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Original Article

Relationship between Vitamin D levels and pain and disease activity in patients with newly diagnosed axial spondyloarthritis

Sisi Deng [a,1], Yi He [b,1], Xinying Nian [a], Erwei Sun [b,**], Li Li [a,*]

[a] Department of Nursing, Zhujiang Hospital, Southern Medical University, Guangzhou, China
[b] Department of Rheumatology and Immunology, The Third Affiliated Hospital of Southern Medical University, Guangzhou, China

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ABSTRACT

Objectives: To explore the relationship between Vitamin D levels and pain and disease activity in patients with newly diagnosed axial spondyloarthritis (axSpA).
Methods: A convenience sample of 131 newly diagnosed axSpA patients and 60 healthy controls was recruited from July 2016 to December 2018. Serum 25-hydroxyvitamin D [25(OH)D] was measured to assess vitamin D levels. Disease activity was assessed by objective indicators [Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), the Bath Ankylosing Spondylitis Metrology Index (BASMI)], patient-reported questionnaires [the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and the Bath Ankylosing Spondylitis Functional Index (BASFI)]. Pain intensity and interference were also assessed.
Results: Vitamin D insufficiency [serum 25(OH) D levels<50 nmol/L]was found in 46 (35.1%) and 25 (43.3%) of the axSpA patients and the healthy controls, respectively. Female patients had higher risk (*OR*:4.928; 95% CI: 1.921−12.642) for vitamin D insufficiency than male patients. Vitamin D was positively correlated with CRP, ESR level, the BASFI, and the BASMI. Logistic regression showed that vitamin D levels were not associated with pain, or disease activity in the newly diagnosed axSpA patients. Gender was the only predictive variable for vitamin D levels.
Conclusions: Vitamin D insufficiency was prevalent in both newly diagnosed axSpA patients and healthy controls. There was no association between vitamin D and pain and disease activity in the newly diagnosed axSpA patients. Monitoring vitamin D levels is important and early intervention for vitamin D insufficiency is needed, especially in female patients.

What is known?

- The predominant symptom of axial spondyloarthritis is pain, which leads to a heavy burden for patients.
- Vitamin D plays an important role in pain.
- The relationship between vitamin D levels and pain intensity was previously unknown in newly diagnosed axSpA patients.

What is new?

- Vitamin D levels were not associated with pain or disease activity in the newly diagnosed axSpA patients.
- Female patients had a higher risk of vitamin D insufficiency than male patients with axial spondyloarthritis.
- Gender was the only predictive variable for vitamin D levels.

1. Introduction

Axial spondyloarthritis (axSpA) is a chronic inflammatory disease comprised of two subsets-ankylosing spondylitis (AS) and non-radiographic axSpA [1]. AxSpA is mainly focused in spine and/or sacroiliac joints [2] and is characterized by back pain. Population prevalence of axSpA is estimated from 0.9% to 1.4% in the United States [1] and is approximately 0.7% in Southern China [3].

The predominant symptom of axSpA is pain, which can lead to functionality limitations, work dysfunction, and increased risk of anxiety and depression [4]. Although previous studies suggested the causes of pain in patients with AS may include inflammatory and neuropathic components, they still have not been completely elucidated [5,6].

* Corresponding author. 253 Gongye Road M., Guangzhou 510282, China.
** Corresponding author. 183 Zhongshan Avenue W., Guangzhou 510630, China.
E-mail addresses: sunew@smu.edu.cn (E. Sun), lli1@smu.edu.cn (L. Li).
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[1] Sisi Deng and Yi He contributed equally to this study and share the first authorship.

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Vitamin D plays an important role in pain [7]. The main sources of vitamin D are obtained from sunlight exposure and food. Vitamin D is hydroxylated, converted to 25-hydroxyvitamin D [25(OH)D] in the liver, and then form into 1,25-dihydroxyvitamin D [$1,25(OH)_2D$] in the kidney [8]. As 25(OH)D is more stable than $1,25(OH)_2D$, it is often used to measure vitamin D levels [9]. In addition, previous studies indicated that poor vitamin D levels were associated with chronic pain [10], knee pain [11], and specific musculoskeletal pain [12]. Durmus et al. reported that the AS patients had lower vitamin D levels than the healthy controls, and that there was a correlation between pain and vitamin D levels in AS patients [13]. However, these studies did not exclude the potentially-confounding effects of medication on vitamin D level. Moreover, the association between vitamin D levels and pain intensity was unknown in newly diagnosed axSpA patients.

Currently, there is controversy regarding the potential immunomodulatory role of vitamin D in axSpA patients. Some studies found that vitamin D levels were lower in axSpA patients than in the control groups [14,15]. One of the explanations is that the immobility of axSpA patients may lead to inadequate sunlight exposure. However, another study did not find any difference between AS patients with excluded supplements of vitamin D and the healthy control group [16]. Some studies found a negative correlation between vitamin D levels and disease activity in axSpA. They speculated that vitamin D insufficiency may have contributed to increased disease activity [17]. However, these studies included patients with medications including non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMARDs), and biologic agents. The DMARDs includes hydroxychloroquine, sulfasalazine, and more. It was reported that hydroxychloroquine and sulfasalazine have been associated with variations of vitamin D levels [18]. To explore whether vitamin D insufficiency plays a role in pain and disease activity, and to eliminate medication treatment effects on vitamin D levels, the objective of this study was to explore relationship between Vitamin D levels and pain and disease activity in patients with newly diagnosed axial spondyloarthritis.

2. Method

2.1. Participants

This study was conducted at the Department of Rheumatology and Immunology in a university-affiliated hospital in Guangzhou, China, from July 2016 to December 2018. According to the sample size calculated by the prevalence of axSpA in the population, we used this formula $n = \frac{u^2_{\alpha/2}\pi(1-\pi)}{\delta^2}$ [19], in which α represents significance level, π represents overall ratio, and δ represents tolerance. To avoid a sample size that is too small, we chose $\alpha = 0.05$, $\pi = 0.5$, $\delta = 0.1$, $u_{0.05/2}$=1.96 and $n = 1.96^2 \times 0.5 \times (1-0.5)/0.1^2 = 96.04 \approx 96$. Inclusion criteria: Patients in this study were newly diagnosed with axSpA according to the Assessment of SpondyloArthritis International Society (ASAS) criteria, reported an average pain score in any joint of $\geq$1 on a 0–10 numeric rating scale (NRS; 0 represents “no pain”, 10 represents “worst pain possible”) in the previous 24 hour, and willing and able to complete the questionnaires. Exclusion criteria:Patients with osteoarthritis, rheumatoid arthritis, gout, cognitive impairment, mental illness, surgical history, chronic heart failure, serious infection within the previous four weeks, taking vitamin D supplements in previous three months, those who were pregnant, or those whose pain was not caused by axSpA were excluded from the study.

The healthy control group was recruited from the same hospital that did physical check-ups from July to December 2018. Height and weight were recorded and body mass index (BMI) was calculated as well.

2.2. Measurements

2.2.1. Laboratory analyses

Blood samples were obtained on the day of inclusion. The erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and vitamin D levels were analyzed with standard techniques at the laboratories. The serum 25(OH)D levels were analyzed with ELISA (Guangzhou PHICON Biotech Co., Ltd, China). The total coefficient of variance (CV) for serum 25(OH)D was 10%.

2.2.2. Pain assessment

The Verbal Descriptor Scale (VDS) is derived from the Present Pain Index of the McGill Pain Questionnaire [20]. Patients choose the word that best describes their current pain from no pain to mild pain, moderate pain, severe pain, extreme pain, and excruciating pain.

The Brief Pain Inventory (BPI) was used to assess pain intensity and pain interference in the previous 24 h [21]. Pain intensity (worst, least, average, and current pain) and pain interference (with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life) score from 0 (no pain or no interference) to 10 (worst pain possible or that completely interferes) on the NRS, respectively.

2.2.3. Disease activity

Disease activity was assessed by objective indicators and patient-reported questionnaires. The patient-reported questionnaires included the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) [22], and the Bath Ankylosing Spondylitis Functional Index (BASFI) [23]. The BASDAI is used to assess patient-reported disease activity which includes six items: fatigue, spinal pain, peripheral arthritis, enthesitis, and intensity and duration of morning stiffness. It is scored from 0 (none) to 10 (very severe). The BASFI is used to assess patient-reported physical function which includes 10 items and scores from 0 (easy) to 10 (impossible).

The objective indicators include erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and the Bath Ankylosing Spondylitis Metrology Index (BASMI). The BASMI is an objective instrument with a total score of 10 which includes five clinical measurements: lateral lumbar flexion, tragus to wall distance, lumbar flexion, maximal intermalleolar distance, and cervical rotation [24]. Spinal mobility was assessed by the BASMI, distance to wall and finger to floor distance.

2.3. Ethical consideration

The study was approved by the institutional review board of the hospital (No. 201608003), and participants’ written informed consents were obtained before data collection. We conducted this study according to the World Medical Association Declaration of Helsinki. The STROBE checklist was applied to ensure rigor of this study.

2.4. Study procedures

Demographic and clinical information were collected by questionnaires and from electronic medical records, which included age, gender, ESR, CRP, serum vitamin D levels, educational level, working status, height, weight, medical history, and medications. Smoking and drinking status were classified as no and/or current. In addition, patients completed self-reported questionnaires including pain and disease activity assessment. The BASMI

examination, finger to floor distance and distance to wall were measured by two trained postgraduate students after the completion of questionnaires.

2.5. Statistical analyses

All analyses were performed using IBM SPSS 19.0 (SPSS Inc., Chicago, IL). $P < 0.05$ was considered statistically significant. According to the Guideline for Vitamin D and Bone Health in Adult Chinese, serum 25(OH)D levels were categorized into either an insufficiency group(<50 nmol/L) or a normal group (≥50 nmol/L) [25]. Pain severity was classified into mild pain or moderate-to-severe pain according to the VDS. Pain status as dependent variable using moderate-to-severe pain as the referent category, and serum 25(OH)D levels as the independent variable which was categorized into groups of <50 nmol/L, 50–75 nmol/L and >75 nmol/L (the referent category).

Descriptive statistics are presented as median and interquartile range (IQR) for skewed distributed variables. The Mann-Whitney *U* test was conducted to compare two groups with non-normal distribution. Correlations were calculated using Spearman rho correlation (r_s). Linearity in the logit was assessed using the Box-Tidswell transformation. The logistic regression was performed to investigate the association between pain status and serum 25(OH)D levels. Predictor analysis of vitamin D insufficiency was performed by univariate logistic regression and multivariate logistic regression with forward stepwise modeling.

3. Results

3.1. Characteristics of participants

A total of 131 patients and 60 healthy controls were included. Demographic and clinical characteristics are shown in Table 1. There was no difference between patients and healthy controls in age and gender. In the patients group, male patients had significantly higher levels in ESR [20.0 (10.0–42.5) vs 11.0 (6.0–24.0), $P = 0.036$], CRP [12.0 (4.0–28.0) vs 3.0 (1.0–4.3), $P < 0.001$], the BASMI [2.4 (1.2–4.1) vs 1.8 (1.1–2.6), $P = 0.044$], distance to wall [0 (0–4) vs 0 (0–0), $P < 0.001$], and finger to floor distance [18.0 (3.0–28.8) vs 0 (0–12.3), $P = 0.001$] than female patients. However, no differences in the BASFI [1.7 (0.5–3.4) vs 1.7 (0.8–4.2), $P = 0.738$], and the BASDAI [2.7 (1.8–4.4) vs 3.2 (2.2–4.1), $P = 0.360$] were found.

3.2. Serum 25(OH) D levels in patients group and healthy controls

A total of 46 (35.1%) patients had vitamin D insufficiency. There were 67 (51.2%) patients with a serum 25(OH)D level between 50 and 75 nmol/L, and 18 (13.7%) had more than 75 nmol/L. Male patients had significantly higher serum 25 (OH) D level than female patients [60.01 (48.96–67.34) vs 44.47 (37.81–57.54) nmol/L, $P < 0.001$]. In the healthy controls, 25 (43.3%) had a serum 25(OH)D level of less than 50 nmol/L, with no significant difference in vitamin D level between genders. Moreover, the healthy controls had significantly lower serum 25(OH)D levels than the patients group ($P < 0.01$) (Table 1).

3.3. Pain intensity and interference in the patients group

The average pain intensity and the overall pain interference were 3.0 (2.0–4.0) and 3.1 (1.6–4.9), respectively. The median pain interference with general activity, mood, walking, work, relations with others, sleep, and enjoyment of life were 4.0 (2.0–5.0), 3.0 (1.0–5.0), 3.0 (1.0–5.0), 4.0 (2.0–6.0), 1.0 (0–4.0), 3.0 (1.8–7.0), and 3.0 (1.0–5.0), respectively.

Based on the VDS, pain severity was classified into mild pain [76 (58%)] or moderate-to-severe pain [56 (42%)]. Logistic analysis showed that there was no significant association between pain and serum 25(OH) D levels (Table 2). There were 61 (48.4%) patients reporting that they had ever used NSAIDs unregularly, however, there was no significant difference in vitamin D levels between users and non-users of NSAIDs.

3.4. Correlation between serum 25(OH) D levels and disease activity in the patients group

Spearman analysis showed that serum 25(OH) D levels were positively correlated with the BASFI, the BASMI, CRP, and ESR (Table 3) ($P < 0.05$).Among patients, the ESR, CRP level and the

Table 1
Demographic and clinical characteristics of the newly diagnosed axSpA patients and the healthy controls.

Characteristics	axSpA patients ($n = 131$)	Control group ($n = 60$)	Z/χ^2	P
Age, years, median(IQR)	28.0 (22.0–34.0)	29.0(27.0–30.0)	−1.218	0.223
Gender, *n* (%)				
Male	101 (77.1)	45.0 (75.0)	0.319	0.572
Female	30 (22.9)	15.0 (25.0)		
BMI, kg/m^2, median (IQR)	20.2 (18.5–22.8)	21.3 (20.0–22.9)	−1.905	0.057
Disease duration, years, median(IQR)	1.0 (0–5.0)	–	–	–
Current smokers, *n* (%)	39 (29.8)	–	–	–
Current drinking, *n* (%)	31 (23.7)	–	–	–
Serum 25(OH)D (nmol/L)	58.03 (45.63–66.29)	51.63 (45.58–57.72)	−2.680	0.007
CRP (mg/L)	8.0 (3.0–23.5)	–	–	–
ESR (mm/h)	15.0 (8.0–39.0)	–	–	–
BASDAI, median(IQR)	2.9 (1.9–4.3)	–	–	–
BASFI, median(IQR)	1.7 (0.7–3.4)	–	–	–
BASMI, median(IQR)	2.2 (1.2–3.8)	–	–	–
Distance to wall, cm, median(IQR)	0 (0–2.0)	–	–	–
Finger to floor distance, cm, median(IQR)	13.0 (0–26.3)	–	–	–
Users of the NSAIDs	64.0 (48.9)	–	–	–
Stiffness, *n* (%)	95.0 (72.5)	–	–	–
Duration of stiffness, min, median(IQR)	5.0 (0–15.0)	–	–	–

Note: axSpA = axial spondyloarthritis; BMI = body mass index; BASDAI = the Bath Ankylosing Spondylitis Disease Activity Index; BASFI = the Bath Ankylosing Spondylitis Functional Index; BASMI = the Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; ESR = erythrocyte sedimentation rate; IQR = interquartile range; NSAIDs = nonsteroidal anti-inflammatory drugs; 25(OH)D = 25-hydroxy vitamin D.

Table 2
Logistic regression analyses for associations between vitamin D status and mild pain before and after adjustment for covariates (*OR*).

Mild pain	Serum 25(OH)D (< 50.0 nmol/L)	Serum 25(OH)D (50.0–74.9 nmol/L)	*P* for trend
Model 1	1.671 (0.509–5.490)	2.377 (0.762–7.413)	0.286
Model 2	1.218 (0.337–4.411)	1.620 (0.473–5.546)	0.683
Model 3	1.354 (0.346–5.292)	1.409 (0.380–5.233)	0.874
Model 4	1.153 (0.283–6.699)	1.452 (0.383–5.512)	0.830

Notes: Model 1: unadjusted; Model 2: adjusted for age, gender, duration of symptoms, season, BMI; Model 3: adjusted for Model 2 plus NSAIDs, CRP, and ESR; Model 4: Model 3 plus the BASMI.BMI = body mass index; BASMI = the Bath Ankylosing Spondylitis Metrology Index; CRP= C-reactive protein; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal anti-inflammatory drugs; 25(OH)D = 25-hydroxy vitamin D.

Table 3
Correlation between vitamin D levels and clinical parameter in newly diagnosed axSpA patients ($n = 131$).

Variable	Vitamin D levels	
	Correlation Coefficient(r_s)	*P*
ESR, mm/h	0.228	0.010
CRP, mg/L	0.335	< 0.001
BASFI	0.205	0.019
BASMI	0.219	0.014

Note: axSpA = axial spondyloarthritis; BMI = body mass index; BASDAI = the Bath Ankylosing Spondylitis Disease Activity Index; BASFI = the Bath Ankylosing Spondylitis Functional Index; BASMI = the Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; ESR = erythrocyte sedimentation rate; NSAIDs = nonsteroidal anti-inflammatory drugs.

BASMI scores were significantly higher in the normal group than the insufficient group ($P < 0.05$) (Table 4). There were significant differences between smokers and non-smokers patients in serum 25(OH)D level [62.56 (52.03–70.13) vs 54.17 (44.46–64.68) nmol/L, $P = 0.021$] and the BASMI [3.10 (1.6–4.87) vs 2.00 (1.05–3.55), $P = 0.039$].

Table 5
Assignment method of independent variables.

Independent variables	Assignment method
Gender	Male = 0, Female = 1
Smoking	No = 0, Current = 1
Drinking	No = 0, Current = 1
Stiffness	No = 0, Yes = 1

3.5. Predictors of vitamin D insufficiency

Vitamin D status served as a dependent variable using the normal group as referent category, and gender, smoking, ESR, CRP, the BASFI, and the BASMI were independent variables. Assignment method of independent variables is shown in Table 5. Only gender was still independently associated with vitamin D levels, and female patients had higher risk for vitamin D insufficiency than male patients (*OR*:4.928; 95% CI: 1.921–12.642) (Table 6).

4. Discussion

In this cross-sectional study, we explored the association between serum 25(OH) D levels and pain intensity and disease activity in newly diagnosed axSpA patients. Vitamin D insufficiency was found in 35.1% of the axSpA patients and 43.3% of the healthy controls in our study, which is similar to the previous study [13]. However, Klingberg et al. [16] reported vitamin D insufficiency was found in around 50% of both the AS patients and the control group. Zhao et al. [26] found that 20% of axSpA patients were deficient in vitamin D [serum 25(OH)D < 30 nmol/L]. This discrepancy may be related to studies done at different latitudes, seasonal variables, and different races across samples. In our study, the finding of vitamin D levels lower in the control group than axSpA patients may be due to vitamin D insufficiency is also prevalent in healthy groups which has become a health problem [9]. We cannot conclude that axSpA patients have poorer vitamin D levels than the healthy controls, and further study is needed to explore this discrepancy.

Our study showed that patients experienced mild to moderate

Table 4
Comparison of disease activity and pain intensity with different vitamin D status in newly diagnosed axSpA patients[median (IQR)].

	Insufficiency group (< 50 nmol/L) ($n = 46$)	Normal group (≥50 nmol/L) ($n = 85$)	Z/χ^2	*P*
Age, years	26.0 (22.0–30.3)	28.0 (23.0–35.0)	−1.639	0.101
Disease duration, years	1.0 (0–4.0)	2.0 (0–5.0)	−1.116	0.264
Gender, *n*(%)				
Male	26.0 (56.5)	75.0 (88.2)		
Female	20.0 (43.5)	10.0 (11.8)	17.002	*0.001
Smoking, *n*(%)				
No	37.0 (80.4)	55.0 (64.7)		
Current	9.0 (19.6)	30.0 (35.3)	3.532	0.060
Drinking, *n*(%)				
No	38.0 (82.6)	62.0 (72.9)		
Current	8.0 (17.4)	23.0 (27.1)	1.544	0.214
ESR, mm/h	13.0 (6.0–29.0)	22.5 (10.0–41.3)	−2.225	0.026
CRP, mg/L	4.0 (1.5–19.5)	12.0 (4.0–28.0)	−3.449	0.001
BASDAI, score	2.8 (1.6–3.8)	2.9 (2.0–4.4)	−0.982	0.326
BASFI, score	1.6 (0.3–3.0)	1.7 (0.9–3.9)	−1.226	0.220
BASMI, score	1.8 (1.0–2.6)	2.4 (1.0–4.1)	−2.465	0.014
Stiffness, *n*(%)	31.0 (67.4)	64.0 (75.3)	−0.963	0.335
Duration of stiffness, min	5.0 (0–15.0)	5.0 (1.0–15.0)	0.333	0.739
Finger to floor, cm	10.0 (0–24.7)	15.0 (0–27.3)	−1.035	0.301
Distance to wall, cm	0 (0)	0 (0–3.0)	−1.928	0.054
Pain intensity	2.6 (1.5–3.6)	2.8 (1.8–4.1)	−0.985	0.325
Pain interference	3.0 (1.4–4.3)	3.4 (1.6–4.9)	−0.899	0.369

Note: axSpA = axial spondyloarthritis; BASDAI = the Bath Ankylosing Spondylitis Disease Activity Index; BASFI = the Bath Ankylosing Spondylitis Functional Index; BASMI = the Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; ESR = erythrocyte sedimentation rate.

Table 6
Univariate and multivariate logistic regression of vitamin D status (the normal group as referent) in newly diagnosed axSpA patients ($n = 131$).

Independent variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*P*	*OR* (95% CI)	*P*
Gender	5.769 (2.392–13.915)	< 0.001	4.928 (1.921–12.642)	0.001
Disease duration, years	0.957 (0.876–1.045)	0.331	–	–
ESR, mm/h	0.980(0.961–0.999)	0.040	–	–
CRP, mg/L	0.963 (0.935–0.991)	0.010	–	–
BASDAI	0.886 (0.724–1.084)	0.240	–	–
BASFI	0.952 (0.801–1.130)	0.573	–	–
BASMI	0.768 (0.611–0.964)	0.023	0.803 (0.629–1.025)	0.078
Smoking	0.446 (0.190–1.047)	0.064	–	–
Drinking	0.568 (0.231–1.396)	0.217	–	–
Stiffness	0.678 (0.308–1.493)	0.335	–	–

Note: axSpA = axial spondyloarthritis; BASDAI = the Bath Ankylosing Spondylitis Disease Activity Index; BASFI = the Bath Ankylosing Spondylitis Functional Index; BASMI = the Bath Ankylosing Spondylitis Metrology Index; CRP=C-reactive protein; ESR = erythrocyte sedimentation rate.

pain and moderate pain interference, particularly in general activity and work. In addition, there was no association between 25(OH) D level and pain intensity, nor pain interference in newly diagnosed axSpA patients. However, some previous studies found a negative relationship between vitamin D and pain intensity in axSpA patients [13,26]. Some of the early studies suggested that vitamin D may play an important role in pain management [7,11,27–29], possibly due to its anti-inflammatory effects [30], whereas other studies did not find this relationship [31,32]. The discrepancy may be caused by medication confounding effect which include biologic agents and/or vitamin D supplementations. The former may decrease inflammation and the latter would increase vitamin D level. Therefore, a randomized controlled trial to determine whether vitamin D supplements improve pain intensity in newly diagnosed axSpA patients is necessary.

Vitamin D plays a role in bone metabolism [27] and may have effects on immune systems [16], but the relationship between vitamin D and disease activity in axSpA patients is still unclear. In this study, serum 25(OH)D was positively correlated with clinical parameters including CRP, ESR, the BASFI, and the BASMI score, which is different from previous studies [13,16,26]. However, these correlations did not exist after exclusion of female patients. In addition, the normal group had significantly higher levels in ESR, CRP, and the BASMI scores than the insufficient group in our study. However, after exclusion of female patients, this difference did not exist. Different from our study, Durmus et al. [13] and Zhao et al. [26] reported that due to the vitamin D insufficiency, the ESR, CRP and the BASDAI scores increased. Another study indicated that vitamin D insufficiency may be the consequence of disease activity rather the cause of it [16]. One of the possible explanations was that gender differences contributed to the discrepancy, because female patients had lower vitamin D level and inflammation than male patients in our study. Another possible explanation was that previous studies included patients with treatment which did not exclude potential confounding effects of medications on vitamin D levels.

Previous studies reported that smokers had lower serum 25(OH) D level than non-smokers in the young male population [33]. However, this difference did not exist between smokers and non-smokers after exclusion of female patients in our study. Gender difference might be the confounding factor.

In our patients group, female had lower vitamin D levels than male, which is consistent with previous studies [34,35]; however, there was no difference between male and female in the healthy controls. Female patients' lower serum 25(OH) D levels may be due to avoidance of sunlight exposure and less time spent on outdoors activities, which might reduce the cutaneous synthesis of vitamin D. Vitamin D is fat-soluble which is stored in fat tissue. Another possible explanation may be a higher level of fat tissue in female than male, which leads to synthesis of more vitamin D3 in the skin and less in blood in female [36]. It was reported that vitamin D level was related to gender and sex hormones in rheumatic disease [18]. Rheumatic disease and axSpA are autoimmune diseases, thus study of gender differences in vitamin D level related to sex hormone in newly diagnosed axSpA is needed.

In this study, male patients had significantly higher levels of CRP, ESR, the BASMI score, distance to wall, and finger to floor distance than female patients. This might indicate that male patients had a higher disease burden than female patients. However, previous research reported that female patients had lower CRP, but higher burden of disease than male patients with AS [37]. In other studies, female patients had higher self-reported disease activity than male patients with AS [38,39]. These discrepancies may be due to studies done by patients in different disease phases and with different medication effects. Given gender difference in disease activity and vitamin D levels in newly diagnosed axSpA patients, more studies are needed to explore this difference.

5. Limitations

There are some limitations in this study. First, we did not measure time spent outdoors, the dietary intake of vitamin D from foods and sun screen use in both groups. Second, we did not include education level and working status in the healthy control. Third, the cross-sectional design of this study did not allow us to determine causal relationship between vitamin D and disease activity. To understand the immunomodulatory role of vitamin D, further studies on whether vitamin D levels change with inflammation decrease and its association with disease activity, and pain intensity after treatment are needed in newly diagnosed axSpA patients.

6. Conclusions

Vitamin D insufficiency was prevalent in both the healthy controls and the newly diagnosed axSpA patients. Even though there was no association between vitamin D and pain and disease activity in newly diagnosed axSpA patients, monitoring vitamin D levels is still important. Female patients had higher risk for vitamin D insufficiency than male patients. Early intervention for vitamin D insufficiency is needed, especially in female patients.

Conflicts of interest

The authors declare that there is no conflict of interest.

CRediT authorship contribution statement

Sisi Deng: Methodology, Investigation, Formal analysis, Writing - original draft. **Yi He:** Methodology, Investigation, Resources, Writing - original draft. **Xinying Nian:** Investigation, Formal analysis. **Erwei Sun:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Li Li:** Conceptualization, Methodology, Supervision, Writing - review & editing.

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Appendix A. Supplementary data

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