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Low Serum 25-hydroxy Vitamin D Levels: Predictive Value of Hematological and Inflammatory Markers in Patients With Urinary Tract Infection

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ABSTRACT

Background: Low vitamin D may increase inflammatory markers in various pathological conditions. We aimed to evaluate the association of urinary tract infection (UTI) with hematological and inflammatory markers mediated by low serum levels of 25-hydroxy vitamin D (25[OH]D).

Materials and Methods: 25(OH)D level and hematological indices, including neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), neutrophil-monocyte ratio (NMR), platelet-lymphocyte ratio (PLR), and mean platelet volume (MPV), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), interleukin-6, and tumor necrosis factor-α were evaluated in 115 UTI patients and 77 controls.

Results: The findings showed an inverse association between elevated hematological (NLR, MLR, and MPV) and serum markers of inflammation (CRP, IL-6, and TNF-α) with serum 25(OH)D levels in UTI patients. Among the several markers evaluated, the MLR could present the association of inflammation with low serum levels of 25(OH)D.

Conclusion: The involvement of vitamin D deficiency might be characterized by an increase in the inflammatory markers in the patients, which can establish the relationship between vitamin D deficiency and UTI. However, further investigations are needed to validate this finding.

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Introduction

Vitamin D, besides its primary function in the maintenance of calcium and phosphate homeostasis, possesses anti-inflammatory and immune regulatory properties. Generally, vitamin D deficiency is recognized as an important public health problem worldwide in all age groups and both genders [1]. Considering the pleiotropic regulatory effects of vitamin D on the immune system's innate and adaptive arms, an inadequate vitamin D level is associated with increased susceptibility to infections and perpetuation of inflammation associated with enhanced levels of inflammatory markers [2, 3].

Urinary tract infection (UTI) is one of the most frequent bacterial infections in women and children, predominantly caused by uropathogenic *Escherichia coli* (UPEC). Although UTI usually infects the bladder (called cystitis), its progression to the kidney can cause pyelonephritis, leading eventually to renal failure [4]. Studies have found an independent association of vitamin D deficiency with UTI [5, 6].

Various measurable parameters can be used to determine an inflammation, including white blood cell (WBC) count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), cytokines, and even immunoglobulin levels. Some readily available inflammatory markers found from routine complete blood count (CBC) have been recently suggested to serve as useful indicators of inflammatory status in various pathological conditions, including infectious diseases [7], malignancies [8], metabolic syndrome [9], cardiovascular [10], and autoimmune diseases [11]. These indicators include neutrophil-lymphocyte ratio (NLR), neutrophil-monocyte ratio (NMR), monocyte-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR).

Considering an inverse relationship between 25-hydroxy vitamin D (25[OH]D) levels and inflammation markers, a significant reduction in the inflammatory markers has been observed after vitamin D supplementation [12, 13]. This observation may suggest a protective role for vitamin D in inflammation.

Given that vitamin D deficiency is one of the environmental risk factors involved in UTI, the immune modulatory role of 25(OH)D is suggested. This study explored whether such an independent association exists between serum 25(OH)D levels, a well-known indicator of vitamin D status, and UTI. We also want to determine whether hematological and serum markers of inflammation mediate this relationship in UTI.

Materials and Methods

Study subjects

A total of 115 women aged 20 to 60 years with urine culture proven with uropathogenic *E. coli* (UPEC) infection were compared with 77 age-matched healthy women as a control group. Other pathogenic strains isolated from the samples, including *Staphylococcus* saprophyticus, *Staphylococcus aureus*, *Enterobacter aerogenes*, *Klebsiella pneumonia*, *Proteus mirabilis*, and *Enterococci*, were excluded from the next analyses in this study. The study subjects were outpatients who attended clinics of Ardabil University of Medical Sciences, Ardabil, Iran. The sample size was estimated using the OpenEpi software, with a statistical power of 80% at a significance level of 0.05. Given seasonal variations in serum 25(OH)D concentrations, the samples were collected at the end of winter 2019 and spring 2020. In patients with lower urinary tract infection (cystitis) presenting urgency, frequency, dysuria, and suprapubic tenderness, UTI diagnosis was confirmed by midstream urine analysis and a positive urine culture defined as a significant growth of a single pathogen with $>10^5$ CFU/mL. Patients with liver, kidney and pancreatic diseases, gastroenteropathy, female genital tract infection, glucocorticoids treatment, anemia, and inflammation-mediated diseases were excluded from the study. We excluded women with a previous episode of infection or asymptomatic bacteriuria, pyelonephritis, and antibiotic therapy in the last 3 months before admission. In the case-control study, we compared the two groups regarding age, body mass index (BMI), education level, marital status, socioeconomic status, urban residency, and serum 25(OH)D levels. The self-reported values for height and weight were used during the data analysis to calculate BMI. The samples were collected from the study subjects following an informed consent.

Laboratory analysis

The sera were obtained from the collected blood specimen and stored at −80°C for the future laboratory analysis, which includes complete blood count (CBC), serum levels of 25(OH)D, C-reactive protein (CRP), the cytokines interlukine-6 (IL-6), tumor necrosis factor-α (TNF-α), and erythrocyte sedimentation rate (ESR). Hemograms were determined by using automated analyzer (Sysmex Corporation, Kobe, Japan). Serum 25(OH)D levels were quantified by using EUROIMMUN kit (Mediziische Labordiagnostika AG, Lübeck, Germany) according to the manufacturer's instructions. Briefly, serum samples and standards diluted in biotin-labeled

25(OH) vitamin D were added to the plates pre-coated with anti-25(OH) vitamin D antibody. After incubation, the plates were washed and detection was conducted by adding streptavidin conjugated to horseradish peroxidase. Following an incubation step, tetramethylbenzidine as the substrate was added to each washed well of plates, and the optical density was determined at 450 nm with an automated plate reader. The cytokines IL-6 and TNF-α levels were quantified using ELISA Kit (U-CYTech Biosciences, Utrecht, the Netherlands) according to the manufacturer's instructions. Results from the analysis were expressed in pg/mL (IL-6 and TNF-α) and ng/mL (25 OH vitamin D). Serum levels of CRP (mg/dL) and ESR (mm/h) were measured using immunoturbidimetric assay and the Westergren method, respectively. Vitamin D status was defined as follows: Deficient, 25(OH)D levels of less than 20 ng/mL; insufficient, 25(OH)D levels between 20 and 30 ng/mL; and sufficient, 25(OH)D levels of higher than 30 ng/mL [5]. Subsequently, we divided the patients into three groups. The values of neutrophil-lymphocyte ratio (NLR), neutrophil-monocyte ratio (NMR), monocyte/-lymphocyte ratio (MLR), and platelet-lymphocyte ratio (PLR) were obtained from the complete blood count (CBC).

Statistical analysis

The Kolmogorov-Smirnov test was employed to test whether the the study variables follow the normal distribution. The normally and non-normally distributed variables were compared between the two study groups via independent t-test and Mann–Whitney U test, respectively. For the categorical variables, the chi-square test was used as well. The Kruskal–Wallis ANOVA was used to test the differences between subgroups of vitamin D. The correlation between vitamin D and any of these parameters was determined using the Pearson's correlation analysis. The association of independent variables and UTI was determined by using a multivariate logistic regression analysis. To determine the discrimination threshold of vitamin D concentration based on the parameters, a receiver operating characteristic (ROC) curve was created by plotting sensitivity (true-positive rate) versus 1-specificity (false-positive rate). Optimal cut-off values, specificity, and sensitivity were subsequently derived from ROC analysis. The Mean±SD was used to express the data. For all data, the level of statistical significance was set at a $P<0.05$. Analyses were performed in GraphPad Prism software, version 5.04 (GraphPad Software, San Diego, CA, USA).

Results

Laboratory findings of patient and control groups

The study included 115 female patients and 77 sex-age matched healthy controls. Based on the characteristics of the study population as shown in Table 1, no significant difference was seen between the two groups in terms of age, marital status, socioeconomic status, and living in an urban area. However, statistically significant differences between patients and controls were exhibited with BMI and education were exhibited. Subsequently, all variables were entered into multivariate analyses. Although high education level appears to be associated with the decreased likelihood of UTI (odds ratio [OR]: 0.75, 95% confidence interval [95% CI], 0.43%-0.86%), an increase in the likelihood of UTI was shown in terms of BMI (OR: 1.14, 95% CI, 1.04%-1.25%). Also, serum 25(OH)D levels significantly exhibited a significant difference between the two groups, which was associated with an increase in the likelihood of UTI (OR: 1.12, 95% CI, 1.02%-1.33%). When comparing the patients with the control group, we found significant differences in WBC, neutrophil, and platelet counts. The NLR and PLR values were significantly higher in the patient group than in the controls. Considering MLR and NMR, we observed an insignificant difference between the two groups. Based on the CRP and ESR results, although ESR values of the patients were not different from the control group there was an increase in CRP levels of the patients compared to the controls. Moreover, the cytokines IL-6 and TNF-α levels were significantly increased in patients compared to the control group. The laboratory findings of the patient and control groups are presented in (Table 2). Additional analyses were performed to investigate the association between vitamin D levels and laboratory parameters and showed statistically significant differences according to serum 25(OH) vitamin D status.

Laboratory findings of patients among vitamin D subgroups

We classified our patients according to their 25(OH) D levels as follows: Deficient, insufficient, and sufficient to determine possible changes in either serum inflammatory markers (IL-6, TNF-α, and CRP) or complete blood count-derived inflammation markers (NLR, MLR, NMR, and PLR). Of 115 patients evaluated, 52 patients (45.2%) had deficient 25(OH)D levels, ie, a concentration less than 20 ng/mL, 34 patients (29.6%) were 25(OH)D insufficient, i.e, a concentration between 20 and 30 ng/mL, and 29 (25.2%) patients were 25(OH)D sufficient, ie, concentration >30 ng/mL.

Table 1. Demographic and laboratory characteristics between patients with urinary tract infections and controls

Variables		Mean±SD/No. (%)		P
		Control (n=77)	Patients (n=115)	
Age (y)		30.46±6.09	32.78±8.13	0.144
Weight (kg)		62.17±11.00	69.28±12.53	0.001
Height (cm)		161.35±4.60	162.57±5.35	0.295
Body Mass Index (kg/m^2)		23.81±2.18	26.20±2.56	0.003
Married		48(62.3)	69(60)	0. 589
Education level	Elementary school or less	24(32)	54(46.9)	0.031
	Middle school/high school	20(26)	30(27)	
	College or higher	33(43)	31(27)	
Socioeconomic status	Low	27(35)	37(32.1)	0.360
	Middle	34(44.1)	53(46.1)	
	High	16(21)	25(22)	
Urban residential		48(62.3)	65(56.5)	0.263
Serum 25(OH) vitamin D (ng/mL)		31.42±10.58	26.80±13.19	0.043

With respect to CBC parameters, the counts of WBC and PLT showed a statistically significant difference while the RBC count was not significant. In this regard, the patients with deficient and insufficient 25(OH)D levels had significantly higher counts of neutrophil and monocyte than sufficient levels of 25(OH)D, with insignificant difference among the three groups for the lymphocyte count. Additionally, the comparison of the study groups did not exhibit statistical significance regarding hemoglobin, mean corpuscular volume (MCV), and red cell distribution width (RDW) values. Whereas the platelet distribution width (MPV) increased in patients with 25(OH) deficiency, platelet distribution width (PDW) values did not differ significantly among the vitamin D subgroups. The NLR level of patients with 25(OH)D sufficiency was lower than that of 25(OH)D deficiency, but the difference was not significant in relation to 25(OH)D insufficiency. A decrease in MLR was observed in the patients with sufficient level of 25(OH)D compared to deficient and insufficient groups. For PLR and NMR, there was no significant difference among the classified subgroups.

Despite an insignificant difference in ESR, it was found that vitamin D deficiency may result in significantly higher CRP levels than sufficient group. Such a difference was not exhibited between deficient and insufficient groups. The IL-6 levels were significantly higher in the deficient group than in both insufficient and sufficient groups. A significant increase in TNF-α levels was shown in patients with deficient levels of 25(OH)D versus the sufficient group, without any difference between the deficient and insufficient groups. Patients' laboratory results according to 25(OH)D subgroups are presented in Table 3. Meanwhile, the possible association between patients' serum 25(OH)D levels and the parameters related to inflammation was examined. The NLR and MLR values and WBC count were negatively correlated with serum 25(OH)D levels (r=−0.444, P=0.002; r=−0.611, P=0.001; r=−0.309, P=0.012). The cytokines IL-6 and TNF-α, along with CRP, also showed an inverse correlation (r=−0.361, P = 0.038; r=−0.341, P=0.035, r=−0.081, P=0.029). The correlation between serum 25(OH)D levels and the other parameters, including NMR and PLR, was insignificant (P>0.005).

ROC analysis of hematological and serum markers of inflammation

The aforementioned markers were examined for their predictability of low serum 25(OH)D levels in UTI patients using ROC curves. The area under the curve (AUC) was calculated as follows: 0.657 for NLR (95% CI, 0.526%-0.789%; P=0.028), 0.785 for MLR (95%

Table 2. Comparing variables between patients with urinary tract infections and control groups

Variables	Mean±SD		P
	Control (n=77)	Patients (n=115)	
WBC (×10³/mm³)	7.67±1.39	8.81±1.64	0.041
Neutrophil (×10⁹/L)	4.25±1.15	5.69±2.07	0.026
Lymphocyte (×10⁹/L)	2.33±0.56	2.45±0.64	0.062
Monocyte (×10⁹/L)	0.31±0.09	0.39±0.19	0.023
RBC (×10¹²/L)	4.46±0.30	5.06 ± 0.34	0.180
Hb (g/dL)	13.01±0.88	13.21±0.76	0.135
MCV (fL)	86.48±3.89	87.66±4.03	0.083
RDW (%)	12.11±1.44	12.91±0.90	0.128
Platelet (10³/mm³)	240.20± 58.85	290.30±46.40	0.044
MPV (fL)	9.18±2.63	9.33±1.36	0.156
PDW (%)	10.09±2.10	10.60±1.42	0.220
NLR	1.82±0.48	2.31±1.31	0.005
PLR	103.09±22.90	118.38±32.26	0.027
MLR	0.13±0.07	0.16±0.10	0.053
NMR	13.58±4.81	14.11±8.93	0.480
CRP (mg/dL)	12.70±6.31	20.78±8.34	<0.001
ESR (mm/h)	19.46±11.09	23.19±13.26	0.112
IL-6 (pg/mL)	21.89±10.14	23.80±13.05	<0.001
TNF-α (pg/mL)	17.30±3.15	28.11±3.64	0.008

Abbreviations: BMI: Body mass index; Hb: Hemoglobin; WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; RDW: Red distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

CI, 0.667%-0.902%; P<0.001), 0.736 for MPV (95% CI, 0.615%-0.857%; P<0.001), 0.643 for CRP (95% CI, 0.512%-0.774%; P=0.043), 0.649 for IL-6 (95% CI, 0.518%-0.781%; P=0.034), and 0.645 for TNF-α (95% CI, 0.514%-0.775%; P=0.040) (Figure 1). The ROC analyses demonstrated that although the MLR and MPV may discriminate patients with vitamin D deficiency, the discriminatory ability of other markers, including NLR, CRP, IL-6, and TNF-α, are weak for identifying patients with vitamin D deficiency (Table 4). However, it should be noted that the MLR is superior to MPV regarding the discriminatory accuracy. Moreover, the discrimination thresholds of 25(OH)D levels determined by the ROC curve and vitamin D threshold of <19.46 ng/mL showed the best discriminatory value for the high MLR (Table 5).

Discussion

In this study, we compared the effect of serum 25(OH) D levels on the inflammatory response by evaluating the hematological inflammatory markers and some serum markers of inflammation, including complete blood count (CBC) indices (NLR, NMR, MLR, and PLR), ESR, serum levels of IL-6, TNF-α, and CRP, in women with bacterial cystitis. Vitamin D is proposed as a key regulator of inflammation [2]. Given that vitamin D deficiency and

Table 3. Laboratory parameters of patients according to deficiency, insufficiency, and sufficiency of Vitamin D

Variables	Vitamin D Groups			P
	Deficient (n=52)	Insufficient (n=34)	Sufficient (n=29)	
Vitamin D (ng/mL)	13.72±4.26	24.04±2.58*	42.64±10.92*≠	<0.001
WBC (×10³/mm³)	9.70±1.73	8.81±1.52*	7.92±1.24	0.224
Neutrophil (×10⁹/L)	6.39±2.24	5.80±1.99	4.87±1.15*	0.013
Lymphocyte (×10⁹/L)	2.38 ± 0.60	2.48±0.78	2.50±0.53	0.648
Monocyte (×10⁹/L)	0.46±0.20	0.40±0.21	0.32±0.09*≠	0.029
RBC (×10¹²/L)	5.18±0.33	4.93±0.21	5.08±0.48	0.363
Hb (g/dL)	13.49±0.87	12.79±0.71	13.35±0.51	0.114
MCV (fL)	88.79±3.32	86.39±6.13	87.82±2.68	0.314
RDW (%)	13.07±0.93	12.80±0.77	12.86±1.01	0.329
Platelet (10³/mm³)	289.0±46.52	287.7±43.43	294.3±45.75	0.889
MPV (fL)	9.80±1.51≠&	9.30±0.94	8.90±0.95	0.009
PDW (%)	11.03±1.69	10.25±0.89	10.52±0.80	0.108
NLR	2.68±1.46	2.30±1.28	1.93±0.50*	0.031
PLR	121.42±27.13	116.0±31.06	117.72±25.05	0.889
MLR	0.18±0.09	0.16±0.10	0.13±0.03*≠	0.014
NMR	14.52±10.17	12.60±8.96	15.21±5.06	0.140
CRP (mg/dL)	23.12±8.55&	19.89±8.01	17.22±6.94	0.043
ESR (mm/h)	23.12±19.28	23.87±13.95	22.19±11.20	0.974
IL-6 (pg/mL)	27.18±15.08≠&	22.86±12.34	21.5±11.02	0.003
TNF-α (pg/mL)	30.21±4.15&	27.25±3.29	26.86±3.50	0.018

Abbreviations: Hb: Hemoglobin; WBC: White blood cell; RBC: Red blood cell; MCV: Mean corpuscular volume; RDW: Red distribution width; MPV: Mean platelet volume; PDW: Platelet distribution width; NLR: Neutrophil-to-lymphocyte ratio, PLR: Platelet-to-lymphocyte ratio; MLR: Monocyte-to-lymphocyte ratio; NMR: Neutrophil-to-monocyte ratio; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

Vitamin D deficiency, insufficiency, and sufficiency were defined as <20 ng/mL, 20-30 ng/mL, and >30 ng/mL, respectively. *Compared with vitamin D level <20 ngmL; ≠Compared with vitamin D level, 20-30 ng/mL; &Compared with vitamin D level > 30 ng/mL.

lower UTIs are frequently reported in women [14], we evaluated the contribution of vitamin D deficiency raised inflammation. The anti-inflammatory role of vitamin D has increasingly received attention concerning counteracting infections and the inflammation response.

Based on alterations in leukocyte and platelet counts, some hematological indices can be calculated and served as the predictive and prognostic factors in various inflammation and immune-mediated diseases due to their easy, cost-effective, and non-invasive determination. We found significantly elevated NLR in patients compared to controls. A comparison of the patients according to 25(OH) D subgroups indicated that vitamin D-deficient patients have high levels of NLR. Han et al. reported the NLR as a useful biomarker for the prediction of vesicoureteral reflux and acute pyelonephritis development, suggesting that NLR, rather than absolute neutrophil or lymphocyte

Table 4. Discrimination performance of hematological and serum markers of inflammation for the prediction of low 25(OH)D levels in patients with urinary tract infections

Variables	Cut-off Points	(%)				LR+	LR−	(%)
		Sensitivity	Specificity	PPV	NPV			Accuracy
NLR	2.08	64.7	59.4	44	71.8	1.56	0.59	57.5
MLR	0.16	82.4	71.9	73.5	75	2.82	0.25	74.2
MPV	9.05	67.6	68.8	58.8	81.2	2.09	0.48	69.6
CRP	19.5	54.5	51.4	51.5	62.8	1.42	0.90	57.3
IL-6	23.3	63.6	51.4	54.5	71.4	1.28	0.72	63.2
TNF-α	26.7	63.6	57.1	63.6	57.1	1.46	0.64	60.2

Abbreviations: LR: Likelihood ratio; PPV: Positive predictive value; NPV: Negative predictive value.

Table 5 The receiver operating characteristic (ROC) analysis for identifying the discrimination threshold of vitamin D concentration

Variable	Cut-off Point	AUC (95% CI)	(%)				P
			Sensitivity	Specificity	PPV	NPV	
MLR (>0.16) 25 (OH)D	≤19.46	0.789 (0.673-0.904)	81	80	75.7	84.3	0.004

Abbreviations: MLR: Monocyte-lymphocyte ratio; AUC: Area under curve; PPV: Positive predictive value; NPV: Negative predictive value.

counts separately, might be useful for the evaluation of inflammatory response [15]. Tabatabaeizadeh et al. significantly reduced neutrophil count and the subsequent NLR level after vitamin D supplementation [16].

Monocyte count and MLR level increased in the vitamin D deficient and insufficient groups compared to the sufficient ones. A study reported vitamin D deficiency-associated persistent inflammation resulting from activated monocyte phenotypes in HIV-infected patients [17]. We also found that the MLR is superior to NLR in predicting vitamin D deficiency in UTI patients.

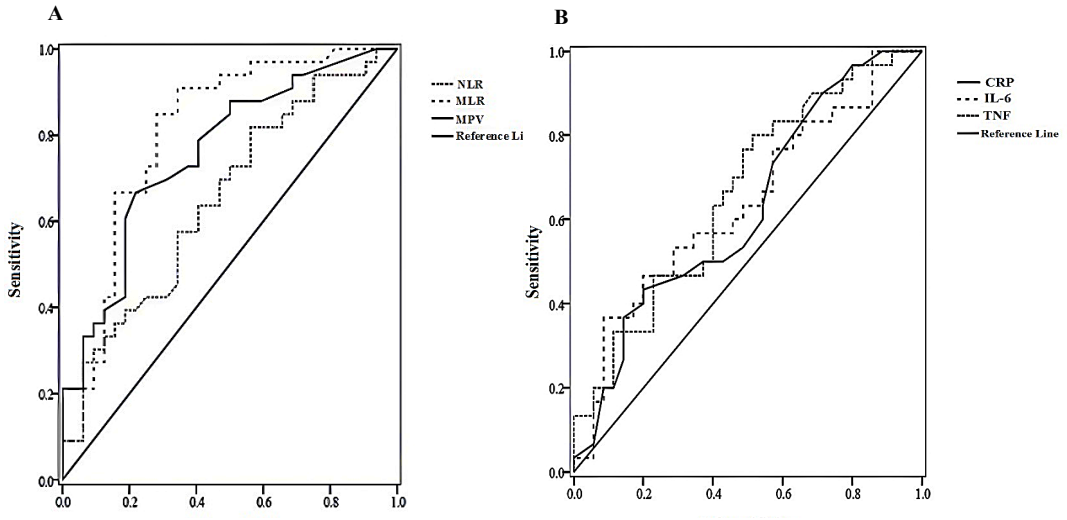

Figure 1. The receiver operating characteristic (ROC) curves for: A) Neutrophil-lymphocyte ratio (NLR), monocyte-lymphocyte ratio (MLR), mean platelet volume (MPV); (B) Tumor necrosis factor (TNF)–α, interleukin (IL)–6, and C-reactive protein (CRP)

Regarding the PLR values of the patients, our results demonstrated an insignificant association of vitamin D levels with the PLR. However, the MPV was negatively correlated with 25(OH)D levels. Although the PDW was slightly higher in the vitamin D deficient group than the other groups, the difference was not statistically significant. An increase in MPV may suggest inflammatory thrombocytosis and platelet activation in response to infection. According to a significant inverse association between MPV and serum vitamin D levels, there might be a possible regulatory role of inflammatory cytokines increase by deficient vitamin D levels [18, 19]. In this regard, Lee et al. suggested the MPV as an adjunctive inflammatory marker with low predictive value in diagnosing acute pyelonephritis [20]. Moreover, our findings showed that MPV has a relatively good predictive ability for 25(OH)D deficiency in UTI patients.

CRP and ESR are widely used to assess inflammation. We found that serum 25(OH)D levels are not related to the changes in the ESR values. Nevertheless, a normal value does not exclude the possibility of infection. Despite inflammation-mediated slow changes in ESR elevation, CRP increases rapidly during infection or tissue injury in response to pro-inflammatory mediators. Therefore, CRP is proposed as an alternative to ESR for inflammation determination due to its higher sensitivity [21].

In the current study, CRP was inversely associated with 25(OH)D. Furthermore, serum CRP level was higher in the patients with deficient or insufficient levels of 25(OH)D than those with sufficient levels of vitamin D, consistent with the previous studies [21, 22]. This finding may propose a picture of the inflammatory situation in the patients. In contrast, Yildirim et al. study failed to prove any association between low 25(OH)D status and CRP as well as IL-6, known as inflammatory markers [23]. According to the ROC curve analysis, the CRP might not properly predict 25(OH)D deficiency in UTI patients.

Regarding pro-inflammatory cytokines, IL-6 and TNF-α were increased in the patients compared to controls. These cytokines were inversely correlated to patients' serum 25(OH)D levels, consistent with the previous study [24]. Our results showed that IL-6 and TNF-α are weak predictors of low 25(OH)D levels in UTI patients.

An association of low serum 25(OH)D levels with more UPEC in the bladder and a dysregulated cytokine response has been reported, hence spreading the infection to the upper urinary tract [25]. A recent study has revealed the impact of multiple pro-inflammatory cytokines on the increased pathogenicity of UPEC [26]. Thus, limitation in these cytokines, known as a host response, may reduce UPEC persistence and colonization in the urinary tract. Studies have reported a reduction in IL-6 and TNF-α expression in relation to the activation of vitamin D receptor (VDR) by supplementing with vitamin D [27]. The underlying molecular mechanism reflecting the anti-inflammation effect of vitamin D may be that VDR inhibits the production of pro-inflammatory cytokines mediated by the activation of transcription factor kappa B [28].

Antibiotic therapy is commonly used to treat UTIs to eliminate uropathogens from the urinary tract and resolve symptoms. The need to reduce antibiotic therapy is of great importance owing to an enhancement of antibiotic resistance associated with developing chronic or recurrent infection. Thus, an association between 25(OH)D deficiency/insufficiency and infection may potentially be considered to provide the supplements to patients with a consequent reduction in the duration of antibiotics consumption. A significant decrease in antibiotic consumption has been established following vitamin D intake from supplements [29, 30]. Moreover, recent data have suggested vitamin D-mediated upregulation of antimicrobial peptides and attenuation of pro-inflammatory mediators [31, 32], as well as an improvement in the maintenance of epithelial barrier integrity [33].

Conclusion

The findings may be useful for assessing UTI-associated inflammatory status mediated by vitamin D deficiency, specifically attributed to the immune modulation by vitamin D as the underlying mechanism demonstrating this relationship; however, it needs further exploration. Moreover, the impact of single or combined vitamin D supplementation with antimicrobial therapy is required to test the attenuation of inflammatory responses.

The present study was performed in a short time with a small sample size and only women as study subjects. It is required to prepare a large sample size with both sexes to determine gender differences between subjects in further assessments. Additionally, a possible impact of confounding variables should be considered in this study. Meanwhile, the induction of hypovitaminosis D may be attributed to infection/inflammation. However, given the anti-inflammatory role of vitamin D, this study might constitute preliminary research for further studies in this area.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Tabriz Branch, Islamic Azad University (Code: IR.IAU.TABRIZ.REC.1396.83).

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Authors contribution's

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interests.

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