Acta Clin Croat 2022; 61:70-78
doi: 10.20471/acc.2022.61.01.09

Original Scientific Paper

MINERAL BONE DENSITY AND VITAMIN D LEVELS IN PATIENTS WITH PSORIATIC ARTHRITIS

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SUMMARY – The objective of this study was to explore the possible differences in bone mass density (BMD) and markers of bone metabolism between patients with psoriasis with concomitant psoriatic arthritis (PsA) and patients with psoriasis only (PV). A comparable sample of both types of patients were included in analysis. In all patients, vitamin D serum levels along with inflammatory markers and parathyroid hormone (PTH) were measured. BMD was assessed with dual-energy x-ray absorptiometry scan in axial and appendicular skeleton. Patients with PsA tended to have decreased BMD in axial skeleton, while BMD in appendicular skeleton was comparable between the groups. No statistically significant correlation was found of inflammatory markers, vitamin D and PTH levels with BMD in either patient group. A negative correlation was recorded between vitamin D serum concentration and PTH levels.

Key words: *Psoriasis; Arthritis, psoriatic; Bone mass density; Vitamin D*

Introduction

Psoriasis is an immune-mediated chronic inflammatory skin disease with estimated 2%-4% prevalence[1]. Psoriatic disease is associated with markers of systemic inflammation that correlate psoriasis with a high frequency of cardiovascular events, diabetes and dyslipidemia[2-7], as well as an increasing number of other recognized comorbid diseases, with psoriatic arthritis (PsA) being the most common and well recognized comorbidity.

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Received February 21, 2020, accepted April 21, 2020

Psoriatic arthritis belongs to a diverse group of inflammatory arthritides, all characterized by chronic inflammation, intra-articular local bone destruction, and systemic bone loss caused by disrupted bone homeostasis[8]. Erosions of periarticular bone are the main feature of rheumatoid arthritis, and they are also found in other spondyloarthritides[9]. The formation of bone erosions depends on increased osteoclast activity, the cells capable of resorbing the mineralized matrix[8].

Osteoclast progenitors are present in peripheral blood and synovial tissues of patients with inflammatory arthritides[8]. They are found to mediate bone loss both locally and systemically; locally forming bone erosions and joint osteolysis, and systemically driving the loss of bone mineral density (BMD) and chronic inflammation-induced osetoporosis[8]. Osteoclastogen-

esis driven by increased osteoclast activity is amplified by proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-17, IL-18, tumor necrosis factor alpha (TNF-α), chemokines (such as CC-chemokine ligand 2 (CCL2), CCL3, CCL4), and apoptotic mediators (Fas-ligand (FasL), TNF-related apoptosis inducing ligand, herpesvirus entry mediator ligand)[10,11]. It has been demonstrated that even the slightest rise in the level of systemic inflammatory mediators results in induction of bone destruction, leading to fractures and arthritis-related disabilities[9].

Osteoporosis is a skeletal disease that results in BMD decrease and disruption of bone microarchitecture, reduced bone strength, and an increased risk of fractures[12,13]. Osteoporosis is defined by the World Health Organization as BMD falling 2.5 standard deviations (SD) below the mean BMD for the same sex young healthy adults, whereas scores between -2.5 and -1 SD are defined as osteopenia. Osteoporosis occurs most frequently in postmenopausal women. Genetic factors, nutritional factors including vitamin D and calcium intake, hormonal status, and sedentary lifestyle cooperatively influence bone mass[12]. Additional factors involve alcohol consumption, cigarette smoking, and impaired physical activity.

A few mechanisms may be involved in the linkage between psoriasis and osteoporosis. The same inflammatory cytokines, including IFN-gamma, IL-6, and TNF-alpha, have crucial role in the pathogenesis of both osteoporosis and psoriasis[14-18]. Other possible mechanisms include the use of anti-psoriatic medications (methotrexate, cyclosporine) and prolonged immobilization.

The issue of bone loss in patients with psoriasis and PsA is still unresolved. Based on the existing facts, the risk of osteoporosis is lower in PsA than in rheumatoid arthritis. In PsA, both osteoclasts and osteoblasts are activated by the inflammatory process, which results in signs of both bone destruction and new bone formation[19]. In rheumatoid arthritis, osteoclast activation is dominating and generalized bone loss is well established[20,21]. The prevalence of low BMD in PsA is dependent on patient selection. A systematic review emphasizes that age, female sex, postmenopausal status, presence of erosions, PsA duration, and cumulative steroid dose were all determinants related to lower BMD[22].

Some data propose that low BMD is not a substantial clinical question in patients with PsA in the biological treatment era[21]. TNF-alpha inhibitors have been shown to increase BMD in lumbar spine and hip in patients with rheumatoid arthritis[23]. There are only few data on the prevalence of osteoporosis in Croatian population. According to the study by Cvijetić *et al.*, the prevalence of osteoporosis in healthy people aged 20 to 79 years is 6% in women and 4% in men[24].

The purpose of this study was to detect the possible differences in BMD and other parameters of bone metabolism between psoriatic patients with concomitant PsA and those without PsA, as well as to correlate inflammatory markers and psoriatic disease severity to BMD.

Patients and Methods

A consecutive series of patients treated for psoriasis at the Department of Dermatology and Venereology, Osijek University Hospital Center during a 2-year period (February 2018 to February 2019) were considered for the study. Inclusion criteria were patients with clinically and histologically confirmed psoriasis with or without PsA, patients between 18 and 65 years of age, and patients who agreed to participate in the study. Patients younger than 18 or older than 65 years of age, patients without histologically confirmed psoriasis, and patients who declined participation were excluded.

Based on the presence or absence of clinically evident PsA, as assessed by a rheumatologist, patients were divided into 2 groups. Experimental group (PsA) consisted of patients with PsA, whereas patients with psoriasis but without PsA were included as a control group (*psoriasis vulgaris*, PV). Data on patient local and systemic therapy were recorded.

Psoriasis severity was assessed using the Psoriasis Area and Severity Index (PASI) score[25], and patient quality of life by the Dermatological Quality of Life Index (DLQI) score[26]. BMD was assessed in both groups using dual-energy x-ray absorptiometry (DEXA) (Lunar Prodigy Primo, GE Medical Systems, GE Healthcare, Chicago, IL, USA). Two areas of interest were defined for measurements: lumbar spine (first to fourth lumbar vertebra) and proximal femur. BMD was expressed in g/cm^2 for defined area. T-score was calculated for individual patients and measurement sites. T-score is the number of SD away from the average value for young individual. Patient BMD was semi quantitatively described as normal,

osteopenia (-1 to -2.5 SD) or osteoporosis (more than -2.5 SD) for both sites measured.

Laboratory workup included inflammatory markers and biochemical parameters of bone metabolism. Erythrocyte sedimentation rate (ESR) was assessed using modified Westergreen method, as *per* International Council for Standardization in Hematology (ICSH)[27], and C-reactive protein (CRP) level was measured using immunoturbidimetric method with latex on an Olympus AU680 analyzer (Olympus Corp., Tokyo, Japan) with reagents from Beckman Coulter (Beckman Coulter Inc., Brea, CA, USA). Vitamin D levels were measured using the liquid chromatography-mass spectrometry method on a Shimadzu LCMS-8040 chromatograph (Shimadzu Corp., Kyoto, Japan) with reagents from Recipe Chemicals + Instruments (Recipe Chemicals + Instruments GmbH, Munich, Germany). Serum calcium (Ca) was measured using photometric analysis with arsenazo III chromogen, and serum phosphorus (P) using photometric analysis with ammonium-molybdate, both on an Olympus AU680 analyzer (Olympus Corp., Tokyo, Japan) with reagents from Beckman Coulter (Beckman Coulter Inc., Brea, CA, USA). Serum levels of parathyroid hormone (PTH) were assessed using chemiluminiscence immunoassay (CLIA) on a Beckman Coulter DxI600 (Beckman Coulter Inc., Brea, CA, USA) using reagents from the same company. Serum levels of alkaline phosphatase (ALP) were measured by photometric analysis as *per* the International Federation of Clinical Chemistry (IFCC) method at 37 °C[28] on an Olympus AU680 analyzer (Olympus Corp., Tokyo, Japan) with reagents from Beckman Coulter (Beckman Coulter Inc., Brea, CA, USA).

Based on vitamin D levels, patients were subdivided in 3 subgroups: patients with vitamin D deficiency (<20 ng/mL), vitamin D insufficiency (21-29 ng/mL) and normal vitamin D levels (>30 ng/mL)[29].

Difference in gender distribution, duration of symptoms, disease severity and quality of life was compared between the experimental and control group. Furthermore, difference between inflammatory markers and biochemical parameters of bone metabolism was evaluated. BMD was compared between the groups for both sites measured and for both scores in relation to reference groups.

SPSS software, version 20.0 (SPSS Inc., Chicago, IL, USA) was used on statistical analysis. The χ^2-test was used for categorical data. Difference between two independent samples with normal distribution was tested using Student's t-test. Mann-Whitney U-test was used to test differences between two independent samples not following normal distribution. Pearson correlation coefficient was used to test the relationship between variables.

This research was conducted in accordance with Helsinki Declaration of 1975 (revised in 1983) and was approved by the Osijek University Hospital Center and Josip Juraj Strossmayer University of Osijek Faculty of Medicine Institutional Review Boards.

Results

Thirty-nine patients, 14 female and 25 male, were included in the study. The mean age (±SD) was 48.08 (±12.34) years in male patients and 57.57 (±15.77) years in female patients, yielding a statistically significant difference (Student's t-test, p=0.044). PsA in addition to psoriasis was noted in 19 patients (PsA group) and *psoriasis vulgaris* in 20 patients (PV group). Demographic characteristics of both groups, duration of symptoms, psoriasis severity and quality of life measures are summarized in Table 1.

Table 1. Patient demographic and clinical characteristics

	PsA	PV	p
Sex: Male (n) Female (n)	 10 9	 15 5	0.146
Age (years), mean ± SD	52.21 (±13.45)	50.8 (±15.26)	0.762
Duration of symptoms (months), mean ± SD	217.63 (±153.59)	131.1 (±143.17)	0.044
PASI score, mean ± SD	11.69 (±13.3)	13.59 (±10.92)	0.628
DLQI score, mean ± SD	6.52 (±7.72)	8.3 (±8.07)	0.488

PsA = psoriatic arthritis; PV = psoriasis; PASI = Psoriasis Area and Severity Index; DLQI = Dermatological Quality of Life Index; SD = standard deviation

There was no statistically significant difference in PsA prevalence between male and female patients (χ^2-test, p=0.146). Considering patient age, there was no statistically significant difference between PsA and

PV group (Student's t-test, p=0.762). Patients with PsA had a longer mean duration of the disease in comparison to PV patients (217.63 months *vs*. 131.1 months), and this difference was statistically significant (Mann-Whitney U test, p=0.044). No statistically significant difference was observed in PASI (Student's t-test, p=0.628) or DLQI (Student's t-test, p=0.488) scores between the groups.

Patients in both groups were treated with local therapy, methotrexate, acitretin, TNF-α inhibitors, ustekinumab and secukinumab, according to disease severity. None of the patients was treated with corticosteroids.

Laboratory findings in the experimental and control group are presented in Table 2. There was no statistically significant difference in ESR, CRP, Ca, P, or ALP serum concentration. Serum PTH values were significantly lower in patients with PsA (Student's t-test, p=0.008).

The mean serum vitamin D level was 17.97 ng/mL (SD 7.00) for all patients. No statistically significant difference was observed in vitamin D levels between genders (Student's t-test, p=0.643). There was no statistically significant correlation between patient age and vitamin D level (Pearson correlation, ρ=-0.030, p=0.855).

Table 2. Differences in laboratory findings

	PsA (Mean ± SD)	PV (Mean ± SD)	p
ESR (mm/3.6 ks)	17.21 (±16.24)	13.55 (±11.77)	0.424
CRP (mg/L)	6.66 (±7.66)	4.01 (±3.88)	0.178
Vitamin D (ng/mL)	20.04 (±7.66)	16.02 (±5.85)	0.073
Ca (mmol/L)	2.38 (±0.09)	2.35 (±0.18)	0.325
P (mmol/L)	1.01 (±0.16)	0.97 (±0.18)	0.542
PTH (ng/L)	41.31 (±15.61)	57.65 (±20.52)	0.008
ALP (U/L)	78.47 (±28.60)	88.7 (±33.22)	0.311

PsA = psoriatic arthritis; PV = psoriasis; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; Ca = calcium; PTH = parathyroid hormone; ALP = alkaline phosphatase; SD = standard deviation

Vitamin D level was 20.04 ng/mL (SD 7.66) in PsA group and 16.02 ng/mL (SD 5.85) in PV group. This difference was not statistically significant (Student's t-test, p=0.073) (Table 2). Distribution of patients according to vitamin D status subgroups is presented in Table 3.

A statistically significant negative correlation was observed between vitamin D and PTH serum levels in all patients (Pearson correlation, ρ=-0.39, p=0.015) (Fig. 1).

Table 3. Patient distribution according to vitamin D levels

	PsA	PV	n
Deficiency	0	4	4
Insufficiency	16	16	32
Normal	3	0	3
N	19	20	39

PsA = psoriatic arthritis; PV = psoriasis

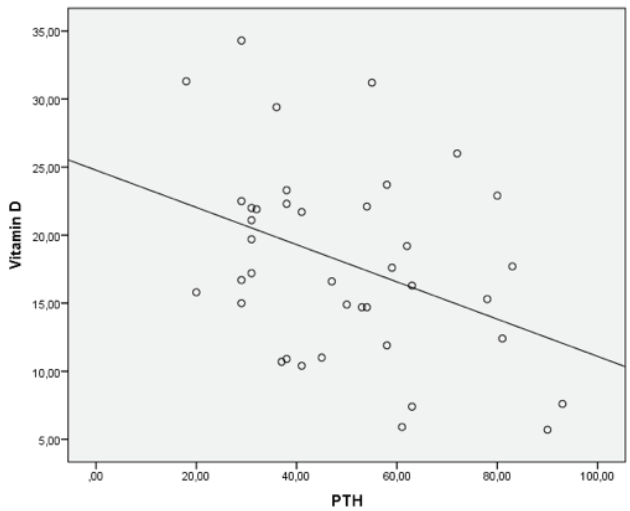

Fig. 1. Correlation between serum parathyroid hormone (PTH) and vitamin D levels.

No correlation was established between vitamin D levels and PASI score (Pearson correlation, ρ=0.015, p=0.926).

In all patients, the mean lumbar BMD was 1.0606 g/cm^2 (SD 0.0268) and mean hip BMD 1.0010 g/cm^2 SD (0.0272). There was a statistically significant difference in hip BMD between male and female patients (Student's t-test, p=0.044).

No correlation was observed between serum vitamin D levels and lumbar BMD (Pearson correlation, ρ=-0.164, p=0.320) or hip BMD (Pearson correlation, ρ=-0.068, p=0.680). No correlation was observed between serum PTH levels and lumbar BMD (Pearson correlation, ρ=0.023, p=0.891) or hip BMD (Pearson

correlation, ρ=-0.077, p=0.640) either. No correlation was observed between disease duration and lumbar BMD (Pearson correlation, ρ=0.524, p=0.721) or hip BMD (Pearson correlation, ρ=0.125, p=0.424).

In all patients, the mean lumbar BMD T-score was -0.85 (SD 1.27) and mean hip BMD T-score -0.2 (SD 1.06). In PsA group, at the hip measurement site, 14 patients had normal bone mass, 5 had osteopenia, and none had osteoporosis; at lumbar measurement site, 10 patients had normal bone mass, 7 had osteopenia, and 2 had osteoporosis. In PV group, at hip measurement site, 17 patients had normal mineral bone mass, 3 had osteopenia, and none was osteoporotic; at lumbar measurement site, 12 patients had normal bone mass, 6 were osteopenic, and 2 osteoporotic (Table 4).

Table 4. Bone mineral mass in patients with psoriatic arthritis and psoriasis

	Normal	Osteopenia	Osteoporosis
PsA			
Hip	14 (73.7%)	5 (26.3%)	0 (0.0%)
Lumbar	10 (52.6%)	7 (36.8%)	2 (10.6%)
PV			
Hip	17 (85.0%)	3 (15.0%)	0 (0.0%)
Lumbar	12 (60.0%)	6 (30.0%)	2 (10.0%)

PsA = psoriatic arthritis; PV = psoriasis

The mean lumbar BMD T-score in PsA patients was -1.03 (SD 1.25), i.e., within the osteopenic range, and in patients with PV it was -0.67 (SD 1.3), i.e., within the normal limits (Fig. 2). The mean hip BMD T-score in PsA patients was -0.95 (SD 1.2), i.e., within the normal range, and in patients with PV it was -0.3 (SD 0.92), also within the normal limits (Fig. 3).

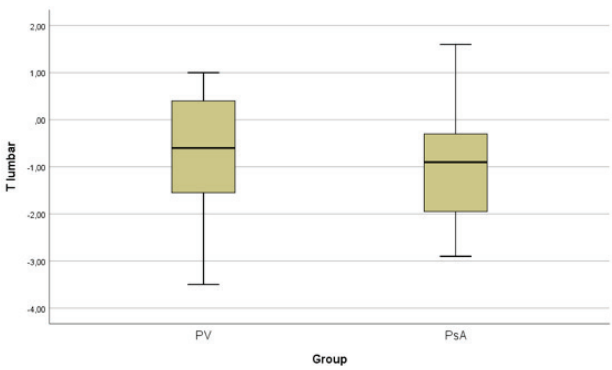

Fig. 2. Lumbar bone mass density in patients with psoriatic arthritis (PsA) and psoriasis (PV).

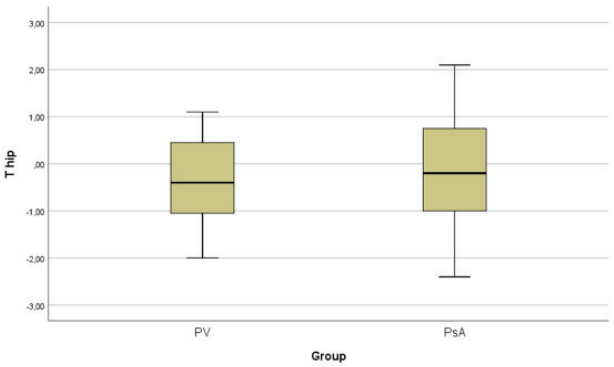

Fig. 3. Hip bone mass density in patients with psoriatic arthritis (PsA) and psoriasis (PV).

Discussion

Limited and conflicting data are available on BMD and vitamin D status in patients with psoriasis and PsA. To our knowledge, our research was the first to explore vitamin D status and BMD together with clinical data and laboratory parameters of inflammation and bone metabolism in Croatian patients with psoriasis and PsA.

In the pathogenesis of psoriasis, non-specific autoinflammation and antigen-specific autoimmunity coexist[30]. Vitamin D exhibits immunomodulatory activity by increasing the innate immune system and modulating the adaptive immune system[31]. Immune-mediated diseases such as rheumatoid arthritis, chronic inflammatory bowel disease, systemic lupus erythematous, multiple sclerosis, and type 1 diabetes are associated with decreased vitamin D serum levels[32-35].

The relation between psoriasis and vitamin D is widely known, yet still controversial[31,36-39]. A meta-analysis has revealed that vitamin D levels are lower in psoriatic patients, and that a small but statistically significant negative correlation exists between 25-hydroxyvitamin D levels and psoriasis severity[31]. Vitamin D insufficiency has been reported to cause an increase in serum PTH levels, leading to increased bone turnover and bone loss that result in an increased risk of osteoporosis[40,41].

Our study confirmed inadequate vitamin D status in our population. We found only 3 patients with adequate vitamin D levels. According to Laktasic-Zerjavic *et al.*, 92.5% of postmenopausal women have inadequate vitamin D status. In their study, vitamin D status was negatively related to age due to a reduced capacity of older skin to synthesize vitamin D. They also found

significant seasonal variations among summer, winter and spring[42].

We did not find a significant difference in vitamin D status between patients with and without PsA. There are few reasons for poor vitamin D status in our sample, which are independent of inflammatory disease. Croatia is located above 35° northern latitude, which effectively stops production of vitamin D from March to October, sedentary lifestyle prevails, dietary intake of vitamin D-rich food is very low, and processed food is not fortified with vitamin D.

In our sample, patients with PsA had a significantly longer duration of symptoms in comparison to psoriatic patients. One can hypothesize that following inflammatory autoimmune process, a longer time frame is required for arthritic symptoms to develop.

In our study, we confirmed negative correlation between vitamin D and PTH serum levels in all patients. Patients with PsA had significantly lower PTH when compared to patients with psoriasis. A negative correlation between PTH and 25-hydroxyvitamin D has already been noted[43-47].

Our study showed suppression of PTH at 25-hydroxyvitamin D serum levels around 25 ng/mL, with negative correlation between serum concentrations of PTH and 25-hydroxyvitamin D at 25-hydroxyvitamin D serum level below 30 ng/mL. There was no association between 25-hydroxyvitamin D and BMD at the hip and lumbar measurement sites.

Patients with PsA had worse BMD in axial skeleton (lumbar measurement site) than patients with psoriasis, and there was no difference in appendicular skeleton mineral bone mass. We found that women had significantly lower BMD at hip site, as one would expect.

In a similar but uncontrolled study, the prevalence of osteoporosis was higher among patients with PsA and BMD was associated with the duration of psoriatic disease[48]. Another cross-sectional uncontrolled study in 72 patients showed an extremely high prevalence of inadequate vitamin D status and negative correlation between 25-hydroxyvitamin D and the severity of skin disease. The lack of correlation between BMD values and 25-hydroxyvitamin D levels was explained with the high proportion of overweight patients. The authors found that BMD was more decreased in patients with PsA than in patients with skin involvement only[49].

A study in 35 postmenopausal women from Sweden showed higher BMD at the hip and lumbar spine than in age-matched controls. They explained these findings with previous UVB treatment, higher body weight, and physical activity[50]. In a Croatian study including 69 patients with established PsA, the authors found a low prevalence of osteoporosis. They report no significant correlation of any measure of disease activity with BMD[51].

We also identified studies in which the association between psoriasis and osteoporosis was assessed between genders. A control-matched study in 43 psoriasis patients showed lower BMD density and lower vitamin D levels in female patients with psoriasis compared to controls[52]. Another population-based case-control study demonstrated higher prevalence of osteoporosis among male patients with psoriasis. The authors have explained their findings by the fact that osteoporosis in women is usually a result of estrogen deficiency and postmenopausal women are generally at a higher risk of osteoporosis. In males, osteoporosis is more commonly a result of a systemic disease such as psoriasis in this particular case[53]. A similar result was demonstrated in a cross-sectional study in 64 psoriasis patients, where males had significantly decreased bone density, but the prevalence of osteoporosis was compared with healthy population[54].

To our knowledge, there are also few studies showing no association of PsA or psoriasis with BMD[55,56]. Observations of lower BMD in lumbar spine from our study support the data reported by Anandarajah *et al.*[57].

A prospective observational control-matched study investigated bone microstructure and volumetric BMD (vBMD) in patients with psoriasis and PsA[58]. They found significantly decreased trabecular BMD and trabecular number in patients with PsA. These findings were associated with the duration of skin disease in patients with PsA. No significant changes were found regarding cortical BMD and microstructure in PsA patients[58]. The fact that trabecular bone predominates in lumbar spine while femoral neck is mainly composed of cortical bone supports our findings. The association of trabecular bone loss with the duration of skin disease suggests that long-term exposure of bone to psoriatic skin inflammation may induce bone damage.

In our study, we found decreased BMD in patients with PsA at the lumbar site. The prevalence of inadequate vitamin D status was high among our patients, without correlation with BMD values, psoriasis severity or laboratory parameters of inflammation.

A major drawback of this study stems from the limited number of patients included. Obviously, prospective research on a larger sample is required to confirm our results. Another important limitation of this study was the lack of age- and gender-matched healthy controls.

In conclusion, while we found that patients with PsA had lower BMD of axial skeleton, and that patients with psoriasis were deficient in vitamin D in general, the connection among psoriasis, PsA and BMD remains vague. Currently, there are no recommendations for osteoporosis screening in psoriatic patients.

Acknowledgment

The authors would like to express their gratitude to Vatroslav Šerić, MD, PhD, Department of Laboratory Diagnostics, and Darija Šnajder, MD, PhD, Department of Nuclear Medicine and Radiation Safety, Osijek University Hospital Center, Osijek, Croatia, for their assistance with the research.

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Sažetak

MINERALNA KOŠTANA GUSTOĆA I RAZINE VITAMINA D U BOLESNIKA S PSORIJATIČNIM ARTRITISOM

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Cilj ovoga istraživanja bio je ispitati moguće različitosti u mineralnoj koštanoj masi između bolesnika s psorijatičnim artritisom (PsA) i psorijazom. U analizu je bio uključen usporediv uzorak obiju skupina bolesnika. U svih ispitanika određena je serumska koncentracija vitamina D, upalni parametri i paratireoidni hormon (PTH). Denzitometrijom je utvrđena mineralna koštana masa aksijalnoga skeleta i apendikularnoga skeleta. Bolesnici s PsA imali su sniženu mineralnu koštanu masu aksijalnoga skeleta, dok je mineralna koštana masa apendikularnoga skeleta bila usporediva između ovih skupina. Nije pronađena statistički značajna korelacija upalnih parametara, serumske koncentracije vitamina D i PTH s mineralnom koštanom gustoćom ni u jednoj skupini bolesnika. Zabilježena je negativna korelacija između serumske koncentracije vitamina D i PTH.

Ključne riječi: *Psorijaza; Psorijatični artritis; Mineralna koštana gustoća; Vitamin D*