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Vitamin D Deficiency and Sub-Clinical Osteomalacia in Axial Spondyloarthropathy

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Abstract

Objectives: The role of bone disease in spondyloarthropathy (SpA) remains of great interest with evidence of an increased risk of bone fragility and fracture. The effects of lifestyle factors such as sun light exposure and vitamin D deficiency on SpA remain uncertain. The study was to examine those factors on skeletal integrity in axial spondyloarthropathy (axSpA) patients associated with sub-clinical osteomalacia.

Material and Methods: 95 axSpA patients and 74 healthy controls in the same season were enrolled. ASAS-endorsed disease activity score (ASDAS), 25-hydroxyvitamin D, parathyroid hormone (PTH), bone turnover biomarkers procollagen type 1 N-terminal peptide (PINP) and osteocalcin(OC), serum C-telopeptides of type I collagen (sCTX), serum alkaline phosphatase (sALP), adjusted calcium, C-reactive protein, bone minimal density (BMD) of total proximal femur and lumbar spine were measured. Questionnaires on daily sun exposure time and other factors were ascertained.

Results: axSpA patients were with significantly decreased vitamin D and raised sALP levels than controls ($p<0.001$). 74% of axSpA patients had vitamin D deficiency. Their vitamin D levels were inversely related to the disease duration ($r=-0.234$, $p<0.05$) but positively to daily sunlight exposure time and calcium ($r=0.064$, $p<0.001$, respectively). axSpA patients had significantly higher bone turnover biomarkers sCTX and OC ($p<0.05$), and significantly lower femoral neck T and Z scores in BMD than controls ($p=0.000$).

Conclusion: Vitamin D insufficiency exist in most (74%) of axSpA patients. axSpA patients exhibited significantly lower vitamin D and raised ALP levels, and with significantly higher bone turnover biomarkers and low BMD than controls, which indicated that subclinical biochemical osteomalacia associated with most axSpA patients.

Keywords: Axial spondyloarthropathy (axSpA); Vitamin D deficiency; Osteomalacia; Bone turnover biomarkers

Introduction

Osteomalacia occurs due to lack of active metabolite of Vitamin D in serum leading to mineralization and bone matrix defects, characterized with diffuse muscular aches and fragility of the bones. It is frequently found in South East Asia despite adequate sun exposure and diet, and in adults starts insidiously as back pain later spreading to the arms and ribs [1]. Although the incidence of vitamin D deficiency may present in various diseases, its use as a preventative supplement is controversial [2]. Rheumatologic point of view these symptomatic problems are very common in our community, which is difficult to predict, diagnose and manage as a Vitamin D deficiency, perhaps some groups of patient may suggests primarily pain is due to their joint diseases. The prevalence of autoimmune disease may be increased due to geographical variation in diet, infection or possibly due to predisposition genetic risk factors associated with vitamin-D metabolism. Nevertheless, an alternative explanation may be vitamin D deficiency, reduced ultraviolet B (UVB) exposure and development and progression of autoimmune diseases [3]. In various autoimmune diseases condition the deficiency of vitamin D might be associated with risk of both susceptibility and severity of the bone mineral density (BMD) due to significant consequence of innate and acquired immunity [4,5]. However, the potential immunomodulatory role of vitamin D in spondyloarthropathy (SpA) has not been discussed widely, especially the interconnection between SpA and osteomalacia.

Spondyloarthropathy is a chronic inflammatory disorder; typically a disease of young men (age 25-45) involving the sacroiliac (SI) joints and the axial skeleton. Clinical feature of Spondyloarthropathy includes the inflammatory back pain and stiffness of the spine. Moreover, fatigue in AS patients is associated with increased pain, stiffness and decreased functional capacity. Glucocorticoids are not commonly used to treat this group of patents, as this increases chances to development of systemic osteoporosis. However, osteoporosis has been reported as an early event in ankylosing spondylitis (AS) whilst it cannot be related only to the spine ankylosis and immobilization [6,7] . Another study also states that AS is associated with lower vitamin D concentration of serum and negatively affect disease activity, but

statistically no significant differences in ALP, Ca, P, OC and PTH levels [8].

The role of BMD in SpA remains of great interest with evidence of an increased risk on bone fragility and fracture. The character of the disease process itself and effects on lifestyle factors such as sun light exposure, hormones or a diet deficient in vitamin D remains uncertain. The study was to examine those factors on skeletal integrity in axial spondyloarthropathy (axSpA) patients associated with sub-clinical osteomalacia.

Materials and Methods

Patients

Between December 2014 to March 2015, 95 consecutive axSpA patients from rheumatology clinic and 74 healthy individuals from the same area in the First Affiliated Hospital of Xiamen University, Xiamen, Fujian Province (located in southern China, 30 degrees north of the equator) were recruited. All axSpA patients met the Assessment of Spondyloarthritis International Society (ASAS) 2009 criteria [7,9] and ASAS axSpA 2013 criteria [10]. Patients younger than 18 or older than 65 years, inflammatory bowel disease (IBD), psoriasis, a preceding symptomatic infection of urogenital or gastrointestinal tract and Bechet's disease or familial Mediterranean fever, pregnancy and postmenopause women, chronic renal insufficiency, renal tubular acidosis, hypophosphatemia, osteomalacia patients with tumor-induced; who had taken drugs for one year that may affect bone metabolism and vitamin D metabolism such as thyroxine, corticosteroids, calcium, vitamin D, bisphosphonates, and anticonvulsants were excluded. The study was approved by the ethics committee of Institutional Review Board (IRB) of the First Affiliated Hospital of Xiamen University. Written informed consents were obtained from all participants.

Clinical and laboratory assessments

Disease activity was assessed by using Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), C-reactive protein (CRP), and ASAS-endorsed disease activity score (ASDAS) [11]. 25-hydroxyvitamin D (25OHvitD), parathyroid hormone (PTH) and bone turnover biomarkers procollagen type 1 N-terminal peptide(PINP) and osteocalcin (OC), and bone resorption marker serum C-telopeptides of type I collagen (sCTX) were assessed at the Department of Clinical Biochemistry in the same hospital by using radioimmunoassays (Elecsys, Roche, Germany). Four groups were identified according to vitamin D levels, normal ≥ 30 ng/ml, insufficiency 20–30 ng/ml, deficiency 10–20 ng/ml, severe deficiency ≤ 10 ng/ml were set up [12]. The alkaline phosphatase (ALP), serum adjusted calcium (Ca), phosphorus (P), C-reactive protein (CRP) were also measured. Radiographs of the pelvis (anterior- posterior view) and MRI /CT scan of sacroiliac joints were obtained from all axSpA patients.

Bone Mineral Density (BMD) measurement

BMD of total proximal femur and lumbar spine were measured by using DEXA (Hologic QDR-4500A dual-energy X-ray). The instrument was calibrated before daily measurement with coefficient of variation control in 0.48%-0.51%. According to World Health Organization (WHO) classification and April 2014 National Osteoporosis Foundation (NOF) released Clinician's guidelines for the prevention and treatment of osteoporosis, measurement results for non-menopausal women and young men (Age<50 years) using Z-Score represent, postmenopausal women or elderly men (age ≥ 50 years) using the T-Score represent. Osteopenia was defined as a T-score (or Z-score) between −1 and −2.5 and osteoporosis as a T-score (or Z-score) ≤−2.5 [12].

Questionnaires

Recruitment questionnaire ascertained average daily sun exposure, dairy consumption, countryside or city living, smoking or non-smoking, indoor or outdoor working environment, calcium and vitamin D tablet consumption. The IOF (International Osteoporosis Foundation) one minute risk test was also completed for each participant.

Statistical analysis

Statistical analysis was performed with SPSS 19.0 software (SPSS, Chicago, IL, USA). The Shapiro-Wilk test was used for the normality of continuous variables. Results were expressed as mean ± SD or median (range) for normally distributed and non-normally distributed data, respectively. Independent samples t test, Mann Whitney U test, and Chi-Square test were used to compare differences in characteristics between groups. Pearson's and Spearman's correlation coefficients were used as appropriate to analyze the relationship between vitamin D, BMD, clinical measures of disease activity, and bone turnover biomarkers for parametric and nonparametric data respectively. P values ≤ 0.05 were considered statistically significant.

Results

Characteristics of axSpA patients and healthy controls

Patients and controls were well matched for age, gender and daily sun exposure time in two groups. 71(83%)of axSpA patients were HLA-B27 positive with a wide variety of disease duration (median date: 3.0, 0.25~20 years). The disease activity ASDAS-CRP were with median scores 2.28, (0.11~5.95), and CRP with median value 5.2, (0.2~99.1) mg/L. The bone resorption biomarker sCTX , formation markers OC and ALP in axSpA patients were significantly higher than controls (Table 1). Though no significant difference was observed between the two groups, there were lower adjusted calcium, and phosphorus and raised PTH in axSpA patients than control (Table 1).

Variables	axSpA (n=95)	Control (n=74)	P value
Age (years)	29 (18~55)	29.5 (18~52)	0.487
Gender (male) (n%)	69 (73	50 (68)	0.474
BMI (kg/m^2)	21.71 ± 3.27	22.89 ± 2.96	0.009
	21.15 (15.62~30.55)	22.77 (17.01~31.14)	
Sun exposure time (n%)	3 (1~4)	3 (1~4)	
5 minutes/daily	11 (11.6)	6 (8)	0.813
10~30 minutes/daily	29 (30.5)	25 (35)	
30~60 minutes/daily	24 (25.3)	16 (22)	
>1 hour /daily	31 (32.6)	25 (35)	

25OHD (ng/ml)	25.1 ± 10.1	34.9 ± 12.6	0.00
PTH (pg/ml)	27.4 (3~101)	25.0 (3~76.6)	0.129
Adjusted Calcium (mmol/L)	2.26 ± 0.12	2.22 ± 0.23	0.2
Phosphate (mmol/L)	1.20 ± 0.19	1.21 ± 0.15	0.888
sCTX (ng/ml)	0.57 ± 0.20 (0.55, 0.13~0.98)	0.43 ± 0.19 (0.37, 0.15~1.13)	0.00
OC (ng/ml)	22.65 (7~51)	18.43 (10~45)	0.018
ALP (U/L)	76.5 (39~165)	63 (32~145)	0.011
P1NP(ug/L)	50.92 (21.2~139.2)	47.86 (22.3~99.9)	0.154
Femoral BMD T-score	-1.10 ± 0.90	-0.52 ± 0.89	0.00
Femoral BMD Z-score	-0.93 ± 0.95	-0.33 ± 0.93	0.00

Table 1: Characteristics of the axSpA and healthy controls study population. axSpA: Axial Spondyloarthritis; BMD: Bone Mineral Density; PTH: Parathyroid Hormone; ALP: Alkaline Phosphatase; P1NP: N-amino terminal propeptide of type I collagen; CTX: CrossLaps of type I collagen cross-linked C-telopeptide; OC: Osteocalcin; LS: Lumber Spine.

Vitamin D levels in axSpA patients and controls

Vitamin D levels in axSpA patients were significantly lower than the control group ($p<0.001$). However there were no significant differences with serum calcium, phosphorus and PTH between two groups (Table 2).

25(OH)D	Normal	Inefficiency	Deficiency	Serious deficiency	P
axSpAn,%	26 (28%)	34 (36%)	30 (32%)	4 (4%)	0
Controls (n,%)	45 (61%)	20 (27%	811%	1 (1%	

Table 2: Vitamin D Levels in axSpA patients and Controls. According to vitamin D level, normal ≥ 30 ng/ml, insufficiency 20–30 ng/ml, deficiency 10–20 ng/ml, Severe deficiency ≤ 10 ng/ml. p value <0.05 statistically significant.

Femoral BMD T-scores in axSpA patients and controls

There were higher proportions of osteopenia and osteoporosis in axSpA patients than controls. The femoral neck T and Z scores in axSpA patients were significantly lower than in control (Table 3).

Femoral BMD T-scores	Normal	Osteopenia	Osteoporosis	P
axSpAn,%	44 (51%)	34 (40%)	8(9%)	0
Controln,%	51 (74%)	18(26%)	0	

Table 3: Femoral BMD T score in axSpA patients and Controls. Normal : T-score ≥-1.0; Osteopenia: T-score between −1.0 and −2.5; Osteoporosis: T-score ≤−2.5.

Correlation between femoral BMD T-scores and other variables in axSpA patients

The femoral BMD T-scores were inversely correlated to the disease duration, ASDAS-CRP, spinal stiffness and ALP (Table 4).

	Femoral BMD Z-scoreA							Lumbar BMD Z-scoreB						
	ASDAS	CRP	ESR	ALP	sCTX	BMI	Spinal stiffness	ASDAS	CRP	ESR	ALP	sCTX	Spinal stiffness	Spinal pain
r	-0.267	-0.299	-0.446	-0.332	-0.26	0.415	-0.218	-0.312	-0.295	-0.504	-0.32	-0.242	-0.29	-0.235
P	0.015	0.006	0.008	0.039	0.017	0	0.048	0.01	0.015	0.005	0.065	0.046	0.017	0.054

Table 4: Correlation between femoral BMD Z-scores, Lumbar BMD Z-scores and other variables in axSpA patients. A: The correlation between femoral BMDZ-scores and ASDAS, CRP, ESR, ALP, sCTX, Spinal stiffness; B: The correlation between lumbar BMD Z-scores and ASDAS, CRP,ESR, ALP, sCTX, BMD, spinal stiffness, back pain; r: correlation coefficient.

Correlation between vitamin D and other disease variables

In axSpA patients vitamin D levels were inversely related to the disease duration (Figure 1A) and positively correlated to daily sunlight exposure time and calcium levels (Figures 1B and 1C).

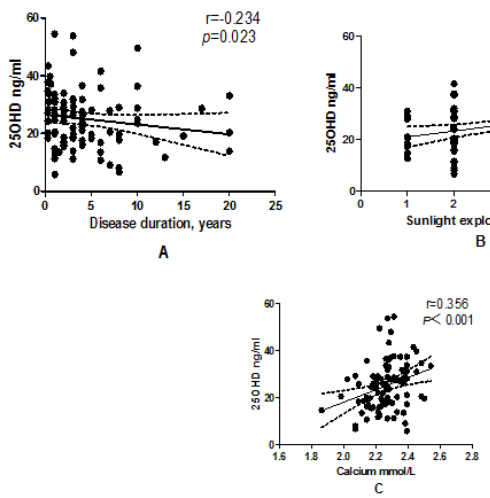

Figure 1: Correlation between vitamin D and other disease variables. 1. A: The 25(OH)D levels were inversely related to disease duration. 1. B: and positively related to daily sunlight exposure time. 1. C: calcium levels Daily sunlight exposure time 1 (5 minutes/daily), 2 (10~30 minutes/daily), 3 (30~60 minutes/daily), 4(1 hour/daily).

Correlations between serum LP and disease activity, bone biomarkers, BMD in axSpA patients

The Spearman Rank correlation test demonstrated that ALP levels significantly correlated with ASDAS-CRP (r=0.348; p=0.022), OC (r=0.351; p=0.021), sCTX (r=0.308; p=0.04), however, inversely related to the femoral BMD T-scores (r=-0.379; p=0.016) in axSpA patients (Table 5).

Variables	r coefficients	P value
ASDAS	0.348	0.022
OC	0.351	0.021
sCTX	0.308	0.04
Femoral BMD Z-scores	-0.379	0.016

Table 5: Correlation between ALP and disease activity, bone biomarkers, BMD in axSpA patients. ASAS-endorsed disease activity score (ASDAS), osteocalcin (OC), serum C-telopeptides of type collagen (sCTX) were significantly positively correlated whereas femoral BMD Z-score was negatively correlated in axSpA patients.

Discussion

For over 100 years predisposing factors to osteomalacia and rickets has been known, however, there are very few studies of the effects of low serum 25OHD levels in AS patient symptoms with bone metabolism, biochemistry and bone structure suggestive of osteomalacia [5]. Rheumatic diseases including AS, rheumatoid arthritis, Sjogren's syndrome, systemic lupus erythematosus, the mild and early phases of osteomalacia might be misdiagnosed and overwhelmed with osteopenia and osteoporosis [1,13,14]. A large extent of epidemiological data also reveals very low levels of 25(OH)D<25 nmol/L in Chinese populations, particularly Nanjing (north latitude 31) during winter and in Beijing (north latitude 40) during autumn [15]. Furthermore, another recent cross-sectional study also describes vitamin D deficiency is prevalent across many urban Beijing residents during winter and spring [16]. Based on these studies we can presume that Vitamin D deficiency is widespread in the Chinese population if individuals are not taking vitamin D-fortified supplements or are lacking of sufficient sunshine exposure. Evidence also showed that patients with vitamin D deficiency may have an increased risk of immune-mediated inflammatory diseases including AS [3], with further inflammatory activity in SpA patients indirectly linked with vitamin D deficiency and predisposition to the development of osteoporosis, which can be considered as early phase of osteomalacia. Furthermore, some studies also revealed that low plasma levels of serum 25(OH)D were presented in AS patients when compared to healthy control [5,17]. Our study showed 25(OH)D was significantly lower in axSpA patients (25.06 ± 10.06 ng/ml) compared to borderline to the normal level (34.90 ± 12.57 ng/ml) in the control group, consistent with the previous study of Baskan et al. [18]. Nonetheless, in our axSpA patients serum 25(OH)D levels found normal levels in 26 (28%), insufficient in 34 (36%), and deficient in 30 (32%) and severely deficient in 4 (4%) compared with a distribution in healthy controls of 45 (61%), 20 (27%), 8 (11%) and 1 (1%) respectively. In addition, we found no significant statistically differences with age groups, consistent with previous study [5]. Taken together, aforementioned data suggests that Vitamin D insufficiency is present in axSpA patients from Xiamen, south China (north latitude 30).

Osteomalacia is not a rare disease. Its importance has increased because of the rising incidence of vitamin D deficiency, and is prone to be missed if just serum calcium is utilized for screening [19]. Although osteomalacia has largely been eradicated in developed countries through standard fortification of various food stuffs including milk and products such as margarine and sun exposure time, food plays a vital role in the pathogenesis of osteomalacia and its silent burden in society [20]. The primary cause of osteomalacia is inadequate vitamin D due to reduced exposure to sunlight. However, it may also be due to other factors such as poor nutrition, malabsorption, chronic liver diseases and phosphate deficiency [19]. In our study, even though there were no significant differences in sunlight exposure between axSpA patients and controls, 25OHD levels of axSpA patients had significantly decreased than control and had closer relationship with sunshine time (Figure 1). It may be due to insufficient amount of sunlight exposure in Xiamen, south China (north latitude 30). Interestingly, there were no significant difference of milk intake and working environment (indoor/outdoor) between patients and controls, inadequate sunlight exposure and vitamin D deficiency in axSpA patients may be important reasons for development of subclinical osteomalacia.

Recent bone biopsy studies from Germany have shown that as 25OHD levels falling below 30 ng/ml suggests rising prevalence of osteomalacia [21]. Furthermore, hypovitaminosis D can lead to hypocalcaemia and then elevated PTH level. Nonetheless, low vitamin D is a poor indicator of osteomalacia [22]. However, in the early phases of osteomalacia biochemicals such as calcium, phosphate and soluble phosphatase are released in serum because of a low 25(OH)D level may be lacking due to compensatory changes conversely the PTH may be lifted and it lead to decalcification of the skeleton [23]. AS patients are associated with low vitamin D in serum concentrations are linked with higher disease activity [3,24]. Although vitamin D concentrations were not associated with higher disease activity in our study, vitamin D levels were significantly lower in axSpA patients. Furthermore, AS patients with osteoporosis it has been shown that the levels of PTH are significantly elevated [18]. In our study axSpA patients serum level of PTH was elevated but not significantly different when compared with healthy control. However, vitamin D levels were inversely related to the disease duration and levels of PTH (Figure 1), which may be due to alteration in vitamin D metabolism and increased bone resorption of prolonged duration. The hypovitaminosis D complicated by secondary hyperparathyroidism is associated with significantly decreased bone mineral density [25].

The accurate method of detecting osteopenia and osteoporosis may be provided by the measurement of BMD at the femoral neck [26]. Low BMD indicative of osteoporosis may be detected in up to 70% of patients with osteomalacia and histologically 40% evidence with femoral fracture [1,27]. In the elderly with osteomalacia, the decrease of BMD might be a result of a related osteoporosis, but, severe bone pain and unexpected low BMD, in the middle aged and young could be due to osteomalacia [1,21]. Despite the most solid analytic test for osteomalacia is the bone biopsy, Cosman et al. have demonstrated, two decades ago, that significant correlations between histological estimation BMD of the spine and proximal femur in patients with different metabolic bone diseases including osteomalacia [28]. Intriguingly, in our axSpA patients the frequencies of osteopenia and osteoporosis were significantly higher than controls (40% *vs* 26%, and

9% *vs* 0) respectively. Consistently, Karberg et al. found that the proportion of osteoporotic patients varies according to the disease duration of AS. In patients with disease duration <5 years, 11% and 15% were osteoporotic at the hip; in patients with disease duration >10 years, 29% were osteoporotic at the hip is assessed by DXA scan [7,29]. Previous study showed that serum bone formation marker OC and resorption markers sCTX seem to be valuable markers to detect bone loss in AS patients [30]. Interestingly our axSpA patients' serum level of OC and sCTX was significantly increased when compared to healthy control. Besides BMD T/Z-score has significant differences between axSpA patients and healthy control group, furthermore, axSPA patients femoral and lumbar BMD Z-scores were negatively correlated with active inflammatory marker such as CRP, ESR and disease activity ASDAS, bone turnover marker sCTX and OC (Table 4). Consistently, the acute phase reactant ESR and CRP was significantly elevated and inversely correlated with vitamin D levels in AS patients [18,24], disease activity ASDAS was negatively correlated with BMD because of vitamin D receptor gene may contribute to BMD differences in patients with AS, as gene polymorphisms are also linked to inflammatory activity [31]. Thus, osteoporotic risk may be significantly increased with raised serum levels of bone turnover markers and low levels of vitamin D. Previous study also have shown that the relationship between vitamin D with CRP and ESR, were significantly negatively correlated [32]. In addition, axSpA patients femoral BMD T/Z-score was negatively correlated with ALP, spinal stiffness and BMI. Furthermore, previous study found that serum alkaline phosphates is a sensitive screening tool for the diagnosis of osteomalacia [20]. Hence, these parameters may specify the reasons of early bone loss in axSpA patients and potential immunomodulatory role of vitamin D to prevent osteomalcia in axSpA during active disease condition. In our observational study, axSpA patients had shown lower 25(OH)D levels below 30 ng/ml and higher bone turnover biomarkers than control and net effects of 25(OH)D on bone structure BMD in axSpA are due to vitamin D deficiency and disease activities.

Recently, the evidence also marked that the disease activity, low BMD and serum levels of ALP are correlated in axSpA patients and ALP was independently associated with ASDAS-CRP [33]. Plasma ALP activity appears to be a sensitive single test in the past which acceptably predicts the presence or absence of histological osteomalacia [34]. Furthermore, previous research has shown that in immigrant Asian populations clinical, biochemical and radiological studies estimated that 5 to 30% of children and adult women have overt rickets or osteomalacia, whereas up to 74% of children and 53% of adults have some sort of biochemical abnormalities that favors the development of rickets or osteomalacia [35,36]. We found that the ALP levels were significantly correlated with ASDAS-CRP and bone turnover biomarkers and increased serum ALP levels were associated with high disease activity, low BMD and higher structural damage scores in axSpA patients. Serum ALP levels is not only reflects the disease activity but also associated with BMD. Our finding is consistent with an earlier result, however, bone turn over markers such as sCTX were not associated with disease activity or BMD [33]. Serum ALP levels may be a useful marker for predicting bone-related complications such as osteomalacia in axSpA patients. Interestingly, our current study also found that the plasma levels of vitamin D in the axSpA group were significantly lower than control group. Bone resorption biomarker sCTX, bone formation markers OC and ALP were significantly higher in axSpA group than controls. Furthermore, in axSpA patients vitamin D levels were inversely related to the disease duration and positively correlated to daily sunlight exposure time and calcium levels. Consistently, ALP levels significantly correlated with ASDAS-CRP, OC, sCTX), inversely related to the femoral BMD T-scores in axSpA patients. Taken together, our data indicate that low Vitamin D levels may lead to subclinical osteomalacia in axSpA patients which is associated with increased PTH and ALP levels, higher bone turnover biomarkers sCTX and OC, low BMD. This evidence shows that of axSpA patients may be associated with high rate of development of subclinical osteomalacia

Limitations

Limitations of this study are the small number of patients of axSPA. Although, all recruited cases in our study were diagnosed cases of axSPA without any infection and other bone diseases history. We did not perform bone biopsy to confirm the chemical osteomalacia. Low levels of vitamin D can also be found in other conditions including acute myocardial infarction, heart failure, chronic kidney disease, diabetes and infections [2,37]. However, these conditions are unlikely to be developed in axSpA patients and no evidence was found in our cases.

Conclusion

There were significantly lower vitamin D levels in Chinese axSpA patients compared to a control group. Vitamin D insufficiency exists in Chinese southern Han population. axSpA patients with low vitamin D, increased PTH and serum ALP levels, higher bone turnover biomarkers sCTX and OC, low BMD indicated that subclinical biochemical osteomalacia associated with most axSpA patients.

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