ORIGINAL ARTICLE

UDC: 577.161.2:616.348-002
DOI: https://doi.org/10.2298/VSP230912060K

The effect of vitamin D serum levels on the values of C-reactive protein and fecal calprotectin in patients with ulcerative colitis in clinical remission

Uticaj nivoa vitamina D u serumu na vrednosti C-reaktivnog proteina i fekalnog kalprotektina kod obolelih od ulceroznog kolitisa u kliničkoj remisiji

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Abstract

Background/Aim. Vitamin D plays a critical role in digestive calcium absorption and, thanks to its immunomodulatory properties, affects intestinal barrier integrity, gut microbiota, and immune system functionality. The aim of the study was to examine 25-hydroxyvitamin D [25(OH)D] levels in patients with ulcerative colitis (UC) in clinical remission, as well as its effects on the values of fecal calprotectin (FC) and C-reactive protein (CRP). **Methods.** The research, conducted as a cross-sectional study, included 62 patients with UC in clinical remission. Serum levels of 25(OH)D and CRP were determined from venous blood specimens, while FC levels were assessed from stool samples. Endoscopic activity was evaluated through colonoscopy and was expressed by the Mayo Endoscopic Score (MES). **Results.** Out of the 62 participants with UC in clinical remission, 38 (61.3%) were males, and 24 (38.7%) were females. The average 25(OH)D level in those patients was 49.87 ± 23.5 nmol/L. Among the patients with UC, six (9.7%) participants had sufficient vitamin D levels (> 75 nmol/L), whereas insufficiency (< 50 nmol/L) and deficiency (50–75 nmol/L) were established in 32 (51.6%) and 24 (38.7%) participants, respectively. In the analyzed sample, 25(OH)D serum levels did not significantly correlate either with FC (r = 0.077, p = 0.551), CRP (r = –0.111, p = 0.392), or MES (r = 0.02, p = 0.787). **Conclusion.** In our investigation, the 25(OH)D serum level did not significantly influence the values of the MES nor the biomarkers of inflammation – FC and CRP.

Key words:
biomarkers; c-reactive protein; colitis, ulcerative; feces; remission induction; vitamin d.

Apstrakt

Uvod/Cilj. Vitamin D igra ključnu ulogu u apsorpciji kalcijuma iz digestivnog trakta i, zahvaljujući svojim imunomodulacijskim svojstvima, utiče na integritet intestinalne barijere, mikrobiotu creva i funkcionalnost imunskog sistema. Cilj rada bio je da se ispita nivo 25-hidroksivitamina D [25(OH)D] u serumu obolelih od ulceroznog kolitisa (UK) u stanju kliničke remisije, kao i njegov uticaj na vrednosti fekalnog kalprotektina (FK) i C-reaktivnog proteina (CRP). **Metode.** Istraživanje, sprovedeno kao studija preseka, obuhvatilo je 62 ispitanika obolelih od UK u stanju kliničke remisije. Nivoi 25(OH)D i CRP u serumu određivani su iz uzoraka venske krvi, dok su nivoi FK određivani iz uzoraka stolice. Endoskopska aktivnost procenjivana je kolonoskopijom i izražena je Mayo endoskopskim skorom (MES). **Rezultati.** Od ukupno 62 obolelih od UK u stanju kliničke remisije, 38 (61,3%) je bilo muškog, a 24 (38,7%) ženskog pola. Prosečna vrednost 25(OH)D kod bolesnika iznosila je 49,87 ± 23,5 nmol/L. Među obolelima od UK, šest (9,7%) učesnika imalo je dovoljan nivo vitamina D (> 75 nmol/L), dok su insuficijencija (< 50 nmol/L) i deficit (50–75 nmol/L) utvrđeni kod 32 (51,6%) i 24 (38,7%) učesnika, redom. U ispitivanom uzorku, nivoi 25(OH)D u serumu nisu značajno korelisali ni sa FK (r = 0,077, p = 0,551), ni sa CRP (r = 0,111, p = 0,392), kao ni sa MES (r = 0,02, p = 0,787). **Zaključak.** U našem ispitivanju, nivo 25(OH)D u serumu nije značajno uticao na vrednosti MES, niti na vrednosti biomarkera inflamacije – FK i CRP.

Ključne reči:
biološki pokazatelji; c-reaktivni protein; kolitis, ulcerativni; stolica; remisija, indukcija; vitamin d.

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Introduction

Ulcerative colitis (UC) and Crohn's disease are both conditions that belong to a group of chronic inflammatory diseases of the digestive system. The etiology of UC is still unknown, and the condition develops due to various factors affecting genetically predisposed individuals and manifests as an inflammatory process that affects the large intestine. The mechanism of the disease has still not been fully elucidated. However, it is well established that it is an immune-mediated inflammatory reaction and disruption of the colonic mucosa. The disease takes a chronic course, including periods of exacerbations and remissions, and the diagnosis is commonly established between 30 and 40 years of age [1]. The effects of vitamin D on the gastrointestinal system, apart from calcium absorption and metabolism, rely on its immunomodulatory properties and are reflected in its effects on intestinal barrier integrity, gut microbiota, and immune system functionality. All these mechanisms are mediated by the vitamin D receptors (VDRs).

In patients with inflammatory bowel disease (IBD), the gut microbiota alters in terms of decreasing the number of butyrate-producing bacteria. During inflammation, VDR signaling is increased and regulates the antibacterial function of natural killer (NK) cells and Paneth cells. Higher 25-hydroxyvitamin D [25(OH)D] levels are related to increased serum cathelicidin that manifests anti-inflammatory and antimicrobial properties [2]. Moreover, it inhibits the maturation of dendritic cells as the most potent antigen-presenting cells, reduces T-cell proliferation, and redirects T-cell differentiation from Th1 and Th17 pathways towards Th2 and Treg [3, 4]. Vitamin D metabolism and signaling play an important role in intestinal homeostasis and barrier integrity. VDR is a transcription factor regulating tight junction proteins such as claudin-2, -5, -12, and claudin-15 epithelial cells. Vitamin D deficiency can lead to a reduced synthesis of these proteins and, consequently, increased permeability and inflammation [5].

It is still doubtful whether vitamin D deficiency is the cause or consequence of the disease activity, but the correlation is clearly negative. Many research papers revealed that patients with higher 25(OH)D levels manifest with lower disease activity, lower risk for clinical relapse, and improved therapeutic response to biologic treatment [6–9]. The optimal concentration of 25(OH)D is based mainly on its effect on the musculoskeletal system and is defined as: adequate [> 75 nmol/L (30 ng/mL)], inadequate or insufficient (50–75 nmol/L), and deficient [< 50 nmol/L (20 ng/mL)] [10]. Even though clear clinical guidelines are unavailable, monitoring of 25(OH)D level is strongly recommended in patients with UC, and it should be maintained at a level above 75 nmol/L. This can be achieved by sufficient exposure to sunlight, adequate dietary intake, or supplementation [11].

Given the controversial results of previous studies, which mostly involved sample populations with varying clinical disease activity, and considering the insufficient data on vitamin D levels in patients with UC in clinical remission in our geographic area, our study aimed to investigate the association between vitamin D levels and inflammatory biomarkers in UC patients in clinical remission.

Methods

The study, designed as a cross-sectional study, included 62 participants with UC in clinical remission, defined as a Simple Clinical Colitis Activity Index (SCCAI) score of 2 or less. The research was approved by the Ethics Committee of the University Clinical Center of Vojvodina (UCCV), Serbia (No. 00-108, from February 27, 2020). The study population consisted of 38 male and 24 female patients. All patients were older than 18 years. The patients did not take corticosteroid therapy during the past six months or vitamin D supplements during the past three months, and they all signed the informed consent to participate in the study. Individuals with primary bone disease (such as Paget's disease), myeloma multiplex, primary hyperparathyroidism, malignancy, and secondary deposits in the bones, as well as patients with chronic kidney disease, pregnant and breastfeeding women, were excluded from the study. After evaluating the previous medical documentation, a comprehensive history of underlying and associated diseases, conditions, and dietary habits was taken. Clinical examination and determination of body weight and body mass index (BMI) were performed. Upon conclusion of the fulfillment of the criteria for the involvement in the study, written consent was obtained from all participants. The evaluation of the clinical disease activity was performed based on the relevant questionnaire (SCCAI), while endoscopic activity was expressed by the Mayo Endoscopic Score (MES) after colonoscopy.

The concentration of serum 25(OH)D and C-reactive protein (CRP) was determined by obtaining venous blood samples, and fecal calprotectin (FC) was determined from fecal samples. All measurements were performed in the Center for Laboratory Diagnostics of the UCCV. The concentration of serum 25(OH)D was determined by the method of chemiluminescence immunoassay – CLIA using Liason XL (Diasorin Inc.) analyzer. The value is expressed in nmol/L. CRP value was measured by an immunoturbidimetric method on an Architect c8000 analyzer (Abbott). The value was expressed in mg/L. The FC value was measured using enzyme-linked immunosorbent assay – ELISA on a Chorus Trio (Diesse) device. The value was expressed in µg/g. A colonoscopy with biopsies was performed in the Endoscopy department of the UCCV on Olympus Evis Exera III endoscope.

Statistical data analysis was performed using the software package JASP 0.17.2. The descriptive statistics parameters and Pearson's correlation coefficient between the variables were calculated.

Power considerations

Statistical power analyses were conducted using GPower statistical software v.3.1.9.7. Regarding Pearson and Spearman correlation coefficients, the results showed that to

perform two-tailed statistical tests for the effect size r = 0.30, with a statistical power of 0.80 and an alpha level of 0.05, sample size N = 84 is sufficient, while for the effect size r = 0.40 (alpha level 0.05, statistical power 0.80), sample size N = 46 is sufficient. Given the results, one may assume that the sample is sufficiently powered to correctly estimate medium-sized correlations (effects) as statistically significant at alpha level 0.05. Provisional power calculations for the Kruskal-Wallis test were calculated using the MultNonParam package in the R statistical computation environment. The results suggest that, for the design containing a three-group factor with ten participants in each group and an alpha level of 0.05 under the assumption of underlying normal distribution, estimated statistical power would approximate 0.88.

Results

The study included 62 participants with UC in clinical remission. The study population consisted of 38 (61.3%) male and 24 (38.7%) female patients with an average age of 44.9 ± 14.1 (22–73) years, average body weight of 78.21 ± 15.5 (48–120) kg, and average BMI of 25.08 ± 4.58 (20.2–40.0) kg/m^2. From the moment of establishing the diagnosis to the moment of being involved in the study, the average duration of the disease was 10.08 ± 7.81 years. As related to the disease extent, 46 (74.2%) participants presented with extensive colitis, while 14 (22.59%) and 2 (3.22%) patients had left-sided colitis and proctitis, respectively. The average vitamin D level was 49.87 ± 23.5 nmol/L.

According to classification, the established vitamin D levels in patients with UC were as follows: 6 (9.7%) patients had sufficient levels (> 75 nmol/L), whereas insufficiency (< 50 nmol/L) and deficiency (50–75 nmol/L) were established in 32 (51.6%) and 24 (38.7%) participants, respectively. The results according to age, duration of the disease, weight, and BMI are presented in Table 1.

The results of the Kruskal-Wallis tests at the level of the entire study group did not reveal any significant differences between participants with different 25(OH)D levels regarding any of the investigated variables.

The average value of FC in the studied sample was 82.69 ± 139.91 μg/g, for CRP, it was 4.598 ± 5.527 mg/L, and for MES, it was 0.855 ± 0.698. Kurtosis values of the variables suggest the absence of any substantial deviations from the values characterizing normal distribution, except for somewhat more pronounced kurtosis for the variables FC and CRP (Table 2).

Calculation of Pearson's correlation coefficient for the variables mentioned above revealed that serum 25(OH)D levels in the analyzed sample did not significantly correlate either with FC [$r = 0.077$, $p = 0.551$, Spearman's rho (ρ) = –0.160, $p = 0.213$] (Figure 1), CRP ($r = –0.111$, $p = 0.392$, $\rho = –0.107$, $p = 0.407$) (Figure 2), or MES ($r = 0.02$, $p = 0.787$, $\rho = 0.021$, $p = 0.874$) (Figure 3).

Table 1

Vitamin D levels in patients (n = 62) with UC in relation to age, duration of UC, BW, and BMI

Parameter	Median	AM	SD	Skewness	Kurtosis	*p-value
Age (years)						
SL	41.813	15.489	0.65	-0.606	22	
IL	47.708	12.063	0.062	-0.587	26	0.136
DL	50.5	12.818	0.754	-1.82	39	
Disease period (years)						
SL	8.625	8.454	3.57	15.479	2	
IL	12.292	7.428	0.338	-1.595	3	0.07
DL	9	3.162	-0.797	-1.868	5	
Weight (kg)						
SL	79.625	18.502	0.506	-0.057	51	
IL	75.609	11.835	-0.346	-0.396	48	0.7
DL	80.667	9.73	-0.757	-0.25	65	
BMI (kg/m^2)						
SL	25.441	5.979	-1.255	7.524	2.2	
IL	24.578	2.473	0.288	2.249	18.5	0.772
DL	25.133	1.183	0.04	-2.446	23.7	

UC – ulcerative colitis; BW – body weight; BMI – body mass index; AM – arithmetic mean; SD – standard deviation. *Kruskal-Wallis test.

Note: Patient groups according to the vitamin D level were as follows: 6 patients were in the group with sufficient level (SL) > 75 nmol/L, 32 patients were in the group with insufficient level (IL) < 50 nmol/L, and 24 patients were in the group with deficient level (DL) from 50–75 nmol/L.

Table 2

Values of FC, vitamin D, CRP, and MES in patients (n = 62) with ulcerative colitis

Parameter	Median	AM	SD	Skewness	Kurtosis	Shapiro-Wilk
FC (μg/g)	17.0	82.7	139.9	2.621	6.896	0.582
25(OH)D (nmol/L)	49.0	49.9	23.5	0.518	0.190	0.967
CRP (mg/L)	2.4	4.6	5.5	2.171	4.219	0.690
MES	1.0	0.855	0.698	0.206	-0.893	0.8

FC – fecal calprotectin; 25(OH)D – 25-hydroxyvitamin D; CRP – C-reactive protein; MES – Mayo Endoscopic Score. For other abbreviations, see Table 1.

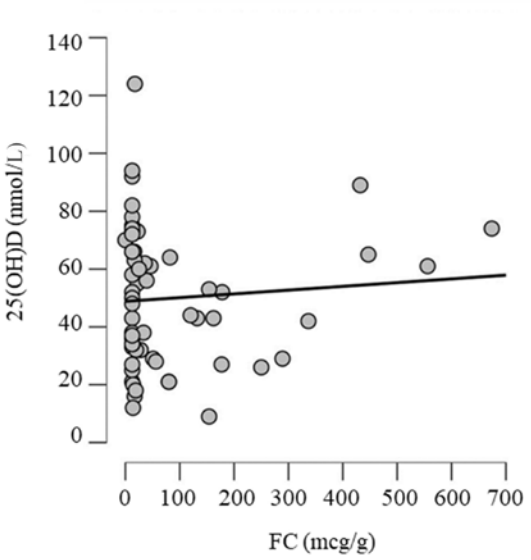

Fig. 1 – Fecal calprotectin (FC) and 25-hydroxyvitamin D [25(OH)D].

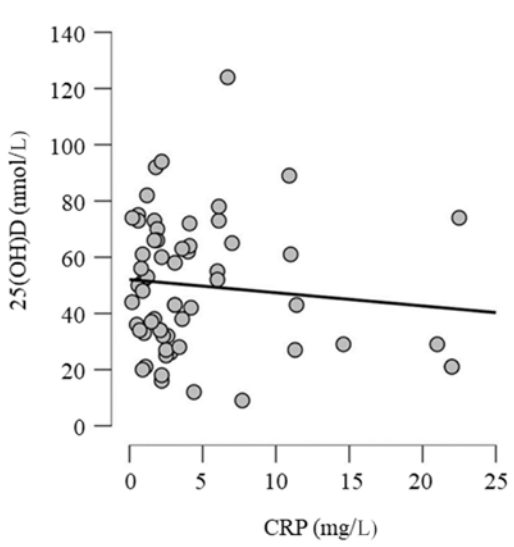

Fig. 2 – C-reactive protein (CRP) and 25-hydroxyvitamin D [25(OH)D].

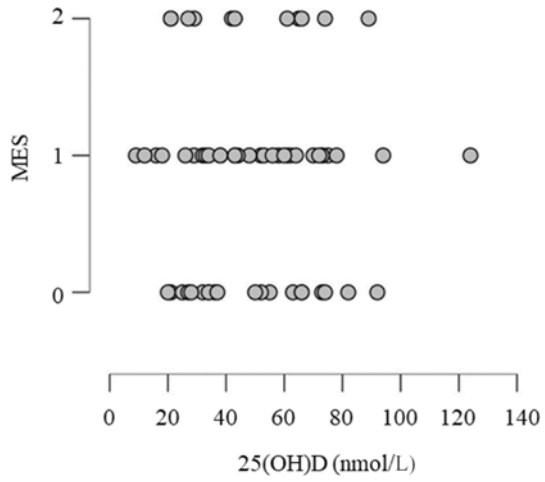

Fig. 3 – Mayo Endoscopic Score (MES) and 25-hydroxyvitamin D [25(OH)D].

Discussion

It is well established that the incidence of IBD is higher in regions with inadequate/reduced exposure to sunlight, which might be associated with vitamin D deficiency [12]. The prevalence of vitamin D deficiency in patients with IBD is higher compared to the general population, ranging around 45–50% in UC. However, routine 25(OH)D monitoring is not conducted in most cases [13]. Most commonly, the deficiency is associated with inadequate dietary intake and reduced exposure to sunlight due to immunosuppressive therapy. It has a seasonal character and is most pronounced in the winter/spring season [14].

In Serbia, a region with a moderate continental climate, our study was conducted in the winter/spring period. The results revealed inadequate serum levels of vitamin D in 91.3% of UC patients in clinical remission, with 51.6% categorized as deficiency (50–75 nmol/L) and 38.7% as insufficiency (< 50 nmol/L).

The prevalence of 25(OH)D deficiency (< 50 nmol/L) among the general population ranges from 24% in the USA to 37% in Canada and 40% in Europe and varies by age, region, and ethnicity [15]. The levels of 25(OH)D, according to vitamin D level classification, in our patients with UC, correspond with the data from the literature. The research conducted by Law et al. [16] on a population of 80 participants with UC revealed similar results: sufficient levels were determined in 10% of patients, while deficiency and insufficiency were detected in 56% and 34% of patients, respectively. According to the Del Pinto et al. [17] meta-analysis, which encompassed 14 studies and 1,891 patients (938 IBD and 953 controls), patients with IBD had 64% higher odds of vitamin D deficiency than the control group. The same group of authors conducted the meta-analysis according to the type of IBD. The analysis of seven studies on the prevalence of vitamin D deficiency in patients with UC revealed more than double the odds for vitamin D

deficiency compared to the healthy controls [odds ratio (OR) = 2.28; 95% confidence interval (CI): 1.18, 4.41; $p = 0.01$]. Taking these data into account, monitoring vitamin D levels in patients with UC would be significant for detecting insufficiency and timely supplementation, given that a favorable effect on the course of the disease has been demonstrated. It has been established that serum vitamin D level negatively correlates with endoscopic and histological inflammation and increases the risk of clinical relapse. As reported by Gubatan et al. [7], 25(OH)D level lower than 35 ng/mL increases the risk of clinical relapse in patients who are in stable clinical remission. Patients with lower vitamin D levels manifest higher clinical disease activity and higher values of inflammatory markers (FC and CRP) [18, 19]. Moreover, vitamin D deficiency is associated with increased disease extent and poorer therapeutic response to anti-tumor necrosis factor therapy [9, 20].

As stated in other available literature data, which is consistent with the results of our research, the correlation between 25(OH)D level and CRP value has not been established [21, 22]. According to the study by Garg et al. [23], cholecalciferol supplementation in patients with IBD did not decrease the values of FC or CRP despite the reduced clinical activity of the disease.

A study by Thomas et al. [24], which included 82 patients with UC, revealed decreased vitamin D and increased CRP values in patients with high endoscopic activity compared to those in remission. A statistically significant negative correlation between vitamin D and the endoscopic score was confirmed ($p = 0.047$), whereas a negative correlation between vitamin D and CRP was below the level of statistical significance ($p = 0.079$). In a study with 90 UC patients in clinical remission, Emami et al. [25] measured the concentration of visfatin, which exerts proangiogenic effects and is considered an indirect inflammation indicator. The obtained results indicated that supplementation of a 300,000 IU mono-dose vitamin D resulted in a moderate increase of visfatin level in a group with vitamin D insufficiency, unlike the group with normal vitamin D levels. This result suggests the anti-inflammatory effects of vitamin D in clinical remission, though its effects on the inflammation biomarkers (FC and CRP) in remission are still unknown.

Most studies of vitamin D effects on UC activity included a sample population with different stages of disease activity and patients with IBD in general, and the investigations of UC patients in clinical remission are still scant.

The importance of our research is in the fact that only patients in clinical remission were selected for the study, which was not the case in most of the available previous research. We fulfilled the aim of the study to assess the effects of vitamin D on the activity parameters only in clinical remission and hence contribute to a better understanding of the vitamin D function and its dynamics in this patient population. Moreover, this could contribute to the fact that vitamin D might have an important role as an inflammatory biomarker for noninvasive patient monitoring.

A major limitation of our study is the small sample size. However, several studies on this topic were also performed on a smaller sample. Therefore, the power of the study was calculated to approximate 0.88.

Conclusion

Vitamin D deficiency is a frequent condition in patients with UC in clinical remission. It requires continuous monitoring of 25-hydroxyvitamin D serum levels and consequent vitamin D supplementation due to its effects on calcium metabolism and the activity and course of the disease. Our research did not reveal any relationship between 25-hydroxyvitamin D serum level and values of biomarkers of inflammation (fecal calprotectin and C-reactive protein) or endoscopic disease activity (Mayo Endoscopic Score) in patients with ulcerative colitis in clinical remission, which weighs in favor of controversy whether the decreased level of vitamin D is a cause or the consequence of bowel inflammation, which is a topic of further research in this field.

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Received on September 12, 2023
Revised on October 24, 2023
Revised on June 30, 2024
Accepted on July 9, 2024
Online First August 2024