Vitamin D and inflammation: evaluation with neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio

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Abstract

Introduction: Association of vitamin D, inflammation and endothelial dysfunction, beside the classic bone metabolism disorders, may explain the pathogenesis of numerous diseases associated with vitamin D deficiency. While large numbers of reports support the relationship of vitamin D with inflammation, several reports fail to confirm this relationship. Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) are novel and inexpensive markers of inflammation that can be studied in all centers. The goal of this study was to investigate the association between 25-hydroxy vitamin D (25(OH)D) and inflammation with the novel inflammatory markers NLR and PLR.

Material and methods: This study was performed retrospectively. Results of the simultaneously performed 25(OH)D, parathyroid hormone, albumin, calcium, phosphorus, alkaline phosphatase and creatinine level measurements and complete blood count were recorded. The data of 4120 patients were included in the study.

Results: Between vitamin D deficient and non-deficient groups there were significant differences in PLR ($p < 0.001$) and NLR ($p = 0.001$). Vitamin D had a significant negative correlation with PLR ($p < 0.001$) and NLR ($p < 0.001$). Multiple regression analysis indicated that 25(OH)D was independently and negatively correlated with PLR (OR = 0.994, 95% CI 0.991–0.998, $p = 0.02$).

Conclusions: Platelet-to-lymphocyte ratio and NLR were significantly associated with 25(OH)D levels, and PLR was found to be an independent predictor of 25(OH)D levels. Our study revealed an inverse association of vitamin D levels and inflammation with these inexpensive and universally available markers.

Key words: vitamin D, inflammation, endothelial dysfunction.

Introduction

Hypovitaminosis D is a common and emerging health problem worldwide [1]. Vitamin D is an essential component of bone and mineral metabolism; its deficiency classically causes growth retardation, skeletal deformities in children, and osteomalacia and osteoporosis in adults. Moreover, vitamin D plays a role in diseases other than those of bone such as cardiovascular diseases, obesity, metabolic syndrome,

insulin resistance, infection, allergy, cancers and autoimmune diseases [2–14].

Although there are studies that failed to find a relationship [10, 15–20], inflammatory cytokines such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), and interleukin (IL)-6 were found to be inversely associated with vitamin D levels [21–25]. Additionally, there are studies suggesting that vitamin D deficiency is associated with elevated TNF-α, IL-6, and CRP concentrations, which are correctable by supplementation [4, 26, 27].

Neutrophil-to-lymphocyte ratio (NLR) and platelet-to-lymphocyte ratio (PLR) were introduced as easily measured, reproducible, and inexpensive markers to determine inflammation. Neutrophil-to-lymphocyte ratio has been found to be associated with different types of malignancies, metabolic syndrome, infectious diseases, cardio vascular disease, end stage renal disease and other inflammatory diseases [28–38]. Also PLR has been found to be associated with different types of malignancies, cardiovascular disease and end stage renal disease [28, 37, 39–42].

The goal of this study was to investigate and evaluate the association between 25-hydroxy vitamin D (25(OH)D) and inflammation with the novel inflammatory markers NLR and PLR.

Material and methods

Study design, data collection and procedures

This study was performed retrospectively using Ataturk University Hospital database. The database was screened from 2008 until 2013. Results of the simultaneously performed measurements of 25(OH)D levels by competitive electrochemiluminescence protein binding assay (Cobas-601, Roche/Cobas Diagnostics, Tokyo, Japan); parathyroid hormone (PTH) levels by chemiluminescence assay (UniCel DXi 800 immunoassay system, Beckman Coulter, Fullerton CA, USA); albumin, calcium, phosphorus, alkaline phosphatase (ALP), and creatinine levels by spectrophotometric assay (AU5800 – Beckman Coulter, Beckman coulter, Mishima, Japan); and complete blood count (CBC) (Beckman Coulter, Fullerton CA, USA) were recorded. Patients whose ages were under 18 years, patients with primary hyperparathyroidism, high creatinine levels (creatinine > 1.2 mg/dl) and patients with abnormal lymphocyte (normal values: 1000–4800/mm^3), platelet (normal values: 150 000–450 000/mm^3) and neutrophil (normal values: 1500–8000/mm^3) count values were excluded from the evaluation to exclude the effects of undesirable factors such as acute infection. In repeated applications, initial tests were recorded. Study participants' age and gender were recorded. The data of 4120 patients who met the criteria were included in the study.

Neutrophil-to-lymphocyte ratio and PLR were calculated as the ratio of neutrophils to lymphocytes and platelets to lymphocytes respectively. Corrected calcium (C-calcium) was calculated by a standard formula: (C-calcium = total calcium + 0.8 × (4 – albumin)).

Patients were separated into groups according to aging stages (young adulthood (18–34 years), young middle-age (35–44 years), later middle age (45–64 years), early old age (65–74 years), middle old age (75–84 years), very old age (over 85 years)). Vitamin D status was classified as vitamin deficiency (< 20 ng/ml) and non-deficiency (> 20 ng/ml) according to Holick *et al.* [43].

Statistical analysis

Statistical analyses were carried out using the Statistical Package for Social Sciences, Windows version 15.0 (SPSS, Chicago, IL, USA). Descriptive statistics for each variable were determined. Results for continuous variables without normal distribution were presented as median (interquartile range (IQR)). Statistically significant differences between the groups were determined by the χ^2 test for categorical variables and the Mann-Whitney *U* test for continuous variables without normal distribution. Kruskal-Wallis analysis was used to compare means of several groups without normal distribution. Associations between the variables were explored using Spearman's rho (for data that are not normally distributed). Binary logistic regression analysis was also performed to define variables associated with 25(OH)D. A *p*-value less than 0.05 was considered significant.

Results

Baseline characteristics and laboratory data of patients according to aging stages are given in Table I. Briefly, while there were no significant differences between groups according to the sex distribution, there were statistically significant differences with respect to the following variables between groups: 25(OH)D, PTH, ALP, calcium, C-calcium, phosphorus, albumin, creatinine, WBC, PLR and NLR.

When patients were separated into two groups according to 25(OH)D levels (group 1 – 25(OH)D < 20 ng/ml; group 2 – 25(OH)D ≥ 20 ng/ml), while there were no significant differences between groups according to age, phosphorus and WBC, there were statistically significant differences between groups for the following variables: PTH, ALP, calcium, C-calcium, albumin, creatinine, PLR and NLR (Table II).

Table I. Demographic, clinic and laboratory characteristics of subjects according to aging stages

Parameters	Young adulthood (18–34 years) (*n* = 927)	Young middle age (35–44 years) (*n* = 632)	Later middle age (45–64 years) (*n* = 1630)	Early old age (65–74 years) (*n* = 645)	Middle old age (75–84 years) (*n* = 251)	Very old age (≥ 85 years) (*n* = 35)	*P*-value
Sex (female/male)[a]	616/311	431/201	1095/535	418/227	159/92	21/14	0.583
25OHVitD [ng/ml][b]	10 (6–17)	10 (6–17)	10 (6–17)	9 (5–17)	9 (5–17)	6 (4–8)	< 0.001
PTH [pg/ml][b]	40.2 (29.0–55.1)	43.3 (32.1–59.8)	44.3 (31.6–62.4)	47.5 (33.1–69.5)	58.0 (38.8–84.3)	62.9 (47.0–79.4)	< 0.001
ALP [U/l][b]	72 (58–94)	71 (57–88)	83 (66–104)	85 (67–114)	84 (68–109)	88 (76–124)	< 0.001
Calcium [mg/dl][b]	9.6 (9.2–9.9)	9.5 (9.0–9.8)	9.4 (9.0–9.8)	9.4 (8.9–9.8)	9.2 (8.7–9.6)	8.9 (8.5–9.4)	< 0.001
C-calcium [mg/dl][b]	9.6 (9.2–9.9)	9.5 (9.0–9.8)	9.5 (9.1–9.8)	9.5 (9.1–9.8)	9.4 (9.0–9.7)	9.2 (8.6–9.5)	< 0.001
Phosphorus [mg/dl][b]	3.6 (3.2–3.9)	3.4 (3.0–3.8)	3.5 (3.1–3.9)	3.4 (3.0–3.8)	3.3 (2.9–3.7)	3.2 (2.8–3.7)	< 0.001
Albumin [g/dl][b]	4.5 (4.3–4.7)	4.4 (4.1–4.6)	4.3 (4.0–4.5)	4.1 (3.7–4.3)	4.0 (3.6–4.2)	3.7 (3.5–4.0)	< 0.001
Creatinine [mg/dl][b]	0.67 (0.59–0.80)	0.69 (0.60–0.80)	0.70 (0.60–0.80)	0.75 (0.60–0.90)	0.80 (0.67–0.95)	0.90 (0.68–0.96)	< 0.001
WBC [× 10^3/mm^3][b]	7.1 (6.1–8.4)	7.4 (6.3–8.5)	7.2 (6.1–8.4)	7.0 (5.9–8.3)	7.1 (6.1–8.0)	7.6 (5.6–8.4)	0.003
PLR[b]	120.0 (97.8–152.6)	122.0 (96.8–159.1)	120.1 (96.8–157.9)	129.2 (101.7–161.8)	140.0 (108.5–178.4)	146.9 (112.9–188.0)	< 0.001
NLR[b]	2.28 (1.78–2.90)	2.33 (1.88–2.94)	2.30 (1.79–2.96)	2.58 (1.94–3.31)	2.84 (2.12–3.75)	2.90 (2.17–3.84)	< 0.001

[a]χ^2 test for categorical and [b]Kruskal-Wallis test for continuous variables [median (IQR)]. 25OHVitD – 25-hydroxy vitamin D, PTH – parathormone, ALP – alkaline phosphatase, C-calcium – corrected calcium, WBC – white blood cells, PLR – platelet-to-lymphocyte ratio, NLR – neutrophil-to-lymphocyte ratio.

Table II. Demographic, clinic and laboratory features of subjects according to vitamin D groups

Parameters	Vitamin D < 20 ng/ml (*n* = 3326)	Vitamin D ≥ 20 ng/ml (*n* = 794)	*P*-value
Age [years]	51 (36–63)	50 (36–62)	0.375
PTH [pg/ml]	46.5 (33.4–65.5)	36.9 (26.4–49.1)	< 0.001
ALP [U/l]	80 (64–102)	76 (60–95)	< 0.001
Calcium [mg/dl]	9.4 (9.0–9.8)	9.6 (9.1–9.9)	< 0.001
C-calcium [mg/dl]	9.5 (9.1–9.8)	9.6 (9.2–10.0)	< 0.001
Phosphorus [mg/dl]	3.5 (3.1–3.9)	3.5 (3.1–3.9)	0.320
Albumin [g/dl]	4.3 (4.0–4.5)	4.4 (4.1–4.6)	< 0.001
Creatinine [mg/dl]	0.7 (0.6–0.8)	0.7 (0.6–0.9)	< 0.001
WBC [× 10^3/mm^3]	7.15 (6.10–8.40)	7.20 (6.10–8.30)	0.777
PLR	124.77 (99.62–162.00)	117.75 (93.33–148.00)	< 0.001
NLR	2.38 (1.86–3.08)	2.25 (1.77–2.95)	0.001

Mann-Whitney U test [median (IQR)]. PTH – parathormone, ALP – alkaline phosphatase, C-calcium – corrected calcium, WBC – white blood cells, PLR – platelet-to-lymphocyte ratio, NLR – neutrophil-to-lymphocyte ratio.

The correlations between 25(OH)D and several other parameters were tested using bivariate correlation analysis. As shown in Table III, 25(OH)D was significantly positively correlated with male sex, calcium, C-calcium, phosphorus, albumin, creatinine, and WBC, and negative correlated with age, PTH, ALP, PLR, and NLR.

We also performed logistic regression analysis to define the variables of 25(OH)D (Table IV). Age, sex, PTH, ALP, calcium, phosphorus, albumin, cre-

Table III. Bivariate correlation results between 25 (OH) vitamin D and other significant parameters

Parameters	Correlation coefficient (r_s)	*P*-value
Age [years]	–0.057	< 0.001
Male sex	0.252	< 0.001
PTH [pg/ml]	–0.301	< 0.001
ALP [U/l]	–0.088	< 0.001
Calcium [mg/dl]	0.188	< 0.001
C-Calcium [mg/dl]	0.159	< 0.001
Phosphorus [mg/dl]	0.050	0.001
Albumin [g/dl]	0.187	< 0.001
Creatinine [mg/dl]	0.189	< 0.001
WBC [× 10^3/mm^3]	0.032	0.043
PLR	–0.128	< 0.001
NLR	–0.075	< 0.001

PTH – parathormone, ALP – alkaline phosphatase, C-Calcium – corrected calcium, WBC – white blood cells, PLR – platelet-to-lymphocyte ratio, NLR – neutrophil-to-lymphocyte ratio.

atinine, NLR and PLR were included in this model. Sex (male), PTH, calcium, creatinine and PLR were found to be independent variables of 25(OH)D.

Discussion

This was the first study evaluating the relationship between vitamin D deficiency and inflammation with the novel inflammatory markers NLR and PLR. There were three main findings of the present study. First, PLR and NLR were significantly higher in patients with lower 25(OH)D levels. Second, 25(OH)D levels were significantly correlated with PLR and NLR as well as age, male sex and PTH, ALP, calcium, phosphorus, albumin, and creatinine levels. Finally, PLR was found to be an independent predictor of 25(OH)D levels along with PTH, calcium, sex and creatinine.

Vitamin D insufficiency and deficiency are considered to be a global problem, affecting a large percentage of the population [1]. Although the association of vitamin D deficiency and many chronic inflammatory diseases has been described in the literature, there is not a clear consensus regarding the relationship between vitamin D and inflammatory markers [4–9, 15–24, 26, 27].

This relationship was studied with cross sectional studies and clinical trials. Amer *et al.* studied the association of 25(OH)D and CRP in 15 167 patients and observed a statistically significant inverse relation between 25(OH)D at levels < 21 ng/ml and CRP in a cross sectional study [21]. They reported that 25(OH)D at a level ≥ 21 ng/ml is associated with an increase in serum CRP. The authors concluded that the role of vitamin D supplementation to reduce inflammation might be beneficial only among those with a lower serum 25(OH)D. In several other cross sectional studies, low 25(OH)D levels were inversely correlated with inflammatory markers such as high-sensitivity C-reactive protein (hs-CRP), IL-6, TNF-α and asymmetric dimethylarginine concentrations – a marker of endothelial dysfunction [22–25, 44]. Our study supports the findings of studies mentioned above and revealed an inverse association between 25(OH)D levels and the novel inflammatory markers NLR and PLR.

In contrast to these studies, several studies have found no association of 25(OH)D with in-

Table IV. Binary logistic regression for normal vitamin D levels

Parameters	*B*	Odds ratio	95% CI		*P*-value
			Lower	Upper	
Age [years]	0.005	1.003	0.995	1.011	0.493
Sex (male)	–0.324	1.696	1.241	2.316	0.001
PTH	–0.014	0.981	0.975	0.987	< 0.001
ALP	–0.002	0.999	0.997	1.001	0.382
Calcium	0.399	1.319	1.063	1.637	0.012
Phosphorus	–0.038	0.860	0.706	1.047	0.134
Albumin	0.155	1.116	0.794	1.568	0.527
Creatinine	0.805	2.398	1.046	5.494	0.039
PLR	–0.004	0.994	0.991	0.998	0.002
NLR	0.038	1.080	0.920	1.270	0.347

PTH – parathormone, ALP – alkaline phosphatase, WBC – white blood cells, PLR – platelet-to-lymphocyte ratio, NLR – neutrophil-to-lymphocyte ratio.

flammatory markers such as IL-6 and hs-CRP [15, 20]. Yildirim *et al.* studied the association of 25(OH)D with CRP, erythrocyte sedimentation rate and white blood cells (WBC) in the population with and without chronic kidney disease [16]. They could not find a significant relation between inflammatory markers and 25(OH)D levels. There was also no association between 25(OH)D levels and WBC in our study, while there were statistically significant relations between 25(OH)D levels and PLR and NLR. These findings can be attributed to the sensitivity of NLR and PLR. Moreover, PLR was found to be superior to NLR in terms of inflammation [28]. Also, PLR was superior to NLR in our study. While PLR was a predictor of 25(OH)D, this association was not seen with NLR in logistic regression analysis.

In addition to the cross-sectional studies, the association of 25(OH)D and inflammatory markers has been investigated in clinical trials and conflicting results have been reported. In a 12-week randomized controlled trial, Shab-Bidar *et al.* studied the association of 25(OH)D supplementation and inflammatory markers in patients receiving a vitamin D fortified drink (1000 IU/day 25(OH)D), compared with those receiving an unfortified drink [27]. Comparison of the changes of the variables revealed that a significant increase in serum 25(OH)D was accompanied by a significant decrease in TNF-α, IL-6, hs-CRP, and serum amyloid A, and an increase in the anti-inflammatory cytokine IL-10. In another clinical trial, Dutta *et al.* randomized prediabetic individuals into three groups (25(OH)D < 30 ng/ml, receiving cholecalciferol; 25(OH)D < 30 ng/ml, receiving calcium carbonate; and 25(OH)D > 30 ng/ml, also receiving calcium carbonate) and followed them over 2 years [4]. At the end of the study, the authors reported improvement in glycemic status, insulin resistance and inflammation following an increase in serum 25(OH)D levels, in the 25(OH)D receiving group. A study performed by Timms *et al.* in a population free of known diabetes or major illness revealed that vitamin D insufficiency was associated with increased CRP, correctable by supplementation [26]. In contrast to those studies, some clinical trials have failed to demonstrate beneficial effects of 25(OH)D supplementation on inflammatory markers [17–19, 45].

The PLR and NLR were used to determine inflammation in different types of malignancies, metabolic syndrome, infectious diseases, cardiovascular disease, end stage renal disease and other inflammatory diseases [28–37, 39–42]. However, these easily measured, reproducible, and inexpensive markers are not used to determine the association of inflammation and vitamin D deficiency, on which there is no clear consensus yet. In this study, we observed that NLR and PLR levels tended to rise with increasing age. Additionally, without a significant effect of age, in the vitamin D deficient group compared to the non-deficient group, PLR and NLR were high.

There are studies that support an association of endothelial dysfunction and vitamin D deficiency and explain the relation between vitamin D deficiency and inflammation with endothelial dysfunction [22, 44, 46, 47]. Furthermore, there are studies revealing the relation of NLR, PLR and endothelial dysfunction [37, 48, 49]. In this perspective, NLR and PLR might be simple and inexpensive endothelial dysfunction markers in vitamin D deficiency.

Limitations of this study include the weakness of a retrospective study and the cross-sectional nature. Based on our data, seasonal differences, the role of obesity, and the reason for the patients' admission to the hospital were not investigated. Despite the difficulties in using retrospective study results, the strength of our study is the large cohort of patients.

In conclusion, PLR and NLR were significantly higher in patients with lower 25(OH)D levels, and PLR was found to be an independent predictor of 25(OH)D levels. Our study demonstrated an inverse association of vitamin D levels and inflammation with these inexpensive and universally available markers. Further and larger studies are required to confirm our findings, and to better elucidate the relationship between vitamin D deficiency, NLR and PLR.

Conflict of interest

The authors declare no conflict of interest.

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