

Serum Concentration of Vitamin D in Patients with Vulgar Psoriasis



^{1,2}Marina Vekić Mužević

¹ Tatjana Matijević

^{3,4} Irina Bagić

^{3,4} Vjenceslav Vrtarić

^{5,6} Elvira Lazić Mosler

¹ Institute of Dermatovenereology, University Hospital Center Osijek, Osijek, Croatia

² Department of Infectious Diseases and Dermatovenereology, School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

³ Department of Neurosurgery, University Hospital Center Osijek, Osijek, Croatia

⁴ School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

⁵ Division of Dermatovenereology, General Hospital Dr. Ivo Pedišić, Sisak, Croatia

⁶ School of Medicine, Catholic University of Croatia, Zagreb, Croatia

of healthy individuals. The investigated features were demographical data, body mass index (BMI), disease severity, vitamin D serum levels, inflammatory markers, and parathyroid hormone (PTH) levels.

Results: The study included 112 participants, 60 in the case group and 52 in the control group with the median age of 49 years. Physical activity was higher in the control group, while the body mass and the BMI were higher in the case group. Participants' BMI negatively correlated to vitamin D serum levels, as well as C-reactive protein values in the control group and PTH in the case group. There was no significant difference in nicotine and alcohol consumption, sun exposure or vitamin D levels between the two groups.

Conclusion: Both groups presented with vitamin D serum levels in the deficiency range. The seasons of the year and the participants' BMI affected vitamin D status. Vitamin D levels were equally distributed between the groups without influence on disease severity.

Keywords: psoriasis, vitamin D, body mass index, parathyroid hormone, C-reactive protein

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Corresponding author:

Irina Bagić

A: Department of Neurosurgery, University Hospital Center Osijek; J. Huttlera 4, 31000 Osijek, Croatia

E-mail: irina.bagic@gmail.com

Phone: +385 31 511 382

Abstract



Introduction: Psoriasis is a chronic, inflammatory systematic disease that primarily affects the skin. Various factors influence the disease outcome and severity, among which the influence of vitamin D serum levels could potentially be important for disease pathogenesis and therapeutic strategies.

Aim: To analyze vitamin D serum levels in patients with psoriasis in comparison to healthy individuals, together with markers of inflammation and disease severity.

Methods: The study included patients with psoriasis that formed the case group, while the control group consisted

Introduction

Vitamin D is a fat-soluble, secosteroid pre-hormone that has an important role in calcium-phosphorus homeostasis regulation and normal skeletal architecture maintenance¹. Our body receives vitamin D through two main sources, one being endogenous cutaneous production and the other being dietary intake. Cutaneous production in the presence of sunlight or other sources of ultraviolet (UV) radiation is the primary site for vitamin D synthesis. Precursor of vitamin D, 7-dehydrocholesterol, located in the epidermal keratinocytes, converts to previtamin D3 or cholecalciferol when exposed to UVB light, followed by thermal isomerization to vitamin D3². Dietary vitamin D, with its two main forms, ergocalciferol (D2) and cholecalciferol (D3), is crucial for achieving optimal vitamin D serum levels. However, very few naturally occurring foods have significant amounts of vitamin D; among the exceptions are mostly fatty fish, egg yolk and some forms of mushrooms^{3,4}.

Historical events, such as the rickets epidemic from the early 1900s, have taught us and established vitamin D food fortification as a primary vitamin D insufficiency prevention strategy, although vitamin D insufficiency remains a common problem in the general population^{4,7}. Public health campaigns have raised awareness of this problem among the general population, thus resulting in increased vitamin D supplementation intake^{4,8}.

Independent of the source, vitamin D has to be transformed to metabolically active form, also known as calcitriol or 1,25-hydroxyvitamin D (1,25(OH)D). The first hydroxylation reaction takes place in the liver, where it is regulated by the CYP2R1 and CYP27A1 enzymes to form 25-hydroxyvitamin D (25(OH)D), and the second reaction occurs in the kidney, and is catalyzed by the CYP27B1 enzyme^{2,9}. Vitamin D status is commonly determined by measuring 25(OH)D serum levels, with the majority being bound to the vitamin D binding protein (DBP) and less than 1% in free form¹⁰.

Serum 25(OH) levels depend on various factors such as diet, vitamin supplementation, UV exposure, skin type, nicotine and alcohol consumption, the BMI, the seasons of the year, and physical activity. Important predictors of unfavorable vitamin D status are age, the female gender, the BMI, and excessive alcohol intake. On the contrary, the summer season is associated with lower risk of vitamin D deficiency¹¹⁻¹³. Melanin partly absorbs UV radiation,

therefore dark-skinned individuals require more time to achieve optimal concentrations of previtamin D3 in comparison to light-skinned individuals, consequently being under a greater risk of vitamin D deficiency^{14,15}. Furthermore, studies have shown that physical activity by itself is associated with higher 25(OH)D levels, independent of UV exposure¹¹.

Vitamin D deficiency has been reported in different diseases, such as malignancies, cardiovascular diseases, different autoimmune diseases, and metabolic disorders. Nevertheless, most studies have not proven causality, hence the relevance of low vitamin D levels in these conditions still remains unclear^{16,17}. One of the thoroughly explored target organs for the active form of vitamin D is skin. Skin keratinocytes are not only the place for vitamin D synthesis, but they also express vitamin D receptors (VDR) for modulation of multiple skin functions, while the active form of vitamin D regulates almost every step of epidermal differentiation^{18,21}. One especially interesting and highly researched area is the immunomodulatory role of vitamin D; studies have shown the ability of vitamin D to inhibit the proliferation of T lymphocytes, induce CD4+CD25+ regulatory T lymphocytes, inhibit the production of pro-inflammatory cytokines including TNF-alpha, IL-1 beta, IL-6, and IL-8, and to stimulate the production of Th2 cytokines. Vitamin D downregulates dendritic cell maturation and migration (S), but it simultaneously increases the antimicrobial peptides (AMPs) synthesis, therefore increasing cutaneous innate immune system^{9,18,22,23}.

One of the model prototypes of a disease in which T lymphocyte dysregulation and excessive production of pro-inflammatory cytokines plays a central role in pathogenesis is psoriasis. Psoriasis is a chronic multifactorial, inflammatory disease with a prevalence of approximately 2-3% in the general population²⁴⁻²⁶. Although it primarily affects the skin, psoriasis is considered to be a systemic disorder associated with other conditions like psoriatic arthritis, cardiovascular diseases, diabetes, obesity, non-alcoholic fatty liver disease, and inflammatory bowel disease^{26,27}. Plaque psoriasis is the most common type with characteristically erythematous scaly skin lesions, usually seen on the scalp, elbows, knees, the umbilical and the lumbar area, although it can affect any body site²⁶. Psoriasis Area and Severity Index (PASI) is a generally accepted tool for the assessment of disease severity and extent²⁸. Typical histological findings in psoriatic lesions are keratinocyte hyperproliferation, abnormal differentiation, and skin infiltration with activated inflammatory cells, predominantly CD4+ T helper 1 cells (Th1) and CD8+ cytotoxic T

lymphocytes^{9,29}. These cells secrete type 1 cytokines like TNF- α and INF- γ , which then activate myeloid dendritic cells and IL-12 and IL-23 secretion. IL-12 and IL-23 then activate Th1 and Th17 cells that produce IL-17 cytokines, which further activate keratinocytes to produce pro-inflammatory cytokines. Once initiated, this feedback cycle of inflammation is self-continued²⁶.

Therefore, based on the antiproliferative, pro-differentiating, and immunomodulating properties of vitamin D, topical application of its preparations and analogs is an important therapeutic option in the treatment of psoriasis. Studies have shown comparable efficacy to corticosteroids when used as monotherapy with superior effects when used in combination with a potent topical corticosteroid agent⁴. Furthermore, a question of a possible role of vitamin D in the pathogenesis of psoriasis has arisen³⁰. Indeed, many studies have reported low serum levels of 25(OH)D in patients with psoriatic disease. Nevertheless, the evidence of causality is still missing. Several studies have observed a benefit of vitamin D supplementation with inconsistent results¹⁷.

In this study, we compared vitamin D serum levels between patients with psoriasis and healthy controls, together with several markers of inflammation and disease severity.

Methods

This study was designed as a case-control study and it was performed at the Department of Dermatovenereology, Osijek University Hospital Centre, Osijek, Croatia, from December 2017 to June 2019. The inclusion criteria for the case group were the following: patients with histologically confirmed vulgar (plaque) psoriasis, with or without psoriatic arthritis; patients aged between 18 and 90; patients who consented to participate in the study. The exclusion criteria for the case group were the following: patients with other forms of psoriasis; patients younger than 18 or older than 90; patients who refused to participate in the study; patients with connective tissue diseases, autoinflammatory diseases, hyperparathyroidism, renal insufficiency, malignant diseases, alcoholism, liver diseases, and malabsorption; patients who took exogenous vitamin D3 during the three months preceding inclusion in the study; patients on hormonal

replacement therapy; relatives of the case or the control group subjects. The control group consisted of healthy volunteers in the age group between 18 and 90 who agreed to participate in the study.

Basic demographical and anthropometric parameters were obtained. The body mass index (BMI) was calculated by dividing the participants' body weight in kilograms with a square of body height in meters. Additionally, in patients with psoriasis, the Psoriasis Area and Severity Index (PASI) was investigated.

Based on disease severity, patients were divided into three groups: mild disease (PASI 0-10), moderate disease (PASI 10-20), and severe disease (PASI >20). Data on nicotine intake, alcohol consumption, involvement in physical activity (defined as participation in physical activity for minimum of 30 minutes three times a week), and sun exposure (defined as exposure to direct sunlight in a week prior to inclusion in the study for more than 15 minutes) were recorded. Vitamin D 25(OH)D serum levels were assessed using LC-MS/MS chromatographic method (LC-MS/MS chromatograph Shimadzu 8040, Shimadzu Corporation, Kyoto, Japan, using reagents from Recipe Chemicals + Instruments GmbH, Munich, Germany). Vitamin D status was defined as a sufficiency for serum concentrations of ≥ 30 ng/mL, insufficiency for serum concentrations between 21 and 29 ng/mL, and as a deficiency for serum concentrations under 20 ng/mL. Other laboratory workup included inflammatory markers such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), as well as parathyroid hormone (PTH) serum concentration for the case group.

The data were statistically analyzed. The categorical data were presented with absolute and relative frequencies. Differences between categorical data were tested using the chi-square test. The distribution of numerical data was tested using the Shapiro-Wilk test. The numerical data were described using the median and interquartile range. The means were defined using 95% confidence interval (CI). To test the differences between numerical data between independent samples, the Mann-Whitney U test was used, along with the Hodges-Lehmann median difference. To test the differences between three or more independent samples, the Kruskal-Wallis test (post-hoc Conover test) was employed. Correlation was assessed using the Spearman correlation coefficient (Rho). All P values are two-sided. Significance was set at $\alpha=0.05$. Statistical software MedCalc[®] version 19.6 (MedCalc Software Ltd, Ostend, Belgium; <https://www.medcalc.org>; 2020) was used for data computing and analysis.

Results

The study included 112 participants, 60 in the case group and 52 in the control group. The median age of the participants was 49 years with an interquartile range from 39 to 58 years, ranging from 23 to 88 years. There was no statistically significant difference in gender or age distribution between the case and the control group (Tables 1 and 2).

Nicotine consumption was noted in 41 (36.6 %) and alcohol consumption in 42 (37.5 %) subjects, without significant difference between the groups. Out of 40 (37.5 %) participants who confirmed physical activity involvement, participants in the control group confirmed

higher engagement in regular physical activity when compared to the case group. Sun exposure one week prior to entering the study was confirmed in 78 (69.6 %) of participants, with no statistically significant difference between the groups. Psoriatic arthritis was noted in 17 (28.3 %) patients with psoriasis (Table 3).

Body mass and BMI were statistically significantly higher in patients with psoriasis than in healthy controls (Table 4).

Median vitamin D serum concentration was 19.6 ng/mL among all participants. There was no statistically significant difference in vitamin D serum concentration between the case and control groups (Table 5). When analyzing vitamin D status categories, sufficiency was observed in 11 (9.8 %), insufficiency in 45 (40.2 %), and deficiency in 56 (50 %) participants. There was no correlation between the vitamin D status in patients with

Table 1. Distribution of the participants according to gender

	N (%)			P*
	Control group	Case group	Total	
Gender				
Male	32 (61.5)	38 (63.3)	57 (50.9)	0.845
Female	20 (38.5)	22 (36.7)	55 (49.1)	
Total	52 (100)	60 (100)	112 (100)	

*chi-square test

Table 2. Age distribution of the participants

	Median (interquartile range)		Difference†	95% CI	P*
	Control group	Case group			
Age (years)	47.5 (38– 57)	52 (42 – 61)	7	1 to 13	0.389

*Mann Whitney U test; †Hodges-Lehmann median difference

Table 3. Distribution of subjects according to nicotine and alcohol consumption, physical activity, Sun exposure and presence of arthritis

	N (%)			P*
	Control group	Case group	Total	
Nicotine consumption	19 (36.5)	22 (36.7)	41 (36.6)	0.99
Alcohol consumption	17 (32.7)	25 (41.7)	42 (37.5)	0.33
Physical activity	12 (23.1)	28 (46.7)	40 (35.7)	0.009
Sun exposure	39 (75)	39 (65)	78 (69.6)	0.25
Diagnosis				
Vulgar psoriasis	-	43 (71.7)	43 (71.7)	-
Psoriatic arthritis	-	17 (28.3)	17 (28.3)	

*chi-square test

Table 4. Body height, weight and Body Mass Index distribution

	Median (interquartile range)		Difference [†]	95% CI	P*
	Control group	Case group			
Height [cm]	168 (164 – 175.8)	173.5 (165.3 – 180)	4	0 to 7	0.08
Weight [kg]	76.5 (64 – 91.5)	90 (75 – 106.3)	11	4 to 18	0.004
Body Mass Index [kg/m ²]	26.7 (22.97 – 29.7)	29.3 (25.24 – 35.21)	3.01	0.8 to 5.23	0.01

*Mann Whitney U test; [†]Hodges-Lehmann median difference

Table 5. Vitamin D serum concentration

	Median (interquartile range) [ng/mL]	Difference	95% CI	P*
Group				
Control	20.6 (10.8 – 24.2)	-0.7	-3.8 to 2.2	0.66
Case	19.1 (11.5 – 22.7)			

*Mann Whitney U test; [†]Hodges-Lehmann median difference

Table 6. Distribution of vitamin D serum concentrations in all participants

	Median (interquartile range) [ng/mL]	Difference	95% CI	P*
Gender				
Male	19.2 (14.9 – 23.2)	0.3	-2.6 to 3.5	0.83
Female	20.7 (10.5 – 25.6)			
Exposure to Sun				
No	15.1 (10.4 – 20.5)	5.8	2.2 to 9.2	0.001
Yes	21.1 (16.5 – 24.9)			
Nicotine consumption				
No	19.4 (12 – 23.7)	0.1	-3 to 3.5	0.92
Yes	20.7 (10.8 – 23.9)			
Alcohol consumption				
No	19.4 (11 – 23)	0.6	-2.4 to 3.8	0.62
Yes	20 (11.3 – 24.4)			
Physical activity				
No	19.3 (10.5 – 23.7)	1.8	-1.2 to 5.4	0.24
Yes	19.7 (16.2 – 23.5)			
Season				
Spring	17.6 (11.3 – 21.4)			<0.001 ^{†§}
Summer	24.0 (21.7 – 30.4)			
Fall	20.5 (19.1 – 24.6)			
Winter	15.5 (10.4 – 21.9)			

*Mann Whitney U test; [†]Hodges-Lehmann median difference

[†]Kruskal Wallis test (Post hoc Conover)

[§]at the level P<0.05, statistically significant differences are spring vs. summer, summer vs. winter

psoriatic disease and disease duration (Table 7). Serum concentration of vitamin D was lower in patients with severe disease, but there was no statistically significant difference (Table 8).

Among all participants, statistically higher vitamin D serum concentration was observed in those participants who confirmed sun exposure one week prior to inclusion in the study. There was statistically significant difference in vitamin D serum concentration in

participants who enrolled in the study during summer months, in comparison to other seasons (Table 6).

Statistically significant negative correlation between vitamin D serum concentration and BMI was observed. There was also statistically significant negative correlation between CRP and vitamin D serum concentration in the control group, while there was a statistically significant negative correlation between vitamin D and PTH serum concentration in the case group (Table 7).

Table 7. Correlation between vitamin D serum concentration and age, PASI, disease duration, BMI, CRP, ESR, and PTH

	Spearman correlation coefficient Vitamin D serum concentration		
	Rho	95% CI	P
All participants			
Age	0.041	-0.146 to 0.225	0.67
BMI	-0.200	-0.371 to 0.015	0.03
CRP	-0.125	-0.303 to 0.063	0.19
ESR	0.046	-0.141 to 0.229	0.63
Control group			
Age	0.153	-0.125 to 0.409	0.28
BMI	-0.191	-0.441 to 0.087	0.18
CRP	-0.315	-0.542 to -0.047	0.03
ESR	-0.018	-0.289 to 0.256	0.89
Case group			
Age	-0.108	-0.353 to 0.150	0.41
BMI	-0.229	-0.456 to 0.027	0.08
PTH	-0.417	-0.607 to -0.183	<0.001
CRP	0.035	-0.221 to 0.287	0.79
ESR	0.107	-0.151 to 0.351	0.42
Disease duration	0.071	-0.187 to 0.319	0.59
PASI	-0.150	-0.389 to 0.108	0.25

Table 8. Vitamin D serum concentration, ESR, CRP, and disease severity

	Median (interquartile range)			P*
	Mild disease (n = 34)	Moderate disease (n = 13)	Severe disease (n = 13)	
ESR	8.5 (4.0 – 16.0)	10.0 (5.0 – 25.5)	15 (5.8 – 39)	0.35
CRP	2.6 (1.2 – 4.9)	3.6 (1.4 – 6.9)	3.8 (1.5 – 10.1)	0.62
Vitamin D	20.7 (14.9 – 23.7)	19.7 (10.9 – 23.6)	15.0 (11.7 – 19.6)	0.43

*Kruskal Wallis test (Post hoc Conover)

Discussion

The participants included in this study presented with vitamin D concentrations in the deficiency range (median vitamin D concentration was 19.6 ng/mL). Therefore, there was no significant difference in vitamin D levels between the patients with psoriasis and healthy individuals. There are several possible explanations for inadequate vitamin D status among the participants included in this study. Primarily, when analyzing geographical position, Croatia is located above 35° of northern latitude, which consequently results in very low vitamin D skin production during winter season, regardless of the amount of sun exposure³¹. Other conditions that could also contribute to inadequate vitamin D status include a sedentary lifestyle and low dietary intake of vitamin D rich foods.

Seasonal variations of vitamin D status were confirmed in this study, with significantly higher serum concentrations of vitamin D during the summer season when compared to the other seasons, while sun exposure directly correlated to vitamin D status. However, there was no notable correlation between gender and vitamin D status, although existing literature suggests that the female gender is associated with lower levels of vitamin D¹¹.

Psoriasis has been recognized as a systemic inflammatory disease and obesity has been reported as an independent risk factor for this disease³². In this study, patients with psoriasis had higher BMI when compared to the control group, and a higher BMI was associated with lower vitamin D levels. According to existing literature, a correlation between obesity and vitamin D insufficiency was marked at BMI above 30 kg/m². Lower vitamin D levels in obese people are a result of a volumetric dilution of a fat-soluble vitamin D^{31,33}. Also, according to a study by Wortsmans et al., vitamin D insufficiency is a consequence of a sequestration process that occurs in the body fat compartments, resulting in a lower bioavailability³⁴. Impaired hepatic 25-hydroxylation, commonly found in patients with non-alcoholic fatty liver disease is also frequently dysfunctional in obese patients^{35,36}.

Other factors that could contribute to inadequate vitamin D status are alcohol consumption, reduced physical activity, and smoking. Interestingly, causality between alcohol consumption and vitamin D status can be both

positive and negative. Low vitamin D levels were observed in patients who never consume alcohol, as well as in those who consume it excessively. However, Shirazi et al. found a positive correlation between moderate alcohol consumption and vitamin D status^{37,38}. In this study, there was no significant association between alcohol consumption and vitamin D status, although we found slightly higher values of vitamin D among alcohol consumers. However, it is important to emphasize that excessive alcohol consumption was an exclusion criterion for this study, therefore all of the participants were moderate alcohol consumers. Smoking, despite previous reports about negative impact on vitamin D levels, did not negatively correlate to vitamin D levels³⁹. In their study about determinants of vitamin D status in the general population of Denmark, Thunsen et al. found that a sedentary lifestyle correlated with inadequate vitamin D status³⁷. This study has shown a positive correlation between physical activity and vitamin D status in the case group.

As previously mentioned, in this study patients with psoriasis did not have lower vitamin D levels when compared to healthy controls. However, Gisondi et al. have demonstrated that vitamin D deficiency is frequently found in patients with psoriasis. They also observed remarkable seasonal fluctuation of vitamin D levels. Additional causality of low vitamin D status with disease severity was lacking⁴⁰. In this study, lower vitamin D levels among patients with severe disease were observed, but there was no statistically significant correlation. A study by Zuchi et al. about serum levels of 25-hydroxy vitamin D in psoriatic patients provided similar results⁴¹. Still, a comprehensive meta-analysis confirmed lower vitamin D levels in patients with psoriasis, as well as an additional correlation between vitamin D status and disease severity⁴².

Inflammatory biomarkers, such as CRP, may be a useful tool for grading disease severity, alongside with PASI. A cross-sectional study by Coimbra et al. reported that CRP could be a potential biomarker for disease severity⁴³. A majority of the participants included in this study received systematic therapy, hence there was no correlation between CRP and the PASI values.

When assessing the results of this study and comparing them with the existing literature, the main limitations are a small sample size and the characteristic group of participants that presented with vitamin D levels in the deficiency range.

Conclusion

In summary, patients with psoriasis, as well as healthy individuals, presented with vitamin D serum levels in the deficiency range. Seasonal variations of vitamin D status were observed, with significantly higher serum concentrations during the summer season. Participants with higher BMI values presented with lower vitamin D levels. Despite previous findings about lower vitamin D levels in patients with psoriasis and possible association with disease severity, there was no similar correlation in this study.

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SERUMSKA KONCENTRACIJA VITAMINA D U BOLESNIKA S VULGARNOM PSORIJAZOM

^{1,2} Marina Vekić Mužević

¹ Tatjana Matijević

^{3,4} Irina Bagić

^{3,4} Vjenceslav Vrtarić

^{5,6} Elvira Lazić Mosler

¹ Institute of Dermatovenereology, University Hospital Center Osijek, Osijek, Croatia

² Department of Infectious Diseases and Dermatovenereology, School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

³ Department of Neurosurgery, University Hospital Center Osijek, Osijek, Croatia

⁴ School of Medicine, Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

⁵ Division of Dermatovenereology, General Hospital Dr. Ivo Pedišić, Sisak, Croatia

⁶ School of Medicine, Catholic University of Croatia, Zagreb, Croatia

Sažetak

Uvod: Vulgarna psorijaza kronična je, upalna, sustavna bolest koja se primarno očituje promjenama kože. Različiti čimbenici utječu na ishod liječenja i težinu ove bolesti, a među njima se posebno izdvaja potencijalno važna uloga serumskih koncentracija vitamina D kako u patogenezi tako i kao terapijska opcija.

Cilj: Analiza serumskih koncentracija vitamina D u bolesnika koji boluju od vulgarne psorijaze u usporedbi sa

zdravom kontrolnom skupinom, kao i procjena težine bolesti i utjecaja upalnih markera.

Metode: U istraživanje su uključeni bolesnici koji boluju od vulgarne psorijaze i kontrolna zdrava skupina ispitanika. Istraživana su obilježja kao što su osnovni demografski podaci, indeks tjelesne mase (BMI), klinički stupanj bolesti, serumske vrijednosti vitamina D, upalni parametri te vrijednosti paratireoidnog hormona (PTH).

Rezultati: U istraživanje je uključeno 112 ispitanika, 60 oboljelih te 52 ispitanika u kontrolnoj skupini s medijanom dobi od 49 godina. Znatno je viša bila razina tjelesne aktivnosti u kontrolnoj skupini, dok su među oboljelima zabilježeni veća tjelesna masa i BMI. Utvrđena je negativna korelacija između serumskih vrijednosti vitamina D i BMI-ja, kao i razine C-reaktivnog proteina u kontrolnoj skupini, odnosno vrijednosti PTH-a u oboljelih. Prilikom ispitivanja utjecaja konzumacije alkohola i nikotina, izloženosti Sunčevim zrakama i serumskih vrijednosti vitamina B nije bilo znatnih razlika između skupina.

Zaključak: Zabilježene su niske koncentracije vitamina D u obje skupine ispitanika. Godišnja doba i BMI utječu na razinu vitamina D. Nije uočena snižena koncentracija vitamina D u bolesnika sa psorijazom ili utjecaj na težinu bolesti.

Ključne riječi: psorijaza, vitamin D, indeks tjelesne mase, paratireoidni hormon, C-reaktivni protein