

# Risk factors associated with osteoporosis and fracture in psoriatic arthritis

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## Abstract

**Background:** Although there are few studies mentioned there may be some relationship between psoriatic arthritis (PsA) and osteoporosis, clinical data in real world still need to be clarified in China. The aim of this study was to assess the areal and volumetric bone mineral density (BMD), frequency of fracture, and risk factors in patients with PsA.

**Methods:** A total of one hundred PsA patients who visited Peking University First Hospital and one hundred age- and sex-matched healthy controls with DXA data were enrolled in the study. Patients with clinical fractures confirmed by X-ray during follow-up were also recorded. Clinical characteristics of the patients were recorded and compared between the abnormal BMD group and the normal BMD group, as well as between the fracture and non-fracture groups. Risk factors for fracture and low BMD were analyzed.

**Results:** Mean BMD at the total hip and femoral neck was significantly lower in PsA patients than that in healthy controls ( $0.809 \pm 0.193$  vs.  $0.901 \pm 0.152$  g/cm<sup>2</sup>,  $P = 0.041$ ;  $0.780 \pm 0.146$  vs.  $0.865 \pm 0.166$  g/cm<sup>2</sup>,  $P = 0.037$ , respectively). Moreover, lumbar spine BMD was negatively correlated with psoriasis duration, swollen joint count and DAS28-CRP ( $r = -0.503, -0.580, -0.438$ ;  $P < 0.05$ ). Total hip BMD and femoral neck BMD were negatively correlated with HAQ ( $r = -0.521, -0.335$ ;  $P < 0.05$ ). Fractures occurred in 29 patients during the follow-up period. Logistic regression analysis showed that older age (OR 1.132 [95% CI: 1.026–1.248],  $P < 0.05$ ), higher HAQ score (OR 1.493, 95% CI: 1.214–1.836,  $P < 0.01$ ), higher disease activity index for psoriatic arthritis (OR 1.033, 95% CI: 1.002–1.679,  $P < 0.05$ ) and hip joint involvement (OR 6.401, 95% CI: 4.012–44.180,  $P < 0.05$ ) were risk factors for fracture in the multivariate model.

**Conclusions:** Increased risks of osteoporosis and fracture were found in PsA patients compared to healthy controls. Besides age, high disease activity and hip joint involvement were risk factors for decreased BMD and fracture.

**Keywords:** Psoriatic Arthritis; Osteoporosis; Fracture; Risk factors

## Introduction

The prevalence of psoriasis (PsO) is estimated to be 1% to 3% of the worldwide population.<sup>[1]</sup> Further, psoriatic arthritis (PsA), the most prevalent comorbidity of psoriasis, develops in 19.7% of the global population and in 14% of Asian patients with psoriasis.<sup>[2]</sup>

The skeletal presentations of PsA are diverse, with spinal manifestations resembling ankylosing spondylitis and destructive characteristics of peripheral joints resembling rheumatoid arthritis.<sup>[3]</sup> With the improvement in molecular biology and immunopathology, abnormal bone remodeling discovered in experimental, and clinical research has focused on PsA.<sup>[4]</sup>

Osteoporosis is a systemic skeletal disease characterized by bone loss and microarchitectural damage. A possible link

between PsA and osteoporosis was initially proposed in a cross-sectional study by Frediani *et al.*<sup>[5]</sup> In this study, demineralization was observed in more than two thirds of PsA patients without axial involvement. Demineralization was not related to the indices of inflammation or disease duration, but correlated with the Health Assessment Questionnaire (HAQ) score, age, and years since menopause.<sup>[5]</sup> Nevertheless, further evidence based on the small number of patients demonstrated that PsA can lead to bone loss (such as erosion) and bone formation (such as ankylosing spondylitis), which may contribute to the difficulty in uncovering the role of osteoporosis in PsA.<sup>[6,7]</sup>

Although bone health was not included in the guidelines on psoriatic comorbidities,<sup>[8]</sup> some recent studies have shown that patients with PsA have an increased risk of osteoporosis.<sup>[9]</sup> A recent systematic review and meta-analysis showed that patients with psoriatic disease are more likely to develop fractures than non-psoriatic

## Access this article online

Quick Response Code:



Website:

www.cmj.org

DOI:

10.1097/CM9.0000000000001810

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Chinese Medical Journal 2021;134(21)

Received: 22-06-2021 Edited by: Li-Shao Guo

controls, and the high risk of fracture may not be associated with lower bone mineral density (BMD) or a higher risk of osteoporosis.<sup>[10]</sup> Fragility fractures are a potential cause of severe disability and increased mortality risk. However, whether PsA is a risk factor for osteoporosis and fracture remains debatable.<sup>[11]</sup> A couple of previous studies proposed that the association was partially interfered with by treatment such as disease modified anti-rheumatic drugs (DMARDs).<sup>[12,13]</sup> So far, many questions need to be answered, such as whether PsA patients should be routinely screened for low BMD and whether proper management should be provided to reduce the risk of fracture, especially in treatment-naïve patients. Therefore, we set out to address these issues by analyzing osteoporosis, fracture, and risk factors in our cohort of PsA patients.

## Methods

### Ethical approval

This study was approved by the Clinical Research Ethics Committees of Peking University First Hospital (No. 2019-267). The study was conducted in accordance with the *Declaration of Helsinki*. The entire research scheme was explained in detail to each participant, and written informed consent was obtained.

### Population and study design

PsA patients were consecutively recruited between January 2008 and January 2021 from the Rheumatology and Clinical Immunology Department, Peking University First Hospital. Patients with active disease were regularly followed up every 1 to 3 months, while patients with stable disease were followed up every 3 to 6 months. Clinical characteristics, serological tests, and BMD results were recorded at baseline, and disease activity scores were recorded at each follow-up time point.

The inclusion criteria were as follows: > 18 years of age; fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR);<sup>[14]</sup> with dual-energy X-ray absorptiometry (DXA) data at the first visit to our clinic. Patients with any of the following conditions were excluded: (1) axial joint involvement; (2) known prevalent metabolic bone diseases such as hyperthyroidism, hyperparathyroidism, or hypogonadism; (3) other rheumatic diseases; (4) malignancy; (5) liver or renal disease (serum alkaline phosphatase, gamma-glutamyl trans-peptidase, alanine or aspartate aminotransferase, urea, creatinine, and lactate dehydrogenase twice the upper limit of normal) (6) history of fragility fracture prior to PsA diagnosis.

Age- and sex-matched healthy controls were identified by our hospital staff. To identify the risk factors for reduced BMD, we divided patients with PsA according to their BMD parameters.

### Data collection

#### Demographics and fracture assessment

The following data were collected: age, sex, weight, height, body mass index (BMI), duration of psoriasis, PsA

duration, and symptomatic fragility fracture. Menopause was defined as amenorrhea for at least one complete year. Only low-trauma fractures arising from trauma that would not normally be expected to result in fracture, such as a fall from less than or equal to a standing height, were recorded. The duration of PsA was defined as the time between PsA diagnosis and recruitment in this study.

### Evaluation of PsA disease activity

Physical examination included tender joint count (TJC) and swollen joint count (SJC) based on 66 joints, psoriasis area and severity index (PASI),<sup>[15]</sup> patient global assessment (PGA), evaluator global assessment (EGA), and HAQ.<sup>[16]</sup> Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were recorded. Disease Activity scores-28 (DAS28)<sup>[17]</sup> and disease activity index for psoriatic arthritis (DAPSA)<sup>[18]</sup> were calculated to assess disease activity.

### Bone density measurements

BMD measurements of the lumbar spine (L1–L4), left femoral neck, and total hip using DXA (XR-800, Norland, WI, USA) were used in this study. All DXA scans were performed by an experienced technician. As for the variability of BMD, the *in vitro* coefficient of variance was 0.9% for the spine, 0.8% for L1 to L4 measurements, 1.1% for left femoral neck and 0.8% for total hip. Descriptive statistics were used to summarize the BMD of spine, left femoral neck, and total hip.

T score (comparison with normal, young subjects of the same sex) and Z score (comparison with age-, sex-, and weight-matched controls) were based on the reference values in the DXA machine, expressed as standard deviations (SD). The WHO definition was applied for osteoporosis (T score < -2.5 SD), osteopenia (T score > -2.5 and < -1.0 SD), and normal BMD (T score > -1.0 SD) for female patients and male patients aged over 50 years. The Z score was used in male patients younger than 50 years, and osteopenia was defined as a Z score < -2.<sup>[19]</sup>

### Statistical analysis

The mean  $\pm$  SD and median (interquartile range) were used to prescribe normally and non-normally distributed data, respectively. Student's *t* test and the chi-squared ( $\chi^2$ ) test were conducted to compare the means and proportions of each group. Comparisons between more than two groups were performed using a one-way analysis of variance. Pearson correlation coefficients were used to describe the associations between the clinical characteristics and BMD variables. As BMI was correlated with BMD in a previous study, we adjusted the correlation coefficient based on BMI. A multivariate logistic regression model was used to identify the risk factors for reduced BMD and fracture. Multivariate models included age, sex, menopause status, disease duration of PsO, BMI, continuous use of glucocorticoids, HAQ score, DAPSA, and hip joint involvement. To determine predictors associated with fractures in PsA patients, we constructed multivariate logistic regression models using stepwise selection

(alpha = 0.05) with diagnosis of clinical fracture as the dependent variable and nine independent variables.

All statistical tests were two-tailed, and statistical significance was defined as  $P < 0.05$ . All statistical calculations were performed using SPSS Statistics version 22 (SPSS, NY, USA).

**Results**

**Demographics and baseline characteristics**

A total of 100 patients with PsA who met the CASPAR diagnostic criteria were enrolled in this cross-sectional, age- and sex-matched case-control study. DXA scans of the lumbar spine, left hip, and femoral neck were carried out. Demographic and clinical information are shown in Table 1. PsA patients and controls were comparable with respect to age, sex, weight, height, BMI, smoking and drinking habits, and menstrual status. The use of bone protective treatments, such as vitamin D and bisphosphonates, was also balanced.

The mean age of PsA patients was  $45.9 \pm 16.9$  years, ranged from 18 to 76, with 52% patients aged over 50 years. 40 (40.0%) of them were male. The median (Q1, Q3) disease duration was 96 (10, 173) months. Topical corticosteroids were used in 51.0% (95%CI 49.5%–70.4%) of PsA patients. 30.0% (95%CI 21.3%–35.6%) of all PsA patients received oral glucocorticoids, with the median duration of 46 (20, 142) months. Only 5 (5.0%) patients had calcium and vitamin D supplementation, and none of the patients had bisphosphonates.

BMD data are presented in Table 2. There were only minor differences in BMD values from lumbar spine between PsA patients and controls, but BMD at the total hip and femoral neck were significantly lower in patients than that in controls ( $0.809 \pm 0.193$  vs.  $0.901 \pm 0.152$  g/cm<sup>2</sup>,  $P = 0.041$ ;  $0.780 \pm 0.146$  vs.  $0.865 \pm 0.166$  g/cm<sup>2</sup>,  $P = 0.037$ , respectively). Mean T or Z scores from the lumbar spine, femoral neck, and total hip were  $-1.08 \pm 1.12$ ,  $-1.21 \pm 1.20$ , and  $-1.18 \pm 1.37$  respectively. Of noted, BMD within normal range was only in 28 (28.0%) patients with PsA.

**Table 1: Clinical characteristics of all PsA patients and healthy controls.**

Parameters	PsA patients (n = 100)	Controls (n = 100)	t/χ <sup>2</sup>	P
Age (years)	45.9 ± 16.9	44.3 ± 19.2	0.828	0.564
Male	40 (40.0)	40 (40.0)	0.005	0.982
Menopausal women	48 (48.0)	42 (42.0)	0.002	0.852
Height (cm)	167.4 ± 9.2	162.2 ± 10.4	2.201	0.783
Weight (kg)	65.1 ± 12.9	61.8 ± 9.2	4.534	0.516
BMI (kg/m <sup>2</sup> )	23.2 ± 3.8	21.9 ± 3.0	6.914	0.108
Alcohol use	8 (8.0)	6 (6.0)	0.001	0.612
Smoker	21 (21.0)	10 (10.0)	0.003	0.443
Disease characteristics				
Disease duration of PsO in months	96 (10, 173)	–	–	–
Disease duration of PsA in months	10 (3, 43)	–	–	–
VAS	59 ± 25	–	–	–
PGA	58 ± 25	–	–	–
EGA	46 ± 24	–	–	–
TJC68	7.2 ± 4.6	–	–	–
SJC68	6.6 ± 5.1	–	–	–
DAS 28-ESR	5.5 ± 1.6	–	–	–
DAS 28-CRP	4.9 ± 1.5	–	–	–
DAPSA	30.1 ± 20.6	–	–	–
HAQ score	1.3 ± 0.5	–	–	–
PASI	2.6 ± 1.3	–	–	–
Acute-phase reactants				
ESR (mm/h)	57.6 ± 32.9	–	–	–
CRP (mg/L)	45.9 ± 24.3	–	–	–
Autoantibody status				
Positive low-titer ACPA	2 (2.0)	–	–	–
Positive low-titer RF	3 (3.0)	–	–	–
Treatments				
Former glucocorticoids intake	51 (51.0)	0	–	–
Current glucocorticoids	30 (30.0)	0	–	–
Duration of glucocorticoids intake (months)	46 (20, 142)	0	–	–

Data are presented as mean ± standard deviation for continuous variables or median (Q1, Q3) or n (%) for categorical variables. ACPA: Anticitrullinated protein antibody; BMI: Body mass index; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score for 28 joints; EGA: Evaluator global assessment; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; RF: Rheumatoid factor; PASI: Psoriasis area and severity index; PGA: Patient global assessment; PsA: Psoriatic arthritis; PsO: Psoriasis; SJC: Swollen joint count; TJC: Tender joint count; VAS: Visual analogue scale. –: Not applicable.

**Table 2: Bone mineral density for PsA patients and controls (g/cm<sup>2</sup>).**

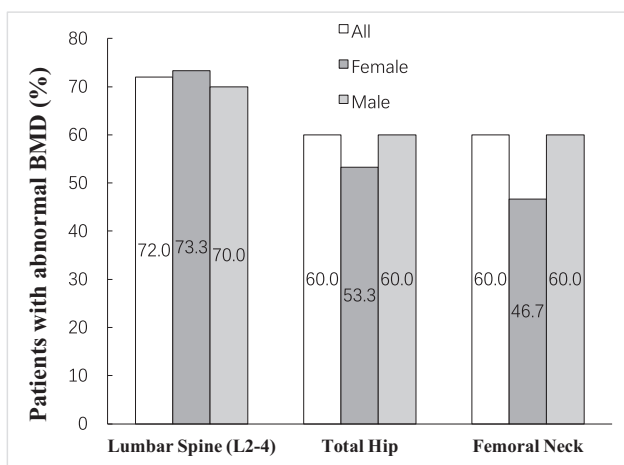
Items	PsA patients (n = 100)	Controls (n = 100)	Unadjusted P value	Adjusted P value*
Femoral neck	0.780 ± 0.146	0.865 ± 0.166	0.047	0.007
Total hip	0.809 ± 0.193	0.901 ± 0.152	0.041	0.004
Lumbar spine	0.927 ± 0.141	0.987 ± 0.136	0.836	0.032

\* P values are adjusted by body mass index. Results are mean ± standard deviation. PsA: Psoriatic arthritis.

**Table 3: BMD Z/T scores of 100 PsA patients.**

Items	BMD (g/cm <sup>2</sup> )	Patients with low BMD, n (%)	Z/T scores	Minimum Z/T scores	F	P
Lumbar spine 2–4	0.927 ± 0.141	60 (60.0)	-1.08 ± 1.12	-2.83	14.8	0.006
Site of the lumbar spine						
L2	0.916 ± 0.166	56 (56.0)	-1.28 ± 1.41	-3.12		
L3	0.936 ± 0.152	68 (68.0)	-1.39 ± 1.29	-3.11		
L4	0.904 ± 0.189	48 (48.0)	-1.20 ± 1.14	-3.21		
Total left hip	0.809 ± 0.193	72 (72.0)	-1.18 ± 1.37	-3.90		
Site of the left hip					36.2	0.001
Femoral neck	0.780 ± 0.146	70 (70.0)	-1.21 ± 1.21	-3.84		
Trochanter	0.638 ± 0.097	68 (68.0)	-1.02 ± 1.01	-2.92		
Interior	0.709 ± 0.121	70 (70.0)	-1.18 ± 1.11	-3.38		

Data are presented as mean ± standard deviation or n (%). Patients younger than 50 years use Z scores, and patients aged > 50 years use T scores. BMD: Bone mineral density; PsA: Psoriatic arthritis.



**Figure 1:** Percentage of patients with abnormal BMD in psoriatic arthritis (n = 100). BMD: bone mineral density.

The BMD values from the lumbar spine (including L2, L3, L4) and left hip (including total hip, femur neck, trochanter, and interior) of 100 patients with PsA are listed in Table 3. Based on WHO definitions,<sup>[19]</sup> 72 (72.0%) patients were diagnosed with reduced BMD (osteopenia or osteoporosis) in at least one site; among these 72 osteopenia or osteoporosis patients, 27 (27.0%) had reduced BMD at one site, 16 (16.0%) at two sites, and 12 (12.0%) at all three sites. Osteoporosis at the femoral neck, total hip and lumbar spine was more frequently observed in PsA patients, however statistically insignificant compared with controls.

The BMD Z/T scores of the lumbar spine were significantly different from those of the left hip (F = 28.2, P < 0.001).

Osteopenia in the lumbar spine, total left hip, and left femoral neck were observed in 72, 60, and 60 patients, indicating that osteopenia is more likely to occur in the lumbar region than hip in PsA patients. The frequency of osteopenia in PsA patients at different regions of interest, based on BMD measurements, is shown in [Figure 1].

**Correlation between clinical characteristics and BMD**

Univariate analysis showed that PsA patients with lower lumbar BMD were older, had longer psoriasis disease duration, higher visual analogue scale (VAS), PGA, EGA, SJC, TJC, and HAQ scores, as well as higher PASI, DAS28-ESR, DAS28-CRP, and DAPSA scores (P < 0.05 for all). Patients with lower femoral neck BMD were older, had lower BMI, longer psoriasis disease duration, higher VAS, PGA, EGA, SJC, and TJC; higher HAQ score; ESR, PASI, DAS28-ESR, DAS28-CRP, and DAPSA scores (P < 0.05 for all). PsA patients with abnormal BMD were more likely to have a longer psoriasis disease duration and more active arthritis [Table 4]. In the PsA group, lumbar spine BMD was negatively correlated with psoriasis duration, SJC and DAS28-CRP (r = -0.503, -0.580, -0.438; P < 0.05), and total hip BMD and femoral neck BMD were negatively correlated with HAQ (r = -0.521, -0.335; P < 0.05). Further information in detail is shown in Table 5.

Abnormal BMD is known to be correlated with female sex and older age.<sup>[19]</sup> Thus, we divided our PsA patients into two groups according to the median age of 50 years. Osteoporosis was more frequently observed in the ≥50 years group than that in the <50 years group based on lumbar spine BMD (48.0% vs. 24.0%, χ<sup>2</sup> = 11.87, P = 0.001). When osteoporosis was defined by left femoral BMD, there was no significant difference between age groups (32.0% vs. 28.0%, χ<sup>2</sup> = 0.43, P = 0.511).

From the aspect of systemic glucocorticoid exposure, the frequency of osteoporosis was higher in patients with glucocorticoid exposure than those without (41.0% vs. 31.0%,  $\chi^2 = 7.33, P < 0.05$ ) based on lumbar spine BMD and (33.0% vs. 27.0%,  $\chi^2 = 6.59, P < 0.01$ ) on left femoral neck BMD.

**Fracture and clinical characteristics in PsA patients**

Fragility fracture occurred in 29 PsA patients during a mean duration of 6 months (3–10 months) of follow-up, with symptomatic fragility fractures in 25 patients. Fractures were located at the hip ( $n = 12$ ), forearm ( $n = 4$ ), foot ( $n = 4$ ), and vertebrae (asymptomatic, found by radiography,  $n = 6$ ). No clinical fractures were reported in the control group.

The comparison of clinical characteristics at baseline between the 29 patients with fracture and the 71 non-fractured patients is listed in Table 6. The fracture group had a higher percentage of females, especially menopausal female patients, lower BMI, and longer disease duration of both psoriasis and PsA at baseline. When looking at the markers of disease activity, we found that VAS, PGA, EGA, SJC, TJC, and HAQ and DAPSA scores at baseline were higher in the fracture group. Patients with more peripheral arthritis and hip joint involvement had more fractures [Table 6].

Fragile fractures tended to be more frequently occurred in the group of age <50 years compared with the group of  $\geq 50$  years, although the difference was statistically insignificant (13.0% vs. 16.0%,  $\chi^2 = 2.07, P = 0.15$ ). Fragility fracture was also more often observed in patients

with current usage of glucocorticoid than those not (65.5% vs. 22.5%,  $\chi^2 = 16.7, P < 0.001$ ).

**Risk factors of abnormal BMD and fracture at baseline**

A multivariate logistic regression model was used to identify predictors for reduced BMD in PsA patients. Older age (OR 40.282, 95% CI: 1.058–33.350,  $P < 0.05$ ) and longer disease duration of psoriasis (OR 1.061, 95% CI: 1.002–1.125,  $P < 0.05$ ) were significantly associated with a higher risk of decreased BMD in the multivariate full model backward selection method, while other factors, such as more inflamed joint counts, higher serum acute reactant, or higher disease activity score were not associated with reduced BMD.

As for factors associated with fractures, multivariate logistic regression analysis showed that older age (OR 1.323, 95% CI: 1.026–1.248,  $P < 0.05$ ), higher HAQ score (OR 1.493, 95% CI: 1.214–1.836,  $P < 0.01$ ), hip joint involvement (OR 6.401, 95% CI: 4.012–44.180,  $P < 0.05$ ), and higher DAPSA score (OR 1.033, 95% CI: 1.002–1.679,  $P < 0.05$ ) were significantly associated with a higher risk of fracture [Table 7].

**Discussion**

The skeleton is composed of 80% cortical bone and 20% trabecular bone, which has an elevated metabolic turnover. Osteopenia and fracture occurred in approximately 60% and 29% of patients with PsA, respectively, in our study. This is within the range of osteopenia (6.3%–61%) and osteoporosis (1.4%–68.8%) reported in previous studies in the PsA population.<sup>[20–23]</sup> Moreover, Attia

**Table 4: Clinical characteristics of abnormal BMD and normal BMD in PsA patients.**

Items	Lumbar Abnormal (n=60)	Lumbar Normal (n=40)	P value	Left hip Abnormal (n=72)	Left hip Normal (n=28)	P value
Age (years)	48.1 ± 17.9	40.1 ± 13.1	0.017	48.2 ± 12.7	44.3 ± 19.2	0.024
Height (cm)	166.8 ± 8.9	168.7 ± 10.2	0.399	165.0 ± 9.7	169.0 ± 8.7	0.041
Weight (kg)	64.0 ± 11.7	67.7 ± 15.5	0.262	62.3 ± 12.2	69.2 ± 13.0	0.008
BMI (kg/m <sup>2</sup> )	23.1 ± 4.0	23.5 ± 3.4	0.590	21.8 ± 3.5	25.3 ± 3.4	<0.001
Duration of PsO (months)	134.5 ± 96.1	51.9 ± 39.6	0.004	142.8 ± 58.7	64.1 ± 47.0	0.003
Duration of PsA (months)	33.5 ± 60.0	33.4 ± 41.4	0.994	40.9 ± 28.6	22.4 ± 20.0	0.101
VAS	59.7 ± 24.8	55.7 ± 24.8	<0.001	63.3 ± 25.6	51.5 ± 21.9	0.019
PGA	59.4 ± 24.9	54.3 ± 24.9	<0.001	62.7 ± 25.8	51.0 ± 21.9	0.021
EGA	49.2 ± 26.0	37.1 ± 18.6	0.020	52.8 ± 25.3	35.3 ± 19.7	<0.001
TJC68	8.6 ± 4.5	3.7 ± 2.8	<0.001	9.3 ± 8.4	4.8 ± 4.0	0.001
SJC68	8.3 ± 4.0	2.6 ± 1.2	<0.001	8.7 ± 9.1	3.6 ± 4.9	<0.001
DAS 28-ESR	5.8 ± 1.7	4.7 ± 1.2	0.001	6.0 ± 1.4	4.6 ± 1.4	<0.001
DAS 28-CRP	5.2 ± 1.6	4.3 ± 1.0	0.002	5.4 ± 1.5	4.3 ± 1.3	<0.001
DAPSA	33.3 ± 22.7	21.9 ± 10.4	0.001	35.2 ± 20.7	22.4 ± 18.0	0.002
HAQ score	27.5 ± 8.6	21.3 ± 10.3	0.003	29.9 ± 8.02	19.7 ± 8.1	<0.001
PASI	2.8 ± 1.5	2.1 ± 0.3	<0.001	2.9 ± 1.4	2.2 ± 1.1	0.013
ESR (mm/h)	59.1 ± 26.9	53.9 ± 45.2	0.476	65.6 ± 31.4	45.7 ± 31.8	0.003
CRP (mg/L)	45.8 ± 22.8	46.1 ± 28.8	0.976	46.2 ± 34.7	45.5 ± 56.3	0.949

BMD: Bone mineral density; BMI: Body mass index; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score for 28 joints; EGA: Evaluator global assessment; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; PASI: Psoriasis area and severity index; PGA: Patient global assessment; PsA: Psoriatic arthritis; PsO: Psoriasis; SJC: Swollen joint count; TJC: Tender joint count; VAS: Visual analogue scale.

**Table 5: Correlation coefficients between clinical characteristics and abnormal BMD in PsA patients (n = 100).**

BMD	Age	PsO	Duration PsA	Duration	HAQ	TJC	SJC	ESR	CRP	PGA	EGA	DAS28	CRP	DAPSA
Lumbar spine	-0.446*	-0.503*	-0.278*	-0.386*	-0.438*	-0.580*	-0.154*	-0.046*	-0.286*	-0.269*	-0.438*	-0.465*		
Total hip	-0.308*	-0.308*	-0.236*	-0.521*	-0.303*	-0.380*	-0.093	-0.140	-0.174	-0.251*	-0.310*	-0.479*		
Femoral Neck	-0.254*	-0.258*	-0.169	-0.335*	-0.126	-0.244*	-0.052	0.032	-0.253*	-0.241	-0.198	-0.194*		

R is correlation coefficient. \* P < 0.05. BMD: Bone mineral density; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score for 28 joints; EGA: Evaluator global assessment; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; PGA: Patient global assessment; PsA: Psoriatic arthritis; PsO: Psoriasis; SJC: Swollen joint count; TJC: Tender joint count.

**Table 6: Demographic characteristics by presence of fracture.**

Items	Fracture patients (n = 29)	Non-fracture patients (n = 71)	P values
Age (years)	41.1 ± 17.1	47.8 ± 16.6	0.070
Female, n (%) (n = 60)	13 (44.8)	47 (66.2)	0.040
Menopausal women, n (%)	13 (21.7)	35 (58.3)	0.040
Disease duration of PsO (months)	189.9 ± 84.9	77.6 ± 45.8	0.004
Disease duration of PsA (months)	42.2 ± 21.2	22.0 ± 15.2	0.072
Height (cm)	170.3 ± 8.6	166.1 ± 9.3	0.140
Weight (kg)	64.7 ± 16.6	65.2 ± 11.2	0.870
BMI (kg/m <sup>2</sup> )	22.2 ± 4.5	23.6 ± 3.5	0.030
Alcohol use, n (%)	4 (13.8)	4 (5.6)	0.172
Smoker, n (%)	5 (17.2)	16 (22.5)	0.555
Multiple peripheral arthritis, n (%)	24 (82.8)	27 (38.0)	<0.001
Hip joint involvement, n (%)	19 (65.5)	8 (11.3)	<0.001
TJC68	12.7 ± 6.3	5.8 ± 3.7	0.003
SJC68	14.2 ± 7.7	4.1 ± 2.1	0.001
VAS	72.1 ± 12.9	53.0 ± 26.3	<0.001
PGA	71.1 ± 13.2	52.2 ± 24.2	<0.001
EGA	60.7 ± 14.3	39.3 ± 25.2	<0.001
DAS 28-ESR	6.5 ± 1.1	5.0 ± 1.6	0.001
DAS 28-CRP	6.0 ± 1.3	4.5 ± 1.4	0.001
DAPSA>28	43.4 ± 19.6	24.6 ± 18.5	0.001
HAQ score	33.5 ± 7.2	22.0 ± 8.5	0.001
PASI	2.7 ± 1.4	2.6 ± 1.4	0.729
ESR (mm/h)	61.1 ± 18.6	55.4 ± 37.8	0.030
CRP (mg/L)	53.1 ± 35.5	42.1 ± 27.5	0.023
Continuous glucocorticoids intake, n (%)	24 (82.8)	26 (36.6)	0.001
Current glucocorticoids, n (%)	19 (65.5)	16 (22.5)	

Multiple peripheral arthritis: more than 5 joints involved. Continuous glucocorticoids intake: more than 3 months. BMI: Body mass index; CRP: C-reactive protein; DAPSA: Disease Activity Index for Psoriatic Arthritis; DAS28: Disease activity score for 28 joints; EGA: Evaluator global assessment; ESR: Erythrocyte sedimentation rate; HAQ: Health Assessment Questionnaire; PASI: Psoriasis area and severity index; PGA: Patient global assessment; PsA: Psoriatic arthritis; PsO: Psoriasis; SJC: Swollen joint count; TJC: Tender joint count; VAS: Visual analogue scale.

showed that psoriatic patients had significantly lower BMD T and Z scores at the spine and femoral neck regardless of presence of arthritis or not.<sup>[21]</sup> PsA patients had significantly lower T and Z scores from the femoral neck and wrist than patients with psoriasis without arthritis.<sup>[21]</sup> Published data for PsA patients are scarce. Three studies compared the ability of DXA of the spine versus hip to distinguish between patients with PsA and controls, but the results were inconsistent.<sup>[5,24,25]</sup> In patients with PsA, no correlation was observed between DXA detected BMD the spine or hip with disease duration<sup>[24]</sup> or disease activity.<sup>[25]</sup> A higher vertebral fracture risk and percentage of osteoporosis in AS has been previously reported<sup>[26]</sup>; therefore, we excluded patients with PsA who had axial bone involvement at baseline.

The link between PsA and osteoporosis remains unclear. Benefiting from our PsA case dataset, we conducted a retrospective study to investigate the BMD of PsA patients. We found a high percentage of Chinese PsA patients with osteopenia, and PsA disease was somehow associated with low BMD and fracture risk.

A large cross-sectional study including 28765 PsA patients in the USA found that PsA patients had significantly higher odds of osteopenia, osteoporosis, and fractures.<sup>[27]</sup> Another Italian study in 2001 reported osteoporosis in 30% of PsA patients.<sup>[5]</sup> Afterwards, Borman *et al* reported that in psoriatic patients with peripheral arthritis had longer duration of joint disease might be a risk factor for osteoporosis.<sup>[28]</sup> Both studies were performed before biologi-

**Table 7: Predictors of fragile bone fracture by univariate and multivariate logistic analysis.**

Items	OR	Univariate 95%CI	P values	OR	Multivariate 95%CI	P values
Age	1.977	1.002–1.952	0.050	1.323	1.026–1.248	0.001
Female	2.410	0.998–5.821	0.050	–	–	–
Menopause (n = 60)	2.636	1.248–5.570	0.010	–	–	–
Disease duration of PsO	1.007	1.003–1.011	0.001	–	–	–
BMI	0.903	0.802–1.017	0.903	–	–	–
Continuous usage of glucocorticoids	6.531	2.534–16.832	0.001	–	–	–
HAQ score	1.323	1.170–1.495	0.001	1.493	1.214–1.836	<0.01
Hip joint involvement	14.962	5.174–43.266	0.001	6.401	4.012–44.18	<0.01
DAPSA	1.046	1.022–1.070	0.001	1.033	1.002 ± 1.679	<0.001

BMI: Body mass index; CI: Confidence interval; DAPSA: Disease Activity Index for Psoriatic Arthritis; HAQ: Health Assessment Questionnaire; OR: Odds ratio; PsO: Psoriasis. –: Not applicable.

cal therapy, which was similar to our current study. We also found that lower BMD and a higher proportion of osteopenia were observed in patients with PsA than in controls.

In our study, hip involvement was a key risk factor associated with fracture (OR = 6.401, 95%CI 4.012–44.180), and hip involvement was the most common fracture (14/29). The hip joint is key for maintaining body balance, especially during walking and sports. When the hip joint is involved, an abnormal gait may lead to more recurrent falls, which may be the reason behind the high incidence of fracture. Pedreira *et al* reported more fractures in PsA patients than in PsO patients in Spain, and recurrent falls also increased the risk of fracture (OR 18.3).<sup>[29]</sup> In a large cross-sectional study of osteoporosis and fracture rates in US PsO and PsA patients, both PsO and PsA were associated with fractures, with femoral (OR 2.07, 95%CI 1.85–2.32), pelvic (OR 1.75, 95%CI 1.41–2.18), tibial/fibular (OR 1.60, 95%CI 1.28–2.01), and vertebral fractures (OR 1.45, 95%CI 1.24–1.70) being the most common fracture sites.<sup>[27]</sup> Thus, focus should be placed on the risk of fracture in PsA patients in the future, especially in those with hip joint involvement and high disease activity in PsA patients.

In addition, we found that the disease activity score in PsA patients was negatively correlated with abnormal BMD, especially in patients with high DAPSA scores.<sup>[30]</sup> A previous study revealed that compared to DAS-28, DAPSA score was more correlated with patient motivation measure scores, and disease activity scores with higher motivation scores correlated significantly with better disease activity control.<sup>[28]</sup> Further studies are needed to evaluate changes in BMD during follow-up and its correlation with disease activity.

Previous studies have been shown that traditional risk factors of fracture, including older age, longer disease duration, and higher HAQ score, may be associated with a higher chance of fracture. However, newly published data showed that there is no increased risk of fractures in patients with PsA.<sup>[31]</sup> The high proportion of steroid usage and higher disease activity in our patient cohort may be the key reason for the difference in results. No previous prospective study on BMD changes have been reported yet. Further,

only 25% of patients underwent BMD measurements in a previous fracture study,<sup>[31]</sup> which is relatively low.

Multivariate analysis showed that higher disease activity, whether reflected by the DAS28 or DAPSA, was significantly associated with abnormal BMD in PsA patients. Previous studies in RA patients indicated that BMD changes have an inverse relationship with disease activity, which was assessed by DAS28, suggesting that when a permanent state of remission is achieved, BMD has better improvement.<sup>[32]</sup> Whether control of inflammation can influence BMD and fracture risk has not yet been established in PsA patients.<sup>[33]</sup> Although the follow-up period was short in our study group, the fracture rate was high (29%). In addition, the high percentage and longer usage of steroids also involved glucocorticoid-induced osteoporosis and fracture. Our results showed that PsA patients need to have BMD measurement, especially who had high disease activity score.

Fragility fracture is defined as a pathological fracture that results from low-energy insults. Fractures are believed to be associated with decreased bone strength, which reflects the integration of both bone quality and bone density. Ogdie *et al* showed that PsA was associated with an elevated risk of fracture in a population-based cohort study which included 9788 patients with PsA.<sup>[34]</sup> The increased risk was higher in men than in women, which has only previously been reported by a UK population-based study<sup>[35]</sup> however, the specific risk factors have not been elucidated before. This may be explained by the increased prevalence of risk factors for fracture in men, such as alcohol and smoking consumption, which was observed in our data. We also found that high disease activity (including pain, swelling in more joints, less physical activities, hip joint involvement, and glucocorticoid usage) might cause bone loss in patients with PsA. Inflammatory cytokines can affect the process of bone remodeling, which has been proven in PsA, spondyloarthritis, and rheumatoid arthritis, with the IL-17 family having been shown to be involved.<sup>[36]</sup> Blocking the IL-17 and TNF pathways seems to have a positive effect on the bone damage observed in inflammatory arthritis.<sup>[36]</sup> In addition, the high percentage of glucocorticoid use may be a key reason for the induction of bone loss and increased fracture. Although GC are less frequently recommended in psoriasis treatment guide-

lines,<sup>[37]</sup> the high percentage and continuous use of GC in our cohort may be one of the reasons for osteoporosis and fracture. Although GC can alleviate arthritis by inhibiting inflammation, it has a negative effect on both bone formation and bone quality. A previous retrospective study did not show fragility fractures in PsA patients treated with biologics, when compared to patients who did not present with fracture ( $P = 0.054$ ).<sup>[31]</sup> Further prospective longitudinal studies to focus on the inflammatory status and its relationship with fracture are needed. A previous study showed that methotrexate or cyclosporine may involve this relationship.<sup>[12]</sup> Further studies in DMARD- and steroid-naïve PsA patients may exclude the effect of these drugs.

Zhu *et al* found significant correlations between indices of articular disease activity and severity and indices of cortical bone density and microstructure<sup>[38]</sup> in a small group of patients with PsA. A higher level of disease activity and severity indicates a higher burden of disease inflammation. In patients with chronic inflammatory diseases, prolonged elevated levels of pro-inflammatory cytokines, such as tumor necrosis factor and interleukin-6, are known to affect bone metabolism.<sup>[39]</sup> The increased bone remodeling results in net bone loss, and ultimately osteoporosis as well as increased bone fragility. In PsA patients, the elevated bone resorption markers correlate with the levels of acute-phase reactants such as ESR and CRP in serum.<sup>[33]</sup> Being consistent with these previous findings, our results indicate that bone loss, at least in part, is related to the chronic inflammatory process in PsA.

Our study has a few limitations. First, this study was carried out in a single center, and so its conclusions should be further validated in other centers. Second, based on the small sample size and heterogeneity of the enrolled patients, the statistical power was low. Third, this is a short time follow up study, and so we could only explore the relationship between previous disease activity and abnormal BMD. Thus, further follow-up studies are needed to determine whether BMD will improve on the basis of control of disease activity. Fourth, we could not collect details of dosage and duration of oral steroid and topical dosage of steroid usage in all PsA patients. Further detailed data are needed to clarify the relationship between steroid use and fracture risk. Despite these limitations, our study provided unique insights. For example, this is the first study to investigate BMD at the lumbar spine as well as the other three anatomic sites of the femur (femoral neck, trochanter, and interior) by DXA in PsA patients. Our findings highlight the importance of paying adequate attention to prevent bone loss and provide a basis for monitoring and intervention in PsA-related bone loss.

In summary, this study suggests that patients with psoriatic disease pose a substantial public health burden with respect to their increased risk of low BMD and fractures. Further work is needed to explore the link between osteoporosis and fracture risk in patients with PsA and possible causative mechanisms.

## Conclusions

In this cohort of PsA patients, an increased risk of osteoporosis and fracture risk was found in comparison

with age- and sex-matched controls. High disease activity was correlated with lower BMD and fracture risk in patients with PsA.

## Acknowledgements

The authors would like to thank all members of the Department of Rheumatology at Peking University First Hospital for their help with data acquisition.

## Funding

This study was supported by a grant from the Clinical Project “Impact of treat to target in psoriatic arthritis patients” by the First Hospital of Peking University (No. 2019-267).

## Conflicts of interest

None.

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**How to cite this article:** Wang Y, Song ZB, Deng XR, Zhang XH, Zhang ZL. Risk factors associated with osteoporosis and fracture in psoriatic arthritis. *Chin Med J* 2021;134:2564–2572. doi: 10.1097/CM9.0000000000001810