The Egyptian Rheumatologist 45 (2023) 289–293

Contents lists available at ScienceDirect

The Egyptian Rheumatologist

journal homepage: www.elsevier.com/locate/ejr

Vitamin D level in ankylosing spondylitis male patients: A potential association with the functional status and platelet count

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ARTICLE INFO

Keywords:
Ankylosing spondylitis
Vitamin D
BASDAI
BASMI
BASFI

ABSTRACT

Introductions: Ankylosing spondylitis (AS), spondyloarthritis (SpA) prototype characteristically involves the axial skeleton and enthesis. The pathogenesis of AS is multifactorial, however it has been reported that one important factor that might contribute is vitamin D deficiency. Vitamin D and platelets share specific roles in immune response, bone health and mineral metabolism.

Aim of the work: To evaluate the serum vitamin D levels in AS patients and to study the relationship to clinical manifestations, disease activity, mobility and functionality.

Patients and methods: The study included 33 male AS patients and 33 matched control. Bath AS metrology index (BASMI), Bath AS disease activity index (BASDAI) and Bath AS functional index (BASFI) were evaluated. Serum 25-hydroxy vitamin D3 level was measured.

Results: The 33 patients had a mean age of 37.2 ± 10.7 years, disease duration of 12.7 ± 6.8 years. 3 were ex-smokers, 15 currently and 15 never smoke. The mean BASDAI was 4.2 ± 2.1, 19 (57.6%) had BASDAI score ≥ 4 (active). The BASMI was 5.7 ± 1.4 and BASFI was 5.3 ± 2.6. Patient's vitamin D level (7.2 ± 5.2 ng/ml) was lower significantly than in the control (21.3 ± 10.1 ng/ml) ($p < 0.001$). There were no differences in the level of vitamin D according to the smoking status ($p = 0.9$). A significant inverse relation was detected between vitamin D level and BASFI ($r = -0.35$, $p = 0.045$) and a significant correlation with the platelet level ($r = 0.38$, $p = 0.027$).

Conclusion: Low vitamin D level may contribute significantly to the pathogenesis of AS. It is significantly related to the impaired function in the disease and to low platelet count.

1. Introduction

Spondyloarthritis (SpA) could be classified into axial and peripheral. Axial SpA (axSpA) could be radiographic with evidence of sacroiliitis, including ankylosing spondylitis (AS), and non-radiographic axial SpA (nr-axSpA) where the diagnosis is supported by magnetic resonance imaging (MRI) evidence of active sacroiliitis and/or a combination of other features [1]. In radiographic axial SpA, the sacroiliac joints and the spines chronic inflammation could eventually lead to bony ankylosis [2]. For the nr-axSpA, the exact outcome of the disease is variable: it could remit, continue as such or evolve to radiographic axSpA [3]. Classic AS is the prototype of radiographic axSpA and characteristically involves the axial skeleton, enthesitis and arthritis [4,5]. AS in Egypt is more prevalent than in Japan, likely due to genetic differences [6]. The pathogenesis of AS is multifactorial, HLA-B27 is widely known to play the strongest genetic association with the disease. Yet, several factors were discovered to be crucial in AS pathophysiology including the IL-23/IL-17 axis and the gut microbiota [7]. One important factor that might contribute to AS pathogenesis is deficiency of vitamin D [8].

The importance of vitamin D as a prohormone for calcium homeostasis and the preservation of bone health is well known [9].It is important to highlight that this vitamin plays other important roles in the body such as modulation of cell growth and differentiation, and immune functions [10]. Different types of immune cells express vitamin D receptors (VDR) [11].Vitamin D deficiency has been linked to higher incidence of autoimmune and inflammatory rheumatic diseases has been confirmed and may affect the disease activity. The adaptive immune system is shifted by vitamin D from Th17 and Th1 to Th2 and

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https://doi.org/10.1016/j.ejr.2023.07.001
Received 30 June 2023; Accepted 6 July 2023
Available online 19 July 2023

Tregs. Therefore, deficiency could promote autoimmunity [12].

In Egyptian patients with AS, the bone mineral density (BMD) decreased and was connected with the disease's activity, functional ability, spinal mobility, and radiological damage [13]. Additionally, Tunisian AS patients had higher bone turnover indicators and lower BMD. Hyperbone remodelling and a decline in BMD were linked to AS's inflammatory activity. Use of anti-TNF appeared to have positive effects on activity and BMD [14]. Furthermore, serum vitamin D levels were decreased in AS and deficiency was related to disease activity and bone turnover. It was also stated that vitamin D may contribute to the pathogenesis and progression in Egyptian AS patients [15].

The aim of our work was to assess serum vitamin D levels in AS patients and to study the relationship with indices of activity, mobility and functionality.

2. Patients and methods

Thirty-three male AS patients who met the modified New York criteria [16] were recruited from the Faculty of Medicine, Cairo University Hospitals'Rheumatology Department and Outpatient Clinic. Thirty-three individuals matching in age- and sex who appeared healthy acted as controls. Patients with associated conditions that may impact the musculoskeletal health were excluded including those with inflammatory bowel disease, malnutrition, renal or hepatic disease. All participants signed a written agreement, which was obtained after the study approval by the local ethics commission.

Every patient had a thorough history taking, thorough comprehensive clinical assessment in addition to laboratory investigations including alanine aminotransferase (ALT), aspartate aminotransferase (AST), complete blood count (CBC), blood urea, creatinine and serum 25-hydroxy vitamin D3. Available patients' spinal and sacroiliac radiographs were reviewed. Bath AS disease activity index (BASDAI) [17], metrology index (BASMI) [18] and functional index (BASFI) [19] were assessed.

Serum 25-hydroxy vitamin D3 was measured using enzyme-linked immunosorbent assay (ELISA) (Human vitamin D3 ELISA Kit, Sunlong Biotech co, China; Cat. No. SL1833Hu).*Assay Range:* 0.5–30 mg/ml with a *sensitivity:* 0.1 ng/ml.

Statistical analysis: SPSS version 26 was employed for the statistical analysis. The data was summarised using the mean, standard deviation, median, minimum and maximum values, as well as its representation in terms of numbers and percentages, were used to summarise it. The Kruskal-Wallis, Mann-Whitney, and Chi Square tests were used to compare quantitative variables. The Spearman correlation coefficient was taken into account. P-values of 0.05 or lower were regarded as significant.

3. Results

This study included 33 AS male patients attending the Rheumatology Outpatient Clinic and Department at Kasr Al Ainy University Hospitals in addition to 33 apparently healthy, age- matched male controls (mean age 40.7 ± 10.5 years; $p = 0.13$). 11 (33.3%) patients were single, 21 (63.6%) married and 1(3.1%) divorced. 3 (9.1%) were ex-smokers, 15 (45.5%) currently smoking and 15 (45.5%) never smoke. 3 (9.1%) gave history of ex-drug abuse. 19 (57.6%) had BASDAI score ≥4 (active). The characteristics of AS patients are shown in Table 1.There was no history of hypertension, diabetes mellitus, cardiac, pulmonary or neurological involvement.

Vitamin D levels in patients' (7.2 ± 5.2 ng/ml; 1.8–20 ng/ml) was lower significantly than in controls (21.3 ± 10.1 ng/ml; 5.4–41 ng/ml) ($p < 0.001$)(Fig. 1).There were no differences in the level of vitamin D according to the smoking status ($p = 0.9$) and between those with and without history of drug abuse ($p = 0.3$).Table 2 shows the serum vitamin D level according to the patients characteristics.

Table 3 reveals the correlation between serum vitamin D level and

Table 1
Characteristics of ankylosing spondylitis patients.

Characteristicsmean ± SD (range) or n(%)	AS patients(n = 33)
Age (years)	37.2 ± 10.7
Age at onset (years)	24.5 ± 9.9
Disease duration (years)	12.7 ± 6.8
Peripheral arthritis	9 (27.3)
Enthesitis	9 (27.3)
Uveitis	8 (24.2)
Dactylitis	6 (18.2)
BASDAI	4.2 ± 2.1 (0–8.8)
BASMI	5.7 ± 1.4 (2.8–8.2)
BASFI	5.3 ± 2.6 (0–9.5)
CRP (mg/dl)	19.2 ± 12.3
Hb (g/dl)	12.7 ± 1.5 (10.2–15.6)
TLC ($x10^3$ /mm^3)	8.4 ± 8.7 (3.6–15.3)
Platelets ($x10^3$ /mm^3)	253.1 ± 75.2 (141–450)
AST (U/L)	19.6 ± 12.7 (8–74)
ALT (U/L)	23 ± 23.9 (19–143)
Cr (mg/dl)	0.9 ± 0.2 (0.4–1.3)
25(OH) vitamin D (ng/ml)	7.2 ± 5.2 (1.8–20)
NSAIDs	33 (100)
sDMARDs	13 (39.4)
TNFi	15 (45.5)
IL-17A inhibitor	4 (12.1)
Biological treatment	19 (57.6)
Glucocorticoids	5 (15.2)

AS: ankylosing spondylitis, BASDAI: Bath ankylosing spondylitis disease activity index, BASMI: Bath ankylosing spondylitis metrology index, BASFI: Bath ankylosing spondylitis functional index.CRP: C-reactive protein, Hb: hemoglobin, TLC: total leucocytic count, PLT: platelets count, AST: aspartate transaminase, ALT: alanine transaminase, Cr: creatinine.NSAIDs: non-steroidal anti-inflammatory drugs, sDMARDs: synthetic disease modifying anti-rheumatic drugs, TNFi:tumour necrosis factor inhibitors, IL-17A: interleukin 17A.

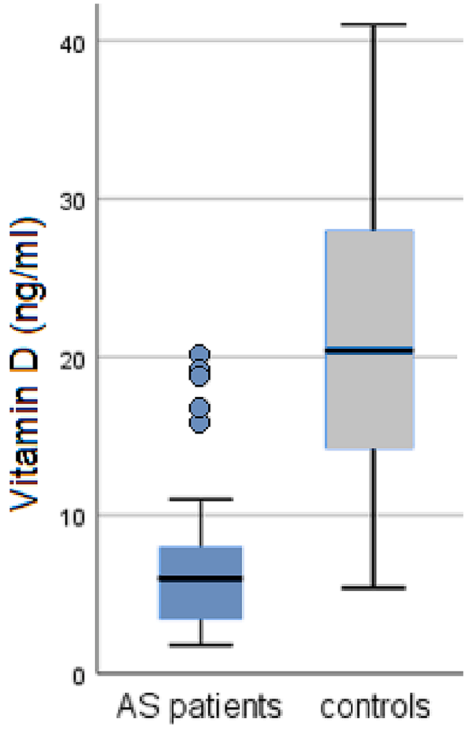

Fig. 1. Serum vitamin D levels in the ankylsoing spondylitis (AS) patients and controls.

Table 2
Relation between serum vitamin D level, and disease clinical characteristics.

Characteristicsmean ± SD	AS patients(n = 33)		p
	yes	no	
Peripheral arthritis (n = 9)	7.7 ± 5.01	7 ± 5.4	0.49
Enthesitis (n = 9)	8.2 ± 6.1	6.8 ± 4.9	0.77
Uveitis (n = 8)	9.1 ± 6.7	6.6 ± 4.7	0.5
Dactylitis (n = 6)	7.3 ± 4.7	6.8 ± 4.3	0.57
LOM cervical spines (n = 31)	7.3 ± 5.3	5.2 ± 2.9	0.8
LOM lumbar spines (n = 31)	6.8 ± 4.9	13.1 ± 8.3	0.11
Limited chest expansion (n = 28)	6.7 ± 5.1	9.98 ± 5.4	0.07
Biological treatment(n = 19)	8.8 ± 6.3	5.03 ± 1.7	0.15

AS: ankylosing spondylitis, LOM: limited range of motion.

Table 3
Correlation between serum vitamin D level and characteristics of ankylosing spondylitis patients.

Characteristics r (p)	AS patients(n = 33)	
Age	−0.31	(0.08)
Age at onset	−0.16	(0.37)
Disease duration	−0.17	(0.35)
BASDAI (total)	−0.23	(0.2)
≥4 (active)	−0.37	(0.12)
BASMI	−0.29	(0.1)
BASFI	−0.35	(0.045)
C-reactive protein	0.33	(0.07)
Hemoglobin	0.13	(0.46)
TLC	0.27	(0.12)
Platelets	0.38	(0.027)
AST	0.06	(0.74)
ALT	0.14	(0.44)
Creatinine	0.02	(0.92)

AS: ankylosing spondylitis, BASDAI: Bath ankylosing spondylitis disease activity index, BASMI: Bath Ankylosing spondylitis metrology index, BASFI: Bath ankylosing spondylitis functional index.TLC: total leucocytic count, AST: aspartate transaminase, ALT: alanine transaminase

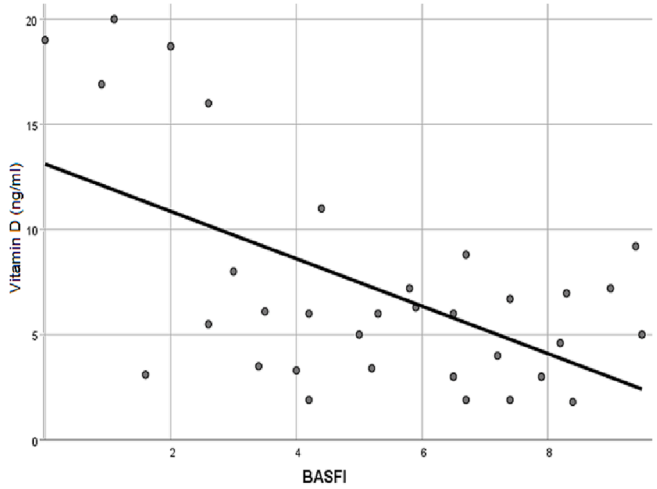

Fig. 2. Inverse correlation between vitamin D levels and the Bath ankylosing spondylitis functional index (BASFI).

characteristics of the AS patients (Figs. 2 and 3).

4. Discussion

The axial skeleton is predominantly affected by the chronic inflammatory condition known as ankylosing spondylitis. The illness causes ankylosis of the spine and sacroiliac joints by causing the formation of new bones [20]. The development of AS results from complex

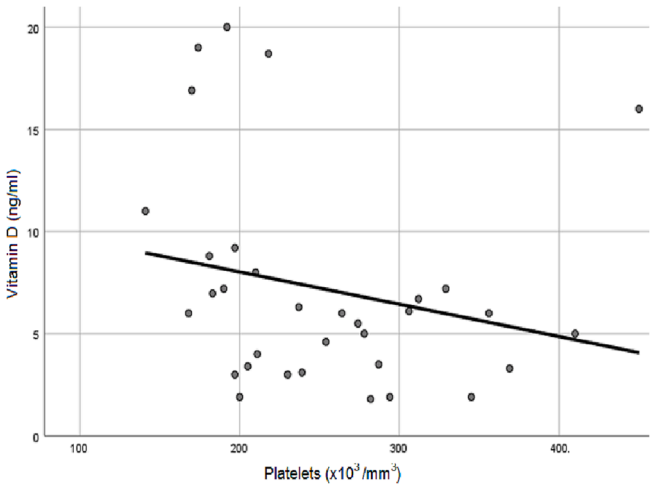

Fig. 3. Inverse correlation between vitamin D levels and the platelets count in ankylosing spondylitis patients.

interactions between genetic background and environmental variables. However, the etiology of radiographic axSpA remains unclear [5]. In addition to its classical effects on calcium-phosphorus metabolism, numerous diseases including cardiovascular disorders, infections, malignancies, diabetes mellitus, inflammatory disorders, multiple sclerosis and fibromyalgia have been associated to vitamin D [21]. Furthermore, vitamin D has multiple immunoregulatory effects, influences both innate and adaptive immune cells and decreases the production of proinflammatory cytokines. [22]. In fact, vitamin D helps to maintain immune homeostasis; therefore, its role in autoimmune diseases etiopathogenesis has become a topic of interest [23]. Vitamin D is thought to contribute to the onset and progression of numerous rheumatic diseases including AS [24].

In the present work, serum vitamin D levels were reduced significantly compared to the control. Similarly, in different countries, Turkey [24], Germany [25], China [26], Iran [27], Morocco [28] and Egypt [15] a significantly lower level has been reported in AS patients. A study from Turkey found that male AS and female undifferentiated SpA (uSpA) patients had significantly lower vitamin D levels [29] while another Turkish study on AS found an insignificantly reduced level compared to the control [30]. On the contrary in another Turkish study, vitamin D levels have no significant difference between the patients and controls and this was attributed to the low number of controls recruited in their work [31].Moreover, a study conducted in Sweden[32] concluded that serum 25(OH)D were substantially greater in AS patients than in the controls. Also, a study in China on newly diagnosed axSpA patients showed significantly lower serum 25(OH)D levels in the controls than the patients being lower in females [33].

In the present work there was no significant difference in the vitamin D level between those receiving biologic therapy and those not. In a Swedish work, there were no discernible variations in serum 25(OH)D between methotrexate users and non-users, sulfasalazine, biologic (anti-tumor necrosis factor) or non-steroidal anti-inflammatory agents (NSAIDs) [32].

No significant correlation between the vitamin D level with the CRP, BASDAI or BASMI was found. Vitamin D and BASFI had a substantial negative correlation. In agreement, *Yazmalaret al.* conducted a study in Turkey did not show any significant correlations between disease activity in AS and seasonal 25(OH)D (winter or summer) yet winter BASDAI scores were significantly higher than that of summer [22]. Furthermore, other studies revealed that there was no correlation significance between levels of vitamin D and disease activity assessed by BASDAI [24,31,34]. In addition, another work revealed the same results when disease activity assessed by ESR, CRP levels and BASDAI [35].

Another study from Sweden found a significant correlated with the AS symptoms duration but not with the age, ESR, CRP, ASDAS, BASDAI, BASFI or BASMI [32]. Vitamin D levels did not show correlation with BASDAI in either the AS or uSpA patients. This discrepancy was attributed to the confounding factors that could influence the BASDAI, such as fibromyalgia [29].However, others showed inverse correlation between serum levels of 1,25(OH)2D3 and disease activity. Neither the proportions of male and female patients nor the seasonality was similar to this study, thus this could be a reasonable explanation to the discrepancy between the two results [36]. Furthermore, 1,25(OH)2D3 serum levels were found to be negatively correlated with disease activity as represented by ESR, CRP and BASDAI due to a reduction in 1,25(OH)2D3 synthesis secondary to suppression of 1 α-hydroxylase activity/down regulation by the TNF-α, an increased 1,25(OH)2D3 binding to vitamin D receptor or disturbance of enteral absorption of vitamin D due to intestinal vitamin D receptor defect [25]. In the Moroccan study, vitamin D level negatively correlated with BASDAI [28].

A study conducted in the United Kingdom on AS patients showed that low vitamin D was present in 20% which was significantly associated with increased disease activity (BASDAI). While there were no significant differences observed for BASFI. Interestingly, 25(OH)D levels did not appear to be impacted by vitamin D supplementation. This emphasizes the fact that, the supplementation dose is unlikely to be sufficient for curing insufficiency [37]. A previously study revealed that no significant difference regarding the activity and functional impairment of SpA patients, assessed by BASDAI and BASFI, based on the different serum levels of 25(OH)D. Factors like different sample sizes and geographical areas could contribute to the heterogonous results [27]. On the other hand, a study conducted in Turkey found that the indicators of disease activity and severity such as CRP, ESR, pain, BASDAI and BASFI were adversely correlated with levels of 25(OH)D3. The discrepancy could possibly be explained by the different sample sizes, presence of female patients in their work and confounding factors specially drugs like glucocorticoids, bisphosphonates, and vitamin D supplementation [30].

In contrast to the present work, in a previous Egyptian study, more disease activity (ESR, CRP, ASDAS and BASDAI), restricted spinal mobility (BASMI) and entheses score were substantially correlated with decreased vitamin D levels. Furthermore, compared with those without peripheral arthritis, serum vitamin D in AS patients with this condition werecosiderably lower [15].Another Turkish study dividing AS patients according to their disease activity as assessed by BASDAI revealed that there were low vitamin D levels with no significant differences. Several factors including sample size, geographic region, dietary habits, dressing habits, life style changes and sunlight exposure could explain the discrepancy [35].

There was a significant correlation in the present work between the vitamin D level and the platelet count. In coagulation, thrombosis, endothelial dysfunction and immunological response, platelets and. vitamin D have complementary functions. Furthermore, a common thread between both is reflected by their function in bone health and mineral metabolism, since low levels of both are linked to abnormal bone remodeling and osteoporosis [38]. Vitamin D receptors are localized and expressed in human platelets [39]. Less vitamin D levels are associated with lower levels of platelets [40].

As the work was only on males, this may limit the applicability of the results on other ethnicities. A design of a larger longitudinal study is advised.

In conclusion, vitamin D levels in AS patients were significantly low. There was a significant negative correlation between vitamin D levels and BASFI. No significant correlation was found between vitamin D levels; and CRP, BASDAI or BASMI.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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