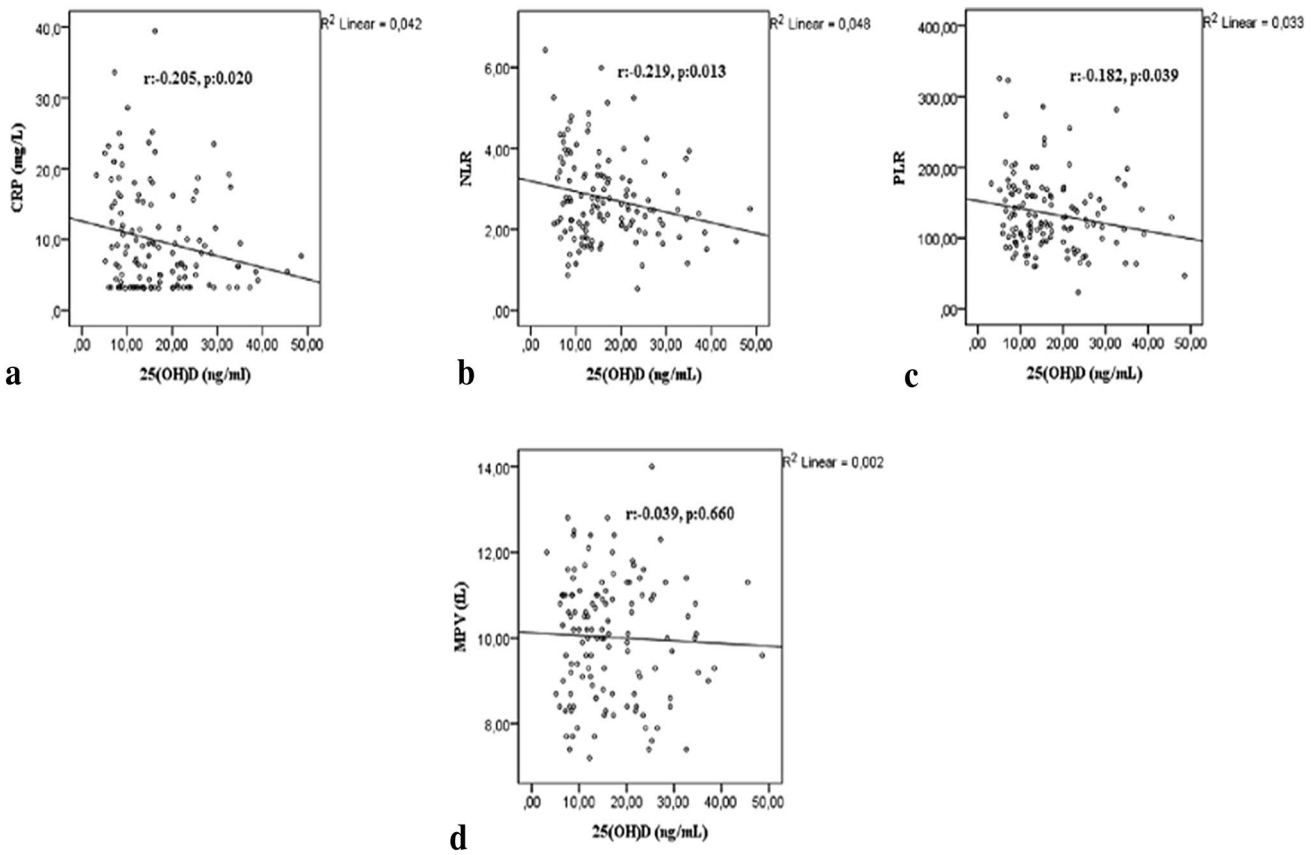

Fig. 1 Scatter plot graphs of the Spearman correlation analysis **a** between 25(OH)D and CRP, **b** between 25(OH)D and NLR, **c** between 25(OH)D and PLR, and **d** between 25(OH)D and MPV. Each symbol represents one patient. The continuous line indicates the least-square linear regression. *25(OH)D* 25-hydroxyvitamin D, *CRP* C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MPV* mean platelet volume

Table 3 Factors associated with serum vitamin D levels

	Univariate			Multivariate		
	$\beta \pm$ SE	95% CI	*p*	$\beta \pm$ SE	95% CI	*p*
Age (years)	−0.086 ± 0.055	−0.195 to 0.022	0.119	−0.073 ± 0.052	−0.176 to 0.030	0.166
Gender (female)	−4.388 ± 1.596	−7.545 to− 1.231	0.070	−4.721 ± 1.585	−7.858 to − 1.583	**0.003**
CRP (mg/l)	−0.258 ± 0.109	−0.474 to − 0.042	0.020	−0.171 ± 0.109	−0.387 to 0.044	0.118
NLR	− 1.865 ± 0.736	− 3.322 to − 0.408	0.013	− 1.068 ± 0.837	− 2.725 to 0.589	0.204
PLR	−0.031 ± 0.015	−0.061 to − 0.002	0.039	−0.008 ± 0.017	−0.040 to 0.025	0.640
MPV (fl)	−0.252 ± 0.570	− 1.380 to 0.877	0.660	0.063 ± 0.571	− 1.067 to 1.194	0.992

Significant *p* value is indicated in bold

CRP C-reactive protein, *NLR* neutrophil-to-lymphocyte ratio, *PLR* platelet-to-lymphocyte ratio, *MPV* mean platelet volume, *CI* confidence interval

previous studies conducted in normal populations and hemodialysis populations. In addition, this finding is also logical due to the traditional religious clothing worn by women, as covering the body inhibits the conversion of vitamin D by the sun. The second possible reason is that females have a higher body fat percentage compared to males. The low vitamin D status in female participants is probably a consequence of an increased sequestration of vitamin D in adipose tissue. We also found a significant but weak inverse relationship between vitamin D levels and both CRP and NLR values. We also found a significant but very weak inverse correlation between PLR and 25(OH)D levels but

we found no correlation between MPV values and 25(OH)D levels. Our regression analysis indicated no significant relationship between 25(OH)D levels and inflammatory markers, although the CRP and NLR values were significantly correlated.

Our study had several limitations. It was a cross-sectional study; therefore, we cannot establish a causal relationship between inflammatory markers and serum vitamin D levels. Another limitation is the rather limited number of inflammatory markers actually studied, although the selected markers are widely used, inexpensive, and proven markers of inflammation. The relatively small sample size was another limitation, although the number of patients was adequate to show the statistical significance of the relationships.

In conclusion, we found that the CRP and NLR values were significantly higher in the vitamin D deficiency group than in the normal group. We showed a significant inverse correlation between serum vitamin D levels and the values for CRP, NLR, and PLR, which are all inexpensive and universally available inflammation markers. Our regression analyses did not indicate any significant relationship between these inflammatory markers and vitamin D levels or vitamin D deficiency. Our results might suggest that an unknown underlying mechanism is responsible for the inverse relationship observed in hemodialysis patients. Our study provides a significant contribution to the literature by adding to the very limited number of studies that have, in general, reported controversial results on this topic. We believe that our study can lead to more comprehensive studies that will better investigate the relationship between vitamin D levels and inflammatory markers in the hemodialysis population.

Compliance with ethical standards

Conflict of interest There is no conflict of interest, and that all the authors have read and approved the manuscript being submitted.

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