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CORRESPONDENCE OF VITAMIN D STATUS WITH FUNCTIONAL SCORES AND DISEASE ACTIVITY AMONG CROATIAN PATIENTS WITH ANKYLOSING SPONDYLITIS: A PRELIMINARY STUDY

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SUMMARY

Background: *Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disease which primarily affects the axial spine and sacroiliac joints. Over the past several years Vitamin D has been recognized as a hormone with significant immunomodulatory effect due to the fact that it inhibits T-cell proliferation and decreases the production of interleukin-2, interferon-γ, and tumor necrosis factor-α. Therefore, vitamin D may play a role in the development and progression of inflammatory diseases. Our aim was to estimate and evaluate the correspondence of vitamin D status with functional scores, spinal mobility and disease activity among patients with AS in Croatia.*

Subjects and methods: *One hundred and fifty (150) AS patients were prospectively enrolled and assessed for disease activity, spinal mobility and functional disability. Blood samples were obtained from all patients and 25(OH)D concentration and inflammatory markers were determined. All patients underwent bone mineral density measurement at the lumbar spine (L1-L4) and proximal femur (total hip and femoral neck) with dual-energy x-ray absorptiometry.*

Results: *The prevalence of 25(OH)D inadequacy considering cut-offs of 75, 50 and 30 nmol/L was 80, 46.7 and 16.7% respectively. The mean 25(OH)D serum concentration was 52.63±23.45 nmol/L. There was no significant difference in mean 25(OH)D concentration regarding patient's age, sex, smoking status, season change, disease activity, spinal mobility or functional scores. However, there was a trend towards lower 25(OH)D concentration in patients with higher disease activity, worse spinal mobility and worse functional scores.*

Conclusion: *Our results showed that there is no significant association between serum 25(OH)D concentration and activity of AS. Given that significant proportion of our patients had inadequate vitamin D status, the role of vitamin D in pathophysiology of AS still remains to be elucidated.*

Key words: *ankylosing spondylitis - vitamin D - osteoporosis*

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INTRODUCTION

Spondyloarthropathies (SpA) are a group of overlapping chronic inflammatory rheumatic diseases with common clinical characteristics that primarily include ankylosing spondylitis (AS), psoriatic arthritis, reactive arthritis and arthritis related to inflammatory bowel diseases (Dougados & Baeten 2011). The international group of experts Assessment of Spondyloarthritis International Society (ASAS) have developed new classifycation criteria for SpA in 2009 on the basis of two main clinical features: axial, with dominant involvement of sacroiliac joints and/or spine and peripheral, with dominant peripheral manifestations, such as arthritis, enthesitis, or dactylitis (Khan 2002, Dougados & Baeten 2011). AS primarily affects the axial spine and sacroiliac joints and one of the most important features is new bone formation, which leads to the development of syndesmophytes and ankylosis of the spine. As a result, pain, spinal deformity, fractures and disability may occur (Dougados & Baeten 2011). The pathological process in AS encompasses inflammation and ossification with accelerated bone loss (Lange et al. 2005). Osteopenia and osteoporosis are well known complications of AS and both substantially increase the risk of spinal fractures (Ghozlani et al. 2009, Vosse et al. 2009). In the last two decades much has been investigated about the association of vitamin D insufficiency and autoimmune diseases (Ponsonby et al. 2002, Zhao et al. 2014). Furthermore, some studies have demonstrated an increased prevalence of some rheumatic diseases in populations with increasing latitudes, with the most plausible explanation lying in the fact that reduced exposure to sunlight causes vitamin D insufficiency, which can consequently have effect on disease progression (Mathieu et al. 2009). Vitamin D generated in the skin during sun exposure to solar ultraviolet B (UVB) radiation from 7-dehydrocholesterol, or ingested in the diet, is transmitted to the liver over the circulation bound to the 'vitamin D–binding protein'. 25-hydroxyvitamin D (25OHD), a biologically inactive form of vitamin D used to determine the status

of vitamin D in humans, is metabolized in the liver, where vitamin D is converted to 25OHD by vitamin D-25-hydroxylase. The biologically active form of vitamin D, 1,25-dihydroxyvitamin D (1,25D), is produced in the kidneys with the help of 25-hydroxyvitamin D-1α hydroxylase (Holick 2007). 1,25D metabolite of vitamin D is difficult to study due to the fact that it has a much shorter half-life than 25OHD. On the other hand, 25OHD concentrations vary during the slightest sun exposure. Vitamin D deficiency is defined as a 25OHD level of less than 50 nmol/L (20 ng/ml) (Bischoff-Ferrari et al. 2006, Holick 2007). Vitamin D is widely recognized as a hormone that plays an important role in calcium and phosphorus homeostasis, but in recent time an emphasis has also been put onto its immunomodulatory effect (Patel et al. 2007). It has been acknowledged that vitamin D has a role in both the adaptive and innate immune systems (Hewison 2012, Zhao et al. 2014). According to Lemire, in vitro data studies have shown that vitamin D inhibits T-cell proliferation and decreases the production of interleukin-2 (IL-2), interferon-γ (IFN-γ), and tumor necrosis factor-α (TNF-α) (Lemire 1992). Therefore, vitamin D may play a role in the development and progression of inflammatory diseases, which is why is important to understand whether 25OHD deficiency represents a risk factor in AS, as adequate supplementation may be beneficial.

The aim of this study was to determine and evaluate the correspondence of vitamin D status with functional scores and disease activity among patients with AS in Croatia.

SUBJECTS AND METHODS

This cross-sectional study was conducted from June 2015 to April 2016 at the Clinic for Rheumatic Diseases and Rehabilitation at the University Hospital Centre Zagreb, Zagreb, Croatia. Patients diagnosed with AS according to ASAS 2009 criteria were prospectively enrolled and assessed for disease activity and functional disability. Each patient signed informed consent and the study has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

A total of 150 patients were included in the study, out of which 105 (70%) were male and 45 (30%) female, the age median was 46 years (range 23-74 years). Table 1 contains characteristics of the patients. Disease duration median was 6 years (range 2-9 years). The subjects did not differ significantly in age distribution (p=0.765). A Total of 143 (95.3%) patients were eligible for bone densitometry screening. Lumbar spine osteoporosis was revealed in 11 (7.7%) patients and hip osteoporosis in 4 (2.8%) patients, out of which 1 patient had both lumbar spine and hip osteoporosis.

Table 1. Clinical and demographic characteristics of Croatian patients with ankylosing spondylitis

Patient characteristics	Number of patients
Sex	
male	105 (70%)
female	45 (30%)
Employment	
employed	72 (48%)
unemployed	19 (12.7%)
student	3 (2%)
housewife	3 (2%)
retired	53 (35.3%)
Physical activity (IPAQ)[1]	
low activity level	45 (30%)
moderate activity level	63 (42%)
high activity level	42 (28%)
Current smoker	58 (38.9%)
25(OH)D concentration (nmol/L)	
<75	120 (80%)
<50	70 (46.7%)
<30	25 (16.7%)
*Bone densitometry	*143 (95.3%)
L1-L4	
normal BMD (T-score ≤1 SD)	83 (58%)
osteopenia (T-score between -1 and -2.5 SD)	49 (34.3%)
osteoporosis (T-score ≥ -2.5 SD)	11 (7.7%)
Total Hip	
normal BMD (T-score ≤1 SD)	86 (60.1%)
osteopenia (T-score between -1 and -2.5 SD)	53 (37.1%)
osteoporosis (T-score ≥-2.5 SD)	4 (2.8%)
HAQ[2] (0-3)	
mild disability (<1)	79 (52.7%)
moderate disability (between 1 and 2)	65 (43.3%)
severe disability (≥2)	6 (4%)
Active disease (BASDAI[3] ≥4)	94 (62.7%)
Extraskeletal manifestations	
iridocyclitis	7 (4.7%)
bowel disease	10 (6.7%)
coxitis	15 (10%)
peripheral arthritis	39 (26%)
Synthetic DMARD[4]	
sulfasalazine	40 (26.7%)
methotrexate	11 (7.3%)
leflunomide	2 (1.3%)
Biologic DMARD	
infliximab	1 (0.7%)
adalimumab	7 (4.7%)
golimumab	9 (6%)
etanercept	14 (9.3%)
Glucocorticoids	15 (10%)

[1]IPAQ - international physical activity questionnaires; [2]HAQ - health assessment questionnaire; [3]BASDAI - Bath Ankylosing Spondylitis Disease Activity Index; [4]DMARD-disease modifying anti-rheumatic drug; *patients eligible for bone densitometry screening

All patients completed specific questionnaires regarding disease activity, functional status and spinal mobility. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used for patient reported disease activity and included patient reported levels of back pain, fatigue, peripheral joint pain and swelling, localized tenderness and the duration and severity of morning stiffness. The BASDAI score ranges from 0 (no disease activity) to 10 (maximal disease activity), with a cut-off of 4 indicating active disease (Zochling 2011). The Bath Ankylosing Spondylitis Functional Activity Index (BASFI) was used to define patient's physical functioning concerning bending, reaching, changing position, standing, turning, climbing steps and patient's ability to cope with everyday life. The BASFI score ranges from 0 (no functional impairment) to 10 (maximal impairment) (Zochling 2011). The Bath Ankylosing Spondylitis Measurement Index (BASMI) was used to quantify the mobility of the patient's axial skeleton and included clinical measures of cervical rotation, tragus to wall distance, lumbar flexion, lumbar side flexion and intermalleolar distance. The BASMI score ranges from 0 to 10, with higher score indicating more severe impairment of spinal mobility (Zochling 2011). Visual analogue scale (VAS) was used for measurement of patient's and doctor's perception of disease activity. VAS was presented as a straight, 100 mm horizontal line, with the left end marked as "no disease activity" and the higher score indicated higher disease activity. Health Assessment Questionnaire (HAQ) was used to assess the functional ability of patients, where HAQ score 0 was considered as mild, score 1 as moderate and score 2 as severe disabilities (Kirwan & Reeback 1986). Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire was used to assess patient's fatigue, with higher score indicating better quality of life (Cella et al. 2005, Singh et al. 2014). The International Physical Activity Questionnaire (IPAQ) short form was used to obtain comparable estimates of patient's physical activity through four main domains, including leisure time physical activity, domestic and gardening activity, work-related physical activity and transport-related physical activity. Subsequently patients were scored as having low, moderate or high level of physical activity (Craig et al. 2003). Data about current employment status, smoking habits, current treatment and extra skeletal manifestations of AS were collected.

Blood samples were obtained from all patients and enzyme-linked immunosorbent assay (ELISA) was used for assessment of 25(OH)D concentration. The concentration of 25(OH)D of ≥ 75 nmol/L was considered as adequate, <75 nmol/L as insufficiency, <50 nmol/L as deficiency and <30 nmol/L as extreme deficiency (Vranešić Bender et al. 2016). Inflammation markers including erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were also measured. All patients underwent bone mineral density (BMD) measurement at the lumbar spine (L1-L4) and proximal femur (total hip and femoral neck) with dual-energy x-ray absorptiometry (DXA) using a Delphi W (S/N 700483) instrument (Hologic Inc., Wlatham, MA, USA). The T-score describes the number of standard deviations (SD) by which the BMD of an individual differs from the expected mean value in young healthy individuals. Osteoporosis was defined as a value of BMD that is 2.5 SD or more below the young female adult mean value (T-score ≥ -2.5 SD) and osteopenia as a T-score that lies between -1 and -2.5 SD (Kanis et al. 2008, Kanis et al. 2019a,b).

Statistical analysis

Statistical analyses were performed using the Statistical Package for Social Sciences (SPSS) version 20. Descriptive statistics were used to describe continuous and categorical variables. Kolmogorov-Smirnoff test was run to determine the normal distribution of the data. Medians and ranges, or means and SD were determined where applicable and relative frequencies were computed for all variables. Independent samples t test or ANOVA was run for the analysis of the numerical values in two, or three or more investigated groups. Tukey's post hoc test was used for the analysis of variance when more than two groups were analysed. Chi square test was done for comparing three or more independent groups. The correlations were calculated using the Spearman's test. A value of $p<0.05$ was deemed statistically significant.

RESULTS

The median scores for inflammatory markers, disease activity, functional status, spinal mobility indices and BMD scores are shown in Table 2.

Table 2. Median values of inflammatory markers, disease activity, functional status, spinal mobility indices and bone mineral density scores in Croatian patients with ankylosing spondylitis

Parameters	Median	Range
ESR (mm/h)	15	2-105
CRP (mg/L)	4.10	0.10-78.20
BASFI[1]	3.98	0-9.40
BASDAI[2]	4.89	0-9.50
Disease activity (VAS[3]) doctor	55	0-100
Disease activity (VAS) patient	55	0-100
Schober index (cm)	3	0.50-6.50
Respiration index (cm)	3	0-7
BMD[4] lumbar spine (g/cm^2)	1.13	0.68-1.71
BMD total hip (g/cm^2)	0.93	0.51–1.56

[1]BASFI - Bath Ankylosing Spondylitis Functional Activity Index; [2]BASDAI - Bath Ankylosing Spondylitis Disease Activity Index; [3]VAS - visual analogue scale; [4]BMD - bone mineral density

Table 3. Mean 25(OH)D concentrations and differences between groups according to sex, seasonal change, functional and disease activity scores and smoking status

Parameters	Mean 25(OH)D3 concentration (nmol/L)	± SD	p-value
Sex			
male	53.51	22.13	0.485
female	50.57	26.42	
Season			
winter	48.42	26.03	0.178
spring	50.66	22.00	
summer	60.53	23.22	
autumn	56.13	20.38	
HAQ[1] (0-3)			
mild (≤1)	49.90	21.00	0.305
moderate (between 1 and 2)	55.96	26.21	
severe (≥ 2)	52.33	21.23	
Smoking			
yes	52.52	21.71	0.948
no	52.78	26.33	
BASDAI[2] (0-10)			
inactive or mild disease (<4)	54.36	22.77	0.486
active disease (≥4)	51.59	23.90	

[1]HAQ-health assessment questionnaire; [2]BASDAI-Bath Ankylosing Spondylitis Disease Activity Index

Table 4. 25(OH)D correlation with clinical, demographic and laboratory parameters in Croatian patients with ankylosing spondylitis

Parameters	25(OH)D concentration	
	r	P value
Age (years)	-0.52	0.525
Disease duration (years)	-0.07	0.932
BMI[1] (kg/m2)	-0.35	0.675
ESR (mm/h)	-0.65	0.434
CRP (mg/L)	0.043	0.601
FACIT[2]	0.059	0.475
BASFI[3]	-0.040	0.629
BASDAI[4]	-0.066	0.420
BASMI[5]	-0.052	0.527
Disease activity (VAS[6]) patient	-0.120	0.144
Disease activity (VAS) doctor	-0.152	0.064

[1]BMI - body mass index; [2]FACIT - F-Functional Assessment Chronic Illness Therapy-Fatigue; [3]BASFI - Bath Ankylosing Spondylitis Functional Activity Index; [4]BASDAI-Bath Ankylosing Spondylitis Disease Activity Index; [5]BASMI-Bath Ankylosing Spondylitis Metrology Index; [6]VAS-visual analogue scale

25(OH)D serum concentration and relationship with clinical, demographic, functional and clinical activity scores

The prevalence of 25(OH)D inadequacy considering cut-offs of 75, 50 and 30 nmol/L was 80, 46.7 and 16.7% respectively. 25(OH)D serum concentration was normally distributed throughout the sample with a mean value of 52.63±23.45 nmol/L. There was no significant difference in mean 25(OH)D concentrations regarding sex, smoking status, HAQ and BASDAI scores. Although there was no significant difference in mean 25(OH)D concentrations regarding season change (p=0.178) the highest mean 25(OH)D concentration was recorded in the summer (60.53±23.22 nmol/L) and the lowest in the winter (48.42±26.03 nmol/L). Results are presented in Table 3.

There was no significant correlation regarding 25(OH)D concentration and patient's age, but the correlation coefficient was negative implying higher concentration of 25(OH)D in younger patients. The same was observed in patients with longer disease duration, lower BMI and lower ESR. Also, there was a trend towards lower 25(OH)D concentration in patients with higher disease activity according to BASDAI scores and patient's and doctor's VAS disease activity assessment, as well as in patients with more severe functional impairment and spinal mobility impairment according to BASFI and BASMI scores. The correlation coefficients are presented in Table 4.

Relationship between patient's age, functional and disease activity scores

Patient's age had significant negative correlation with FACIT-F score (r=-0.253, p=0.002) and significant positive correlation with BASFI, BASDAI, BASMI, patient and doctor VAS disease activity scores (r=0.451, p=0.000, r=0.377, p=0.000, r=0.465, p=0.000, r=0.273, p=0.001, r=0.248, p=0.002 respectively). This indicates that older patients experienced more fatigue, had higher disease activity and more impaired functional status and spinal mobility. FACIT-F score had significant negative

correlations with BASFI, BASDAI, BASMI, patient and doctor VAS disease activity scores (r=-0.552, r=-0.532, r=-0.228, r=-0.445, r=-0.396 respectively, with all p-values of 0.000). This indicates that patients with higher disease activity and more impaired functional status and spinal mobility experienced more fatigue in everyday life.

DISCUSSION

Since the discovery of vitamin D immunomodulatory functions, it's potential role on the pathophysiological mechanisms in inflammatory rheumatic diseases has become a field of great interest (Mermerci Baskan et al. 2010, Erten et al. 2013, Zhao et al. 2017). It is presumed that 25(OH)D concentration is lower in inflammatory diseases because it is known that vitamin D decreases the production of proinflammatory cytokines by inhibiting T helper-1 and T helper-17 cell activity (Cantorna et al. 2015, Zhao et al. 2017). Our study showed inadequate concentration of 25(OH)D in 120 (80%) patients with AS, which is similar to other studies (Lange et al. 2005, Mermerci Baskan et al. 2010, Erten et al. 2013, Zhao et al. 2017). Importantly, none of our patients previously received vitamin D supplementation. We found no significant difference in mean 25(OH)D concentration and disease activity according to BASDAI score, but there was a trend towards lower 25(OH)D concentration in patients with higher BASDAI scores (Table 3 and 4). Also, there was a trend towards lower 25(OH)D concentration in patients with more severe functional impairment and spinal mobility impairment according to BASFI and BASMI scores, as well as in patient's and doctor's higher VAS disease activity assessment scores (Table 4).

So far, conflicting data have been published regarding the relation between vitamin D levels and disease activity in AS. In systematic review of association between 25(OH)D concentration and susceptibility and disease activity of AS, Zhao et al. have shown that 25(OH)D concentration is lower in AS patients than in healthy controls and that 25(OH)D concentration is inversely correlated with markers of AS disease activity (Zhao et al. 2014). In a study by Mermerci Baskan et al. 25(OH)D level was found to be significantly lower in AS patients than in healthy controls (Mermerci Baskan et al. 2010). Bekir et al. found in their cross-sectional study that the 25(OH)D levels were lower (26.78 ng/ml on average) in patients with AS than in healthy controls, although this difference was insignificant (Bekir et al. 2012). However, a significant difference between the normal and deficient subgroups were found when they evaluated the functional status, quality of life, and fatigue in AS with BASFI, ASQoL and MAF scales. This implied a conclusion that the severity of the inflammatory process may increase with the lack of vitamin D (Bekir et al. 2012). Arends et. al, similar to our research, found no association between 25(OH)D concentration and BASDAI, BASFI or BASMI scores (Arends et al. 2011). A most recent study by Guta et al. also found no significant connection between 25(OH)D concentration and BASDAI scores (Guła et al. 2018).

We found no significant difference in mean 25(OH)D concentrations regarding sex, smoking status or HAQ. In contrary to our results, several other studies found that 25(OH)D concentration was lower in smokers, which was explained by possible effect of smoking on systemic inflammation (Zhao et al. 2017). Smoking and consequent systemic inflammation may affect vitamin D absorption and metabolism. Most of the studies, as well as ours, did not show a significant difference in 25(OH)D concentration regarding sex. Considering that HAQ questionnaire is mainly developed for evaluating quality of life regarding patients with peripheral arthritis, which is rare but does occur in AS patients, the lack of correlation with the disease activity and 25(OH)D concentration was expected. Although there was no significant difference in mean 25(OH)D concentrations regarding season change, the highest concentration was recorded in the summer (60.53±23.22 nmol/L) and the lowest in the winter (48.42±26.03 nmol/L) (Table 3.) Most of the studies in the past have either neglected seasonal variations or tried to overcome seasonal variation by sampling patients within a short time window (Zhao et al. 2017).

We found inverse, but non-significant correlation between 25(OH)D concentration and patient's age, disease duration, BMI and ESR. This implied higher 25(OH)D concentration in younger patients, patients with shorter disease duration, lower BMI and lower ESR. Arends et al. also found no association between ESR and 25(OH)D concentration, however Erten et al. and Durmus et al. found significant inverse correlations (Arends et al. 2011, Durmus et al. 2012, Erten et al. 2013). In the study by Zhao et al. vitamin D deficient patients had shorter median symptom duration since diagnosis. This was explained by the fact that patients with longer disease duration were significantly more likely to be commenced on vitamin D supplementation (Zhao et al. 2017). As expected, our results showed that older patients experienced more fatigue, had higher disease activity and more impaired functional status and spinal mobility. Also, patients with higher disease activity and more impaired functional status and spinal mobility experienced more fatigue in everyday life.

CONCLUSION

Our results are contrary to data from several studies that reported a significant association between serum 25(OH)D concentration and activity of AS. The role of vitamin D in pathophysiology of AS and other diseases from SpA spectrum is evident, but still not thoroughly

elucidated. Further research, with pertinent follow-up of vitamin D concentration is mandatory in order to clarify the causal relationship of immunomodulatory effect of vitamin D and inflammatory diseases.

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Contribution of individual authors:

Iva Žagar, Valentina Delimar & Stjepan Čota: study design, data collection, first draft, approval of the final version, statistical analysis.

Doroteja Perić: study design, data collection, first draft, approval of the final version.

Nadica Laktašić Žerjavić & Porin Perić: study design, first draft, approval of the final version.

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