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Does vitamin D deficiency contribute to higher disease activity in patients with spondyloarthritis?

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ABSTRACT

Introduction: : This study aimed to compare serum vitamin D levels in Spondyloarthritis (SpA) patients and control group and to evaluate the associations between vitamin D and disease activity in SpA patients.
Methodology: : In this study, 86 SpA patients according to the International Criteria and 117 age and sex-matched healthy controls were included. In patients, clinical examination was performed and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were recorded. Serum $25(OH)D_3$ concentration was measured using ELISA kit.
Results: : Serum $25(OH)D_3$ levels in SpA patients were significantly lower than healthy controls ($p < 0.001$). Vitamin D deficiency and insufficiency frequency in the SpA group was significantly more than control group ($p < 0.001$). No significant difference was observed in the activity of SpA in different serum levels of 25(OH)D. Also, no significant correlations were observed between serum $25(OH)D_3$ with clinical findings as well as with BASDAI and BASFI ($P > 0.05$).
Discussion and conclusion: : Although our study revealed lower serum $25(OH)D_3$ levels in SpA patients compared to healthy controls, there were not any significant correlations between its serum levels with severity of disease. However, correction of vitamin D status may be beneficial in controlling inflammation and disease activity.

1. Introduction

Spondyloarthritis (SpA) is a heterogeneous group of diseases that includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease-associated spondyloarthritis (IBD-SpA), and undifferentiated spondyloarthritis (unSpA). This group of diseases has several manifestations in common such as inflammatory back pain, peripheral arthritis, enthesitis, dactylitis, uveitis, psoriasis, inflammatory bowel disease (IBD) and HLA-B27 positivity [1]. The prevalence of SpA ranges from 0.20% in South-East Asia to 1.61% in Northern Arctic communities [2].

Vitamin D (cholecalciferol) is a steroid hormone produced in the skin under sunlight or gained from the diet. Vitamin D is necessary for intestinal calcium absorption, calcium and phosphorus regulation in the blood and skeletal and dental health [3]. There is a lot of evidence that vitamin D has a significant effect on innate and acquired immunity and its deficiency may lead to susceptibility and more severe disease in inflammatory disorders [4]. Receptors of vitamin D are expressed on the macrophages, lymphocytes, and dendritic cells. In the adaptive immune system, $1,25(OH)_2D_3$ reduces proinflammatory T helper 1 (Th1) and Th17 cell activity and supports Th2 and regulatory T cells that increase immune tolerance [4]. $1,25(OH)_2D_3$ also reduces B cell proliferation and differentiation. Vitamin D is increasingly identified for its important role in the etiology of inflammatory diseases, such as systemic lupus erythematosus (SLE) [5], rheumatoid arthritis (RA) [6], type 1 diabetes mellitus [7], Behcet's disease (BD) [8], oral aphthous ulcer [9] and multiple sclerosis [10]. Although some studies evaluating the vitamin D status of patients with AS [11–13] have shown decreased vitamin D levels in these patients, conflicting results have been demonstrated regarding the link between vitamin D levels and AS [14]. A case-only study did not find significant correlations between serum $25(OH)D_3$ levels and AS activity [11], while there were some case–control studies that obtained inconsistent conclusions [12,15–18]. Therefore, this study designed to compare serum vitamin D levels in SpA patients and control group and to evaluate the associations between vitamin D and disease activity in SpA patients.

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Table 1
Demographic, clinical and laboratory characteristics of studied groups.

Characteristics	SpA patients (n = 86)	Healthy controls (n = 117)	P^*
Age (years)	36.63 ± 11.8	35.81 ± 7.7	0.211
Sex (male/female)	59/27 (2.19)	82/35 (2.34)	0.470
Type of SpA			
Ankylosing spondylitis	65 (75.6)		
Psoriatic arthritis	5 (5.8)		
Enteropathic SpA	2 (2.3)		
Undifferentiated SpA	14 (16.3)		
Disease duration (months)	60 (6-490)		
Clinical findings			
Pelvis pain	37 (43)		
Low back pain	71 (82.6)		
Neck pain	25 (29.1)		
Arthritis	41 (47.7)		
Enthesopathy	29 (33.7)		
Uveitis	9 (10.5)		
Psoriasis	5 (5.8)		
Colitis	4 (4.7)		
HLA-B27	57 (66.3)		
Sacroiliitis in imaging (Radiography or MRI)	75 (87.2)		
Spondylitis in imaging (Radiography or MRI)	52 (60.5)		
ESR	32 ± 20.35		
BASDAI	4.15 ± 1.65		
BASFI	3.01 ± 1.98		

SpA: Spondyloarthritis, ESR: Erythrocyte Sedimentation Rate, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index, BASFI: Bath Ankylosing Spondylitis Functional Index.
Continuous variables were reported as mean ± SD or median (Min–Max) while categorical variables were expressed as frequency (percentage).
$P < 0.05$ was considered significant.
* P values indicate comparison between groups (independent-sample t test or Chi square, as appropriate).

2. Materials and methods

2.1. Study subjects

In this case-control study, 86 patients aged 20–75 years with the diagnosis of SpA, according to the International criteria [19] were recruited consecutively from the outpatient rheumatology clinic of Connective Tissue Diseases Research Center between March 2018 and September 2018. In addition, 117 age- and sex-matched healthy controls without any inflammatory rheumatic disease were included. The exclusion criteria were as follows: impaired renal function, liver disease, thyroid and/or parathyroid disorders, diabetes mellitus, fibromyalgia, any other inflammatory diseases or overlap syndromes, malignancies, taking vitamin D supplements during past 6 months, receiving steroids or anticonvulsants during past 3 months, using sunscreen, and being pregnant. This study was approved by the Ethics Committee of Tabriz University of Medical Sciences and written informed consent in accordance with the Declaration of Helsinki was obtained from all subjects before inclusion in the study.

Table 3
Disease activity and functional disability scores according to the vitamin D levels (n = 86).

	Serum $25(OH)D_3$ (ng/mL)			P^*
	Sufficient	Insufficient	Deficient	
BASDAI	4.07 ± 1.65	4.17 ± 1.77	4.20 ± 1.57	0.969
BASFI	2.37 ± 1.68	3.50 ± 2.30	2.99 ± 1.73	0.191

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index.
Data were reported as mean ± SD.
$P < 0.05$ was considered significant.
* P values indicate comparison between groups (one-way ANOVA).

Table 4
Correlation between vitamin D levels and clinical findings in patients (n = 86).

	Serum $25(OH)D_3$ (ng/mL)	
Clinical findings	r	P^*
Pelvis pain	−0.058	0.623
Low back pain	−0.050	0.672
Neck pain	−0.011	0.927
Arthritis	0.043	0.716
Enthesopathy	0.078	0.525
Uveitis	0.202	0.083
Colitis	−0.144	0.218
Sacroiliitis	0.112	0.369
Spondylitis	−0.087	0.495

*Spearman correlation analysis.
$P <$ 0.05 was considered significant.

2.2. Clinical and biochemical measurements

At baseline, all participants were examined by a rheumatologist and the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were recorded for patients with SpA [20,21].

Five mL of venous blood samples was collected after 12-h overnight fasting. The serum samples were separated from whole blood and were kept at −70 °C until biochemical analysis. Serum $25(OH)D_3$ (IDEAL TASHKHIS kit, Tehran, Iran) was determined by enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's recommendations, using an ELISA plate reader (Model stat fax 2100, Awareness, Ramsey, MN). The specificity of this kit was 1 and functional sensitivity was 1.2 ng/mL. The inter- and intra-assay CV% were 4.18 and 7.34%, respectively. Serum $25(OH)D_3$ levels < 30 and < 10 ng/mL were classified as vitamin D insufficiency and vitamin D deficiency, respectively.

2.3. Statistical analysis

Statistical analysis was performed using SPSS software version 18.0 (SPSS, Inc., USA). Normal distribution of data was verified with the Kolmogorov–Smirnov test. Continuous variables were reported as

Table 2
Vitamin D status in the study groups.

	SpA patients (n = 86)	Healthy controls (n = 117)	P^*
Serum $25(OH)D_3$ (ng/mL)	24.89 ± 12.5	33.65 ± 14.3	< 0.001
Vitamin D sufficient (> 30 ng/mL)	25 (29.1)	67 (57.3)	< 0.001
Vitamin D insufficient (10-30 ng/mL)	30 (34.9)	33 (28.2)	< 0.001
Vitamin D deficient (< 10 ng/mL)	31 (36)	17 (14.5)	< 0.001

Data were expressed as mean ± SD or frequency (percentage).
* P values indicate comparison between groups (independent-sample t test or Chi square, as appropriate).

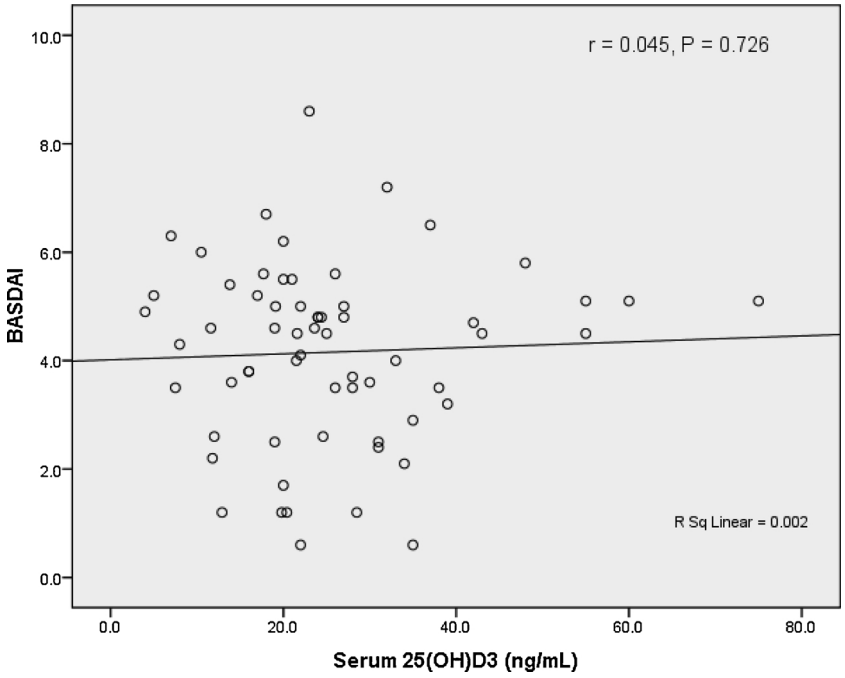

Fig. 1. Correlation between serum 25(OH)D_3 levels and BASDAI in SpA patients (n = 86).

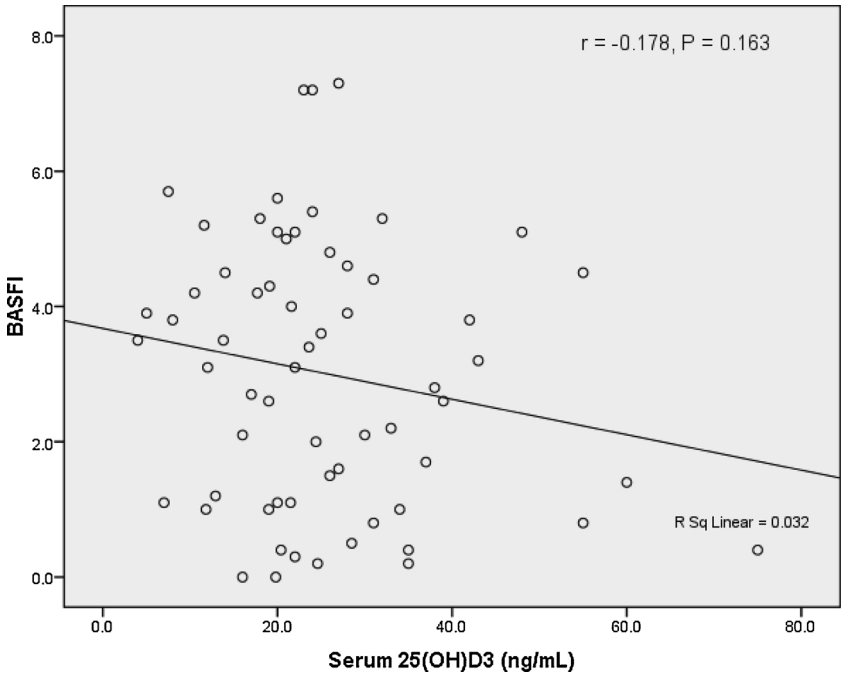

Fig. 2. Correlation between serum 25(OH)D_3 levels and BASFI in SpA patients (n = 86).

means and standard deviations while categorical variables were expressed as frequency and percentage. Comparisons between groups were made by chi-squared test, independent sample *t* test and one-way analysis of variance (ANOVA), as appropriate. *p* value less than 0.05 was considered as statistically significant.

3. Results

In this case control study vitamin D status was evaluated in 86 SpA patients and 117 healthy individuals. Demographic, clinical, laboratory and imaging characteristics of study population are shown in Table 1. No significant differences were observed in the demographic characteristics of case and control groups. As presented in Table 2, serum 25(OH)D_3 levels in SpA patients were significantly lower than healthy controls ($p < 0.001$). Vitamin D deficiency and insufficiency frequency in the SpA group was significantly more than control group (Table 2). No significant difference was observed in the activity of SpA in different serum levels of 25(OH)D_3 (Table 3). According to Table 4, no significant correlations were observed between serum 25(OH)D_3 with clinical findings ($P > 0.05$). In addition, as indicated in Figs. 1 and 2, no significant correlations were observed between serum 25(OH)D_3 with BASDAI and BASFI ($P > 0.05$).

4. Discussion

Vitamin D has known immunomodulatory characteristics. It has been suggested to correlate with disease activity in and affect the susceptibility of many autoimmune conditions including SLE [5], systemic sclerosis [22], BD [10,23] and RA [24]; However, there are conflicting evidence regarding association between serum $1,25(OH)_2D_3$ and SpA susceptibility and severity. Our study showed that serum concentrations of $25(OH)D_3$ were significantly lower in patients with SpA compared to healthy controls. Moreover, there was significant difference in serum $25(OH)D_3$ classification between SpA patients and healthy controls. Consistent with our results, Mermerci et al. [12], Erten et al. [25], and Lange et al. [13] reported decreased levels of vitamin D in AS patients. Our previous study also showed that mean $25(OH)D_3$ level in the BD patients was lower than the control group [8] and insufficiency and deficiency of $25(OH)D_3$ in the BD group was more common than the control group [8]. In another study, we also found that serum $25(OH)D_3$ levels were significantly lower in systemic sclerosis patients compared to healthy controls [26]. In contrast, Yazmalar et al. [27] and Durmus et al. [28] found no significant differences in vitamin D concentrations between AS and control groups.

Based on our study, there were no significant correlations between serum $25(OH)D_3$ levels with disease activity and functional ability in SpA patients. This may be due to confounding factors influencing the BASDAI, such as fibromyalgia, particularly in female patients with chronic rheumatic diseases. In the literature, the results of studies investigating the relationship between vitamin D and disease activity are heterogeneous. Similar to our results, Yazmalar et al. [27] found no association between vitamin D concentrations and BASDAI scores. In addition, Mermerci et al. [12] reported no significant correlation between vitamin D concentrations and BASDAI scores. Arends et al. [11] found no association between vitamin D and BASDAI, and BASFI scores which was consistent with our study. Moreover, Gula et al. [29] found no statistically significant correlation between the level of 25(OH)D and disease activity of axSpA and perSpA in terms of clinical symptoms, and disease activity scores. In our previous study in BD, no correlation was observed between the total Iran Behcet's Disease Dynamic Activity Measure (IBDDAM), ophthalmic IBDDAM, and Behçet's Disease Current Activity Form (BDCAF) with $25(OH)D_3$ levels [8]. Furthermore, no correlation was found between the major symptoms of BD and 25(OH)D value [8]. However, in some studies significant inverse correlations were observed between vitamin D levels and disease activity markers [13,15,18,25,27,30,31]. In addition, results of recent meta-analysis indicated that $25(OH)D_3$ was inversely associated with AS suggesting that higher serum vitamin D levels may decrease the risk of AS [32]. Another systematic review also reported that AS was associated with lower vitamin D concentrations and that low vitamin D concentrations were associated with higher disease activity in AS patients [28]. In a study in systemic sclerosis patients, we observed significant differences in serum $25(OH)D_3$ levels according to gastrointestinal involvement [26]. Also, there was no significant correlation between presence or absence of calcinosis and negative or positivity of auto-antibodies with $25(OH)D_3$ levels [26]. This discrepancy between the results of studies might be due to differences in studied population, seasonal variations, disease duration, baseline disease activity and $25(OH)D_3$ status as well as type, dosage and duration of medical therapies. Furthermore, in majority of studies, BASDAI, a self-reported and subjective scale, was used to assess disease activity. Further studies would be needed to clarify if and how serum $25(OH)D_3$ levels correlate with clinical parameters in SpA.

The limitations of the present study were that the activity level, dietary habits and sunlight exposure frequencies of the patient and control groups were not evaluated. In addition, this study had a cross-sectional design and patients were not followed-up prospectively. We did not evaluate serum calcium, phosphorus, alkaline phosphatase (ALP), parathormone (PTH) and vitamin D binding protein (DBP) levels as well as bone turnover markers in the study. The strength of present study was that we had a control group and compared mean serum $25(OH)D_3$ levels between patients with SpA and normal population.

In conclusion, although our study revealed lower serum $25(OH)D_3$ levels in SpA patients compared to healthy controls, there were not any significant correlations between its serum levels with severity of disease. However, correction of vitamin D status may be beneficial in controlling inflammation and disease activity.

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