Elevated serum Dickkopf-1 is a biomarker for bone erosion in patients with psoriatic arthritis

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Abstract

Background: Psoriatic arthritis (PsA) is an inflammatory arthropathy characterized by psoriasis and bone erosion on radiology. Dickkopf-1 (Dkk-1) is considered to be the main inhibitor of the Wnt signaling pathway and results in reduced osteoblast proliferation. The aim of this study was to investigate the serum level of Dkk-1 and its association with bone erosion in PsA patients.

Methods: Serum Dkk-1 levels were measured by enzyme-linked immunosorbent assay (ELISA) in 69 patients with PsA and 60 controls, including 39 rheumatoid arthritis (RA) patients, and 21 healthy controls (HCs). Rheumatoid factor and anti-cyclic citrullinated peptide levels were also determined by ELISA. The association of Dkk-1 level with clinical and laboratory features of PsA was analyzed. Logistic regression analysis was used to analyze the risk factors for bone erosion in PsA.

Results: Dkk-1 was elevated in 68.1% (47/69) of the patients with PsA, 46.2% (18/39) of RA patients, and 9.5% (2/21) of HCs. Serum Dkk-1 concentration was significantly higher in PsA patients compared with that in HCs. The level of serum Dkk-1 was correlated with a swollen joint count, and levels of complement components 3 and 4. Elevated Dkk-1 level (odds ratio = 4.440, 95% confidence interval: 1.246–15.817, $P = 0.021$) was identified as the risk factor for bone erosion in PsA.

Conclusions: The serum level of Dkk-1 is abnormally elevated in PsA patients. The elevation of Dkk-1 might be involved in the mechanism of bone erosion in patients with PsA.

Keywords: Dickkopf-1; Psoriatic arthritis; Bone erosion

Introduction

Psoriatic arthritis (PsA) is an autoimmune inflammatory disease characterized by peripheral arthritis, spondylitis, enthesitis, dactylitis, and skin psoriasis.[1,2] Progressive bone destruction and aberrant new bone formation can be observed over the course of PsA.[3,4] Laboratory markers in PsA are non-specific, and there is no specific autoantibody distinguishing PsA from other inflammatory arthritis conditions. Elevated inflammatory reactants can be seen in about 30% to 40% of patients with PsA, including white blood cells (WBCs), C-reactive protein (CRP), and blood sedimentation, so-called acute phase reactants that are common but not specific.[4]

The Wnt/β-catenin pathway, considered the classical Wnt signaling pathway, is essential in regulating osteoblast proliferation, maturation, differentiation, and function.[5] Dickkopf-1 (Dkk-1) is a natural inhibitory factor of the Wnt/β-catenin pathway, promoting phosphorylation and subsequent degradation of β-catenin, thereby decreasing bone-forming osteoblasts and increasing bone-resorbing osteoclasts and resulting in a bias toward bone erosion.[6,7] Dkk-1 was involved in bone erosion and inflammation in rheumatoid arthritis (RA).[8] However, the potential role of Dkk-1 in PsA patients is controversial,[9,10] and the relationship between Dkk-1 levels and pathogenesis of bone remolding in inflammatory arthritis is still uncertain.[9-11]

Thus, in our study, we detected the expression of Dkk-1 in serum of PsA patients, compared the level with those of RA and healthy controls (HCs), and analyzed the association between Dkk-1 with clinical and laboratory characteristics of PsA, focusing on its correlation with bone erosion.

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Methods

Ethics approval

This study was approved by the Ethics Committee of the Peking University People's Hospital (No. 2017PHB165-01). All subjects provided written informed consent according to the *Declaration of Helsinki*.

Patients and controls

Sixty-nine PsA patients were enrolled in this study, during the period from February 2007 to April 2020. All patients fulfilled the Classification of Psoriatic Arthritis (CASPAR) criteria for PsA.[12] Serum samples were obtained and stored at −70°C until use. In addition, control samples were taken from 39 patients who met the revised American College of Rheumatology criteria for RA and 21 HCs at the same hospital.[13]

Determination of serum Dkk-1 levels

Serum levels of Dkk-1 were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Cloud-Clone Corp., Texas, USA). Reagent and sample preparation, and assay procedure were performed following the manufacturer's instructions. Absorbance density at 450 nm wavelength was measured using an ELISA reader (Bio-Rad, Hercules, CA, USA). Dkk-1 concentrations were calculated with a standard curve.

Clinical and laboratory evaluation

We collected patients' data from medical records, including age, sex, arthritis/psoriasis duration, initial manifestation of PsA, family history, nail psoriasis, dactylitis, enthesitis, uveitis, tender joint count, swollen joint count, WBC count, hemoglobin, platelet count, erythrocyte sedimentation rate, CRP, immunoglobulins (IgA/IgG/IgM), complement components 3/4 (C3 and C4), rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP) antibody, and human leukocyte antigen-B27 (HLA-B27).

Radiographic assessments

Plain radiographic images of joints were obtained from the hospital's electronic medical records system. The modified Sharp-van der Heijde method was used to score radiographs of the hands of PsA patients noting erosion and joint space narrowing.[14] According to the CASPAR definition, pathological ossification near joint margins (excluding osteophyte formation) was identified as radiographic evidence of new bone formation. Sacroiliitis was defined as a present by New York criteria radiological manifestation: grade ≥3 if unilateral; bilateral grade ≥2 if bilateral.[15] Patients were classified as having PsA with or without the radiographic axial disease (RAD); in keeping with recent studies, the inflammatory RAD was defined as the presence of New York criteria sacroiliitis as above, and/or a number of marginal/paramarginal syndesmophytes of the spine was ≥1.[16,17] At least one bone erosion observed on radiographs was considered erosive change. All radiographs and measurements were interpreted by a trained rheumatologist and expert radiologist who were blinded to patients' information.

Statistics

Data were presented as n (percentage), mean ± standard deviation, or median (P25, P75). Statistical significance between groups was assessed with χ^2 tests, independent samples t-tests, and non-parametric tests in the case of two groups; and with χ^2 tests and one-way analysis of variance with Holm-Sidak multiple comparisons test for three groups. Pearson or Spearman rank correlation coefficients were used to exploring the relationship between Dkk-1 levels and clinical/laboratory parameters. The potential risk factors associated with bone erosion in PsA were analyzed using a logistic regression model. P values < 0.050 were considered significant. The cut-off value of Dkk-1 concentrations was determined using a receiver operating characteristic (ROC) curve.

Results

Characteristics of study participants

The major demographic, clinical and laboratory features, and radiographic evaluations are shown in Table 1. Among 69 patients with PsA, 56.5% were female, the mean age was 52.7 ± 13.0 years, mean arthritis and psoriasis duration were 5.0 (1.6, 13.0) and 12.0 (5.0, 20.0) years, and 17.4% (12/69) of them had a family history of skin psoriasis or PsA. Nail psoriasis, dactylitis, enthesitis, and uveitis were observed in 43.5%, 10.1%, 27.5%, and 2.9% of the PsA patients, respectively. Positive RF (8.7% *vs.* 79.5%, $P < 0.01$) and anti-CCP antibody (5.8% *vs.* 97.4%, $P < 0.01$) were found less frequently in PsA patients compared with RA patients. HLA-B27 was detected in 20.3% of PsA patients. Sacroiliitis on radiography was found in 46.4% (32/69) of the PsA patients. No significant differences in age, sex ratio, arthritis/psoriasis duration, tender/swollen joint count, and bone erosion were found among the groups.

Dkk-1 level was elevated in sera of patients with PsA

As shown in Figure 1, Dkk-1 was elevated in 68.1% (47/69) of the patients with PsA, 46.2% (18/39) of RA patients, and 9.5% (2/21) of HCs. Serum Dkk-1 level in PsA patients (9.269 ± 3.276 ng/mL) was significantly higher than that in patients with RA (7.862 ± 2.487 ng/mL, $t = 2.506$, $P = 0.027$) and HCs (6.250 ± 1.102 ng/mL, $t = 4.323$, $P < 0.010$). In addition, Dkk-1 was increased in RA patients compared with HCs ($t = 2.125$, $P = 0.036$).

Correlation between Dkk-1 and clinical features of PsA

The correlations between Dkk-1 and clinical features of PsA are presented in Table 2. An increased level of Dkk-1 was correlated with elevated swollen joint count ($r = 0.370$, $P < 0.010$), number of platelets ($r = -0.341$, $P < 0.010$), C3 ($r = -0.530$, $P < 0.001$), and C4 ($r = -0.354$, $P < 0.010$) [Table 2 and Figure 2].

Table 1: Characteristics of PsA patients, RA patients, and healthy controls.

Variables	PsA ($n=69$)	RA ($n=39$)	HCs ($n=21$)	$F/\chi^2/Z$	P values
Age (years)	52.7 ± 13.0	55.5 ± 12.8	50.4 ± 9.3	1.270*	0.285
Female/male (n)	39/30	25/14	12/9	0.624†	0.732
Duration of arthritis (years)	5.0 (1.6, 13.0)	9.0 (3.0, 20.0)	NA	−1.684‡	0.092
Duration of psoriasis (years)	12.0 (5.0, 20.0)	NA	NA	–	–
Family history of Ps or PsA, n (%)	12 (17.4)	NA	NA	–	–
Tender joint count, 0–46, n (%)	6.0 (2.0, 12.5)	8.0 (5.0, 12.0)	NA	−1.400‡	0.161
Swollen joint count, 0–44, n (%)	3.0 (0, 8.0)	4.0 (2.0, 7.0)	NA	−1.445‡	0.148
Nail psoriasis, n (%)	30 (43.5)	NA	NA	–	–
Dactylitis, n (%)	7 (10.1)	NA	NA	–	–
Enthesitis, n (%)	19 (27.5)	NA	NA	–	–
Uveitis, n (%)	2 (2.9)	NA	NA	–	–
RF-positive, n (%)	6 (8.7)	31 (79.5)	NA	55.440†	<0.010
Anti-CCP-positive, n (%)	4 (5.8)	38 (97.4)	NA	87.130†	<0.010
HLA-B27-positive, n (%)	14 (20.3)	NA	NA	–	–
Sacroiliitis, n (%)	32 (46.4)	NA	NA	–	–
Bone erosion, n (%)	26 (37.7)	19 (48.7)	NA	1.249†	0.264

Age and disease duration are respectively presented as mean ± SD and median (P25, P75). *Differences were analyzed by one-way analysis of variance (ANOVA) with Holm-Sidak multiple comparisons test for three groups, the statistics value was F. †Significances were assessed with Chi-square test and the value was χ^2. ‡Differences were analyzed by non-parametric test and the value was Z. Anti-CCP: Anti-cyclic citrullinated peptide; HCs: Healthy controls; HLA-B27: Human leukocyte antigen-B27; NA: Not assessed; Ps: Psoriasis; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; RF: Rheumatoid factor; SD: Standard deviation.

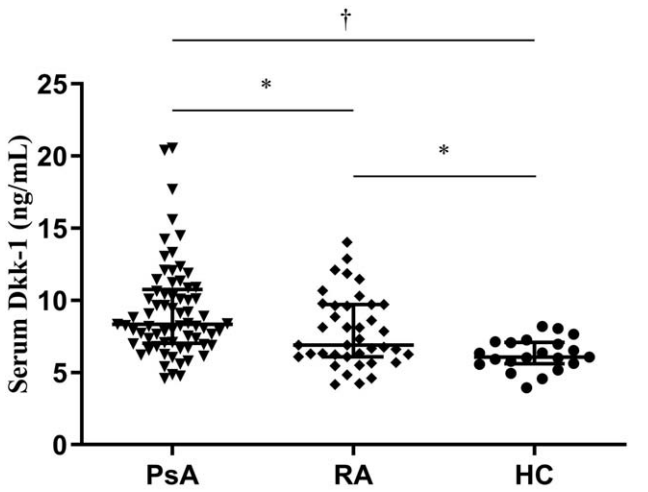

Figure 1: Serum Dkk-1 levels in patients with PsA and controls RA and HC. *$P<0.05$, †$P<0.01$. Dkk-1: Dickkopf-1; HC: Healthy controls; PsA: Psoriatic arthritis; RA: Rheumatoid arthritis.

Dkk-1 and bone erosion in PsA

Using ROC curve analyses, a Dkk-1 cut-off value of 7.651 ng/mL was determined to distinguish the group with elevated Dkk-1 level ($n=47$) from the group with normal Dkk-1 level ($n=22$). The features of these two groups are shown in Table 3. The swollen joint count was higher in PsA patients with elevated Dkk-1 compared with those with normal Dkk-1 (4.0 *vs.* 1.0, $Z=-2.103$, $P=0.035$). C3 was significantly lower in the elevated Dkk-1 group than the normal Dkk-1 group (1.11 ± 0.34 *vs.* 1.29 ± 0.26, $t=-2.133$, $P=0.037$). In terms of radiographic features, sacroiliitis was observed in 57.4% (27/47) of patients with elevated Dkk-1, which was significantly higher than those with normal Dkk-1 levels (22.7%, $\chi^2=7.264$, $P<0.010$);

Table 2: Correlation analysis of serum Dkk-1 and clinical features.

Variables	Pearson or Spearman rank correlation coefficient (r)	P values
Age	−0.048	0.693
Duration of arthritis	−0.086	0.483
Duration of psoriasis	0.005	0.971
Tender joint count, 0–46 joints	0.097	0.429
Swollen joint count, 0–44 joints	0.370	<0.010
JSN score	0.156	0.199
Erosion score	0.235	0.052
Sharp score	0.201	0.098
WBC	−0.186	0.126
Hb	−0.019	0.875
PLT	−0.341	<0.010
ESR	0.090	0.461
CRP	−0.118	0.335
IgA	−0.035	0.778
IgG	−0.086	0.486
IgM	−0.046	0.708
Complement C3	−0.530	<0.010
Complement C4	−0.354	<0.010

CRP: C-reactive protein; Dkk-1: Dickkopf-1; ESR: Erythrocyte sedimentation; Hb: Hemoglobin; Ig: Immunoglobulin; JSN: Joint space narrowing; PLT: Platelet; WBC: White blood cell.

the frequencies of RAD and bone erosion were significantly higher in PsA patients with elevated Dkk-1 than those with normal Dkk-1 (63.8% *vs.* 36.4%, $\chi^2=4.569$, $P=0.033$; 46.8% *vs.* 18.2%, $\chi^2=5.230$, $P=0.022$). Moreover, the Sharp score was notably higher in PsA patients with elevated Dkk-1 levels than those with normal Dkk-1 levels (9.0 [0, 17.0] *vs.* 3.0 [0, 7.0], $Z=-2.067$, $P=0.039$). No significant differences in sex ratio, age, arthritis/psoriasis

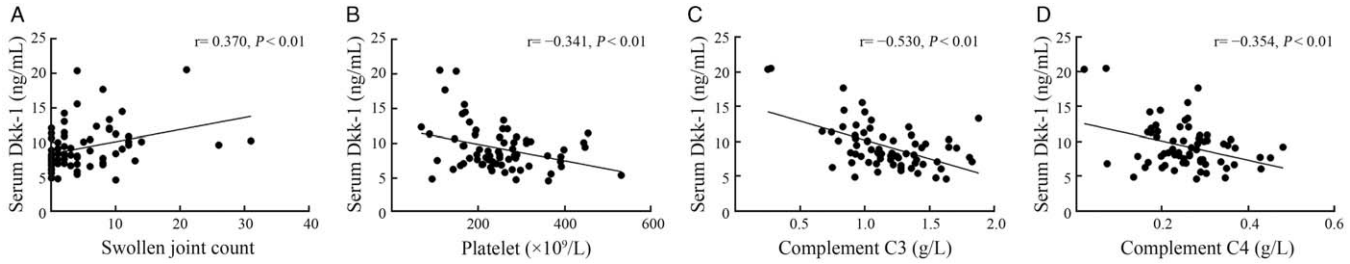

Figure 2: Correlation between serum Dkk-1 levels and swollen joint count (A), platelet (B), and complement components C3 (C) and C4 (D). Dkk-1: Dickkopf-1.

Table 3: Comparison of PsA patients with elevated and normal serum Dkk-1 levels.

Variables	Serum Dkk-1		$t/\chi^2/Z$	*P* value
	Elevated Dkk-1 ($n=47$)	Normal Dkk-1 ($n=22$)		
Age (years)	52.38 ± 13.57	53.36 ± 11.97	−0.290*	0.773
Female/male (*n*)	27/20	12/10	0.051†	0.821
Duration of arthritis (years)	5.0 (0.5, 12.0)	5.5 (2.8, 15.5)	−0.909‡	0.363
Duration of psoriasis (years)	11.0 (5.0, 20.0)	16.5 (4.4, 21.8)	−0.426‡	0.670
Family history of Ps/PsA, *n* (%)	8 (17.0)	4 (18.2)	0†	1.000
Tender joint count, *n* (%)	6.0 (2.0, 13.8)	6.0 (3.5, 10.8)	−0.019‡	0.985
Swollen joint count, *n* (%)	4.0 (1.0, 9.3)	1.0 (0, 4.5)	−2.103‡	0.035
Nail psoriasis, *n* (%)	20 (42.6)	10 (45.5)	0.051†	0.821
Dactylitis, *n* (%)	6 (12.8)	1 (4.5)	0.392†	0.531
Enthesitis, *n* (%)	16 (34.0)	3 (13.6)	3.127†	0.077
Uveitis, *n* (%)	1 (2.1)	1 (4.5)	0†	1.000
WBC ($\times10^9$/L)	6.62 ± 1.75	7.73 ± 4.21	−1.199*	0.242
Hb (g/L)	117.60 ± 18.17	121.58 ± 15.17	−0.892*	0.376
PLT ($\times10^9$/L)	250.00 (180.00, 287.30)	248.00 (198.25, 329.33)	−0.579‡	0.562
ESR (mm/h)	46.00 (15.00, 74.00)	40.50 (15.75, 88.00)	−0.161‡	0.872
CRP (mg/L)	16.60 (5.01, 48.70)	25.50 (8.09, 92.00)	−1.275‡	0.202
IgA (g/L)	3.31 (2.14, 5.04)	3.26 (2.25, 5.05)	−0.262‡	0.793
IgG (g/L)	13.59 ± 3.70	17.29 ± 9.39	−1.781*	0.087
IgM (g/L)	0.90 (0.71, 1.30)	1.02 (0.89, 1.49)	−1.265‡	0.206
Complement C3 (g/L)	1.11 ± 0.34	1.29 ± 0.26	−2.133*	0.037
Complement C4 (g/L)	0.25 ± 0.09	0.26 ± 0.08	−0.548*	0.586
RF-positive, *n* (%)	3 (6.4)	3 (13.6)	0.290†	0.590
Anti-CCP-positive, *n* (%)	3 (6.4)	1 (4.5)	0†	1.000
HLA-B27-positive, *n* (%)	9 (19.1)	5 (22.7)	0.001†	0.981
Sharp score	9.0 (0, 17.0)	3.0 (0, 7.0)	−2.067‡	0.039
Sacroiliitis, *n* (%)	27 (57.4)	5 (22.7)	7.264†	<0.010
RAD, *n* (%)	30 (63.8)	8 (36.4)	4.569†	0.033
Bone erosion, *n* (%)	22 (46.8)	4 (18.2)	5.230†	0.022

*Differences were analyzed by *t*-test for two groups, the statistics value was *t*. †Significances were assessed with Chi-square test and the value was χ^2. ‡Differences were analyzed by non-parametric test and the value was *Z*. Anti-CCP: Anti-cyclic citrullinated peptide; CRP: C-reactive protein; Dkk-1: Dickkopf-1; ESR: Erythrocyte sedimentation; Hb: Hemoglobin; HLA-B27: Human leukocyte antigen-B27; Ig: Immunoglobulin; PLT: Platelet; Ps: Psoriasis; PsA: Psoriatic arthritis; RAD: Radiographic axial disease; RF: Rheumatoid factor; WBC: White blood cell.

duration, tender joint count, the frequency of nail psoriasis, dactylitis, enthesitis, uveitis, autoantibodies including RF, anti-CCP, and HLA-B27 were found between the two groups.

Risk factors for bone erosion in PsA patients

We identified independent risk factors associated with bone erosion in PsA patients using binary logistic regression analysis [Table 4]. Elevated Dkk-1 level was considered an independent risk factor of bone erosion in the multivariate model (odds ratio = 4.440, 95% confidence interval: 1.246–15.817, $P = 0.021$).

Discussion

In this study, we demonstrated that serum Dkk-1 was significantly elevated in PsA patients compared with RA patients and HCs, supporting the idea that Dkk-1 might be involved in the pathogenesis of PsA. A key finding of our study is that increased Dkk-1 was correlated with bone erosion in PsA patients.

Table 4: Multivariate analysis of risk factors associated with bone erosion in patients with PsA.

Variables	OR	95% CI	*P* values
Univariate			
Age	0.995	0.958–1.033	0.786
Dkk-1 elevated	3.960	1.163–13.488	0.028
Duration of arthritis	1.003	0.965–1.043	0.871
Duration of psoriasis	1.028	0.984–1.074	0.222
Tender joint count	1.017	0.969–1.067	0.490
Swollen joint count	1.034	0.955–1.119	0.414
Nail psoriasis	2.545	0.937–6.914	0.067
Dactylitis	4.881	0.872–27.315	0.071
Enthesitis	1.747	0.597–5.113	0.309
Uveitis	1.680	0.101–28.064	0.718
Multivariate			
Dkk-1 elevated	4.440	1.246–15.817	0.021

CI: Confidence intervals; Dkk-1: Dickkopf-1; OR: Odds ratio; PsA: Psoriatic arthritis.

PsA is a chronic autoimmune disorder that attacks enthesis and synovial joints, resulting in bone destruction. Progressive bone erosion and new bone formation are hallmarks of PsA, so finding the main molecules involved in bone erosion is essential for determining the mechanism of PsA. Dkk-1 is a key inhibitor in Wnt signaling by binding to the Wnt co-receptor low density lipoprotein receptor-related protein 5/6 (LRP5/6).[18,19] Wnt signaling via LRP5 impacts accrual and is crucial for peak bone mass establishment.[20] The LPR5 mutation causes high bone density, by reducing the action of a normal antagonist of the Wnt-mediated pathway and thus promoting Wnt signaling.[21] These findings indicate that Dkk-1 is a potential treatment or prevention target of osteoporosis or bone erosion.[8,20-22]

Dkk-1 functions directly in the differential remodeling of human joint architecture by diverse mechanisms. For example, an elevated level of Dkk-1 impairs bone formation by upregulating the expression of inflammatory cytokines including tumor necrosis factor (TNF).[23,24] Additionally, lower Dkk-1 contributes to the appearance of osteophytes.[24] PsA is a heterogeneous disease that may manifest both patterns of osteopathology, either bone loss or bone remodeling.[3,4,16] The mechanism of PsA joint remodeling is unknown thus far.

Fassio *et al*[25] indicated that Dkk-1 was lower in PsA patients compared with the RA and HC groups, while a study from New Zealand reported that PsA patients had increased Dkk-1 concentrations of sera compared with HCs.[9] Jadon *et al*[26] demonstrated that Dkk-1 was significantly higher in PsA patients with axial arthritis than without it. The elevated concentration of circulating Dkk-1 in this study differs from the results from Fassio *et al*. A further consideration is that sera Dkk-1 levels may be varied in different phenotypes. In our study, 55.1% of PsA patients had axial arthritis. The results implied that high levels of Dkk-1 indicated the involvement of axial arthritis in PsA.

Our results showed that patients with elevated Dkk-1 levels had higher swollen joint counts than patients with normal Dkk-1, suggesting that elevated Dkk-1 may indicate more severe disease activity. Elevated Dkk-1 levels in PsA patients have been shown with a radiographic damage score, including Sharp/van der Heijde score and the sacroiliitis ratio. Moreover, patients with elevated Dkk-1 have an increased risk of bone erosion. Increased sera Dkk-1 concentrations have been reported in PsA patients with axial arthritis[26]; similar results are observed in studies of ankylosing spondylitis.[27,28] Because more than half of the PsA patients suffered from inflammatory RAD in our study, we hypothesized that Dkk-1 may be used as a serum marker of radiographic damage in axial spondyloarthritis of PsA patients, which was consistent with conclusions about ankylosing spondylitis from a meta-analysis by Wu *et al*.[29]

Dkk-1 is a key inhibitory factor of osteoblastic activity, and its circulation concentration is confirmed to be associated with the process of bone erosion in RA.[30] Dkk-1 has also been observed to be associated with spondyloarthritis and even with erosive arthritis in patients with systemic lupus erythematosus.[31] The mechanism of Dkk-1 in bone destruction seems to be regulated by cytokines in the local inflammatory microenvironments of joints, such as TNF-α, interleukin (IL)-6, IL-8, IL-17, and matrix metalloproteinases.[22,25,32,33] The cytokines interacted within a complicated regulatory network in inflammatory arthritis, modulating the interactions among immune cells, fibroblast-like synoviocytes, and osteoblasts. Bone erosion and bone formation are successive processes in PsA, indicating that elevation of serum Dkk-1 is a predictive indicator for bone erosion. Further research of the function of Dkk-1 may help to identify the mechanism of bone erosion in inflammatory arthritis.

There are several limitations to our study. First, statistical bias could not be avoided because the sample size was quite limited, and stratification according to the disease duration and severity was not performed, and the sample size was calculated using a univariate method that does not control the confounding effect, and there were fewer HCs than the pre-defined sample size. Second, selection bias could not be ruled out because all cases were collected from a single center in this study. Third, complete longitudinal data such as psoriasis area and severity index score were lacking due to the retrospective design. Therefore, larger sample-based multicenter studies are needed for more accurate information in the future.

To conclude, this study has shown that serum Dkk-1 level is abnormally elevated in PsA patients. Increased Dkk-1 levels are associated with sacroiliitis and might be involved in bone erosion in PsA patients. Further studies of the role of Dkk-1 might be useful in understanding the mechanism of PsA.

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Conflicts of interest

None.

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