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Concise report

# The presence of peripheral arthritis delays spinal radiographic progression in ankylosing spondylitis: Observation Study of the Korean Spondyloarthropathy Registry

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## Abstract

**Objectives.** The aim of this study was to determine whether the presence of peripheral arthritis can affect radiographic structural damage in patients with AS.

**Methods.** A total of 915 subjects comprising 363 patients with a history of peripheral arthritis and 552 patients without a history of peripheral arthritis obtained from the Observation Study of the Korean SpA Registry (OSKAR) were analysed looking at the relationship of peripheral arthritis history in a cross-sectional survey as well as the radiographic damage score according to the presence or absence of peripheral arthritis. Radiographs and clinical information were available for 501 subjects (205 peripheral arthritis patients and 296 without peripheral arthritis) at a mean follow-up of 2.7 years. The modified Stoke AS Spinal Score (mSASSS) was examined by two experienced radiologists to validate the results. Reliability was evaluated using the intraclass correlation coefficient for each radiograph.

**Results.** The agreement between the two readers regarding the mSASSS was good. On simple comparison there was a significant difference in the mSASSS between patients with a history of peripheral arthritis and those without [mean 14.62 (S.E.M. 0.83) *vs* 18.78 (0.79), $P < 0.001$]. The mSASSS change was stratified according to the presence or absence of peripheral arthritis at baseline. After adjusting for multiple comparisons by Bonferroni correction, the patients with peripheral arthritis had less mSASSS change than those without peripheral arthritis [3.08 (S.E.M. 0.61) *vs* 5.18 (0.47), $P = 0.008$].

**Conclusion.** The presence of peripheral arthritis delays spinal radiographic progression in AS.

**Key words:** ankylosing spondylitis, peripheral arthritis, modified stoke AS spinal score.

CLINICAL SCIENCE

## Introduction

AS is characterized by inflammation of the axial skeleton, sacroiliac joints and, to a lesser degree, peripheral joints and certain extra-articular organs, including the eyes, skin and cardiovascular system [1]. The most characteristic feature in AS is subchondral eburnation and syndesmophytes, possibly leading to ankylosis and spinal fusion. Peripheral joint involvement is a presenting feature in only 10–20% of patients and occurs during the disease course in 30–40% of patients [2]. Previously we reported a higher frequency of peripheral arthritis in our population [3]. While there has been considerable interest recently in the rate of progression of structural damage in AS [4–7], only limited data are available regarding peripheral arthritis in the rate of progression of structural damage [4, 8]. Moreover, these earlier studies did not focus on peripheral arthritis for radiographic spinal change in AS. A clear relationship between spinal bone formation and peripheral arthritis in patients with AS has not been established.

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Therefore the objective of this study was to determine whether the presence of peripheral arthritis can affect the progression of structural damage in patients with AS.

## Materials and methods

### Patients and study design

The Observation Study of the Korean SpA Registry (OSKAR) is an ongoing, longitudinal observational study on the clinical, functional and structural outcomes of SpA in Korea [3]. A total of 915 patients from OSKAR who met the modified New York criteria for AS [9] were included in this study. First, all data were stratified in relation to the history of peripheral arthritis for cross-sectional analysis. We then compared the radiographic damage score between groups. Second, we collected clinical and radiographic parameters according to the presence or absence of peripheral arthritis at the time of radiographic examination. After that, we analysed the available radiographic spinal progression at follow-up. The study was approved by the institutional review boards of Hanyang University Hospital and Chonnam National University Hospital and written informed consent was obtained from all participants.

### Assessment of radiographic progression

The radiographs were obtained when clinical parameters were assessed. All clinical data were blinded and radiographs were scored independently by two radiologists (S.L, K.B.J.). The modified Stokes AS Spinal Score (mSASSS) has been identified as the most sensitive scoring method [10], thus the cervical and lumbar spine was scored according to the mSASSS method. We excluded patients who had more than three vertebral sites missing. In cases with fewer than three vertebral sites missing, the missing scores were substituted by the mean score of the vertebra of the same spinal segment of the patient, in accordance with previous analysis [11].

### Clinical data and definition of each data type

All clinical parameters were examined by the rheumatologists in our registry. Clinical data included age, sex, duration of disease, age at onset of disease-specific symptoms, peripheral arthritis, history of uveitis, family history of AS, NSAID index [12] and the use of a TNF blocker. When symptom onset occurred in individuals $<$16 years of age, the disease was termed juvenile-onset AS, otherwise it was classified as adult-onset AS. A 44-joint count has been proposed to measure overall peripheral joint involvement, which includes the sternoclavicular joints, acromioclavicular joints, shoulders, elbows, wrists, knees, ankles, MCP and MTP joints and PIP joints of the hands [13]. Accordingly, these joints were examined in this study (except shoulder joints). Peripheral arthritis was defined as the presence of swelling in at least one peripheral joint. To avoid confusion with other painful structures, such as entheses, bursae or tendons, examinations for peripheral involvement should involve only swollen, not tender, joints [13]. Enthesitis was very hard to validate among our examiners, especially at the iliac crest, spinous process and superior iliac spine. It was also reported that the clinical assessment of enthesitis was problematic, showing a sensitivity of only 22.6% and a positive predictive value of $<$60% [13, 14]. Thus we excluded enthesitis as a clinical parameter in this study. All cases of uveitis were diagnosed by an ophthalmologist. Family history was defined as whether the subject had any first-degree relatives (parents, siblings or offspring) diagnosed with AS. Since cigarette smoking is associated with radiographic severity [7, 15], we collected smoking history stratified as none, ever and current. Outcome assessments were also performed. These included BASDAI, BASFI, patient global assessment (PGA), spinal pain and night back pain. Laboratory tests included the CRP level and HLA-B27 status.

### Statistical analyses

Intra- and interreader reliability was evaluated using the intraclass correlation coefficient (ICC) for each radiograph. Clinical comparisons were performed using *t*-tests for continuous measures that were normally distributed. Mann–Whitney *U* tests were performed for continuous measures that were not normally distributed, and chi-square tests were used for categorical variables. Comparison of radiographic scores was by an analysis of covariance (ANCOVA) model after adjusting for confounding factors using Bonferroni correction. *P*-values $<$0.05 were considered statistically significant. All statistical analyses were performed using SPSS version 17.0 software (IBM, Armonk, NY, USA).

## Results

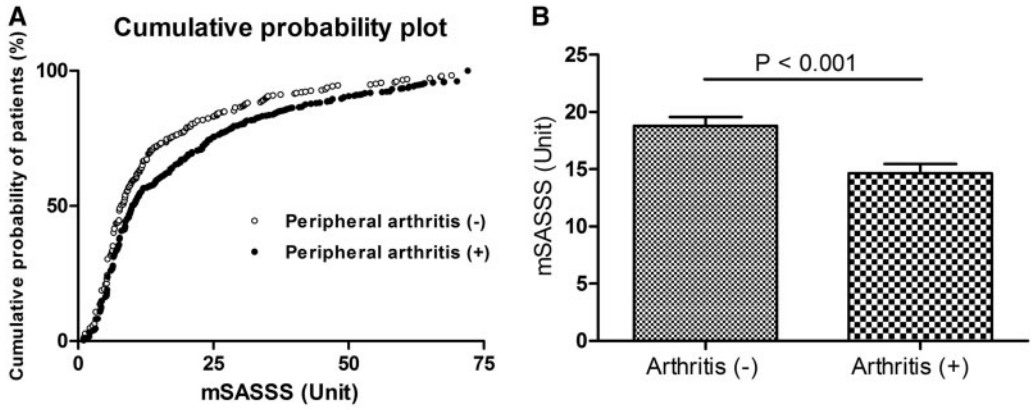
### Agreement between readers

The agreement between the two readers regarding the mSASSS was very good with an ICC of 0.75 (95% CI 0.61, 0.82) and 0.71 (95% CI 0.58, 0.82). Agreement regarding the mSASSS change score was moderate with an ICC of 0.57 (95% CI 0.47, 0.68) and 0.64 (95% CI 0.45, 0.76).

### Demographic features between the patients with and without peripheral arthritis

Nine hundred and fifteen patients with AS comprising 363 patients with a history of peripheral arthritis and 552 patients without a history of peripheral arthritis were assessed. Thirteen of 915 patients (1.4%) were found to have psoriasis. Seven patients (0.7%; two with Crohn's disease and five with ulcerative colitis) were found to have IBD. The cumulative probability plot illustrates the difference in mSASSS values in the arthritis group and non-arthritis group (Fig. 1A). On simple comparison, there was a significant difference in the mSASSS between patients without a history of peripheral arthritis and those with peripheral arthritis [mean 18.78 (S.E.M. 0.79) *vs* 14.62 (0.83), $P < 0.001$] (Fig. 1B).

FIG. 1 Comparison of radiographic scores for all patients ($n = 915$) in the two assessed groups




(**A**) Cumulative probability plots show the distribution of the mSASSS in patients with AS in relation to the history of peripheral arthritis. (**B**) Significant differences between patients without a history of peripheral arthritis and those with arthritis were observed [mean 18.78 (S.E.M. 0.79) *vs* 14.62 (0.83), $P < 0.001$]. mSASSS: modified Stoke AS Spine Score.

### Correlation of radiographic progression score with history of peripheral arthritis in AS patients

Since different clinical factors were observed between the peripheral arthritis and non-peripheral arthritis groups, which included gender, disease duration, age of onset, eye involvement, familial history, smoking status, CRP and TNF blocker use (see supplementary Table S1, available at *Rheumatology* Online), we re-evaluated the data using the ANCOVA model for confounding clinical parameters. After adjusting for confounding factors, the mSASSS was lower in patients with a history of peripheral arthritis than in those with no history of peripheral arthritis [mean 19.56 (S.E.M. 1.06) *vs* 22.67 (0.81), $P = 0.005$].

### Analysis of radiographic progression in AS according to the presence or absence of peripheral arthritis

To confirm whether the presence of peripheral arthritis influenced radiographic progression we assessed mSASSS change stratified by the presence or absence of peripheral arthritis. Radiographs and clinical information were available for 501 patients (205 patients with peripheral arthritis and 296 patients without) at a mean follow-up of 2.7 years. Clinical characteristics are presented in supplementary Table S2, available at *Rheumatology* Online. The ANCOVA model for confounding clinical parameters was used because different clinical factors were observed between groups, such as age of onset, eye involvement, smoking status, CRP, TNF blocker use and baseline mSASSS. After adjusting for multiple comparisons by Bonferroni correction, the patients with peripheral arthritis had less mSASSS change than those without peripheral arthritis [mean 3.08 (S.E.M. 0.61) *vs* 5.18 (0.47), $P = 0.008$] (Table 1).

TABLE 1 Change in mSASSS between patients with and without peripheral arthritis after adjusting for confounding factors

| Dependent variable: change in mSASSS | | | | | |
|---|---|---|---|---|---|
| Peripheral arthritis at baseline | Mean | S.E. | 95% CI | | *P*-value |
| | | | Lower bound | Upper bound | |
| Absence | 5.18[a] | 0.47 | 4.26 | 6.11 | 0.008 |
| Presence | 3.08[a] | 0.61 | 1.88 | 4.27 | |

[a]Adjustment for multiple comparisons by the Bonferroni correction (covariates: age, gender, disease duration, juvenile-onset AS, uveitis ever, smoking state, CRP, use of TNF blockers and baseline mSASSS). mSASSS: modified Stoke AS Spinal Score.

## Discussion

There has been considerable interest in the rate of progression of structural damage in AS and SpA. Although there is substantial heterogeneity in radiographic severity between studies, gender, hip involvement, CRP level, smoking, disease duration, age, history of iritis, delay in diagnosis and baseline radiographic damage have been suggested as important predictors of radiographic progression [4–7, 15–17].

Several studies have investigated the relationship between peripheral arthritis and radiographic progression in AS [6, 8, 18]. AS patients with peripheral joint disease may have clinically and radiographically less severe spinal disease course than those without peripheral joint disease [8]. The absence of peripheral arthritis has been associated with multiple syndesmophytes or fusion of multiple lumbar vertebrae in AS [18]. On the other hand, the presence of peripheral arthritis at baseline reportedly did not reveal significant associations with spinal radiographic progression over 2 years in patients with axial SpA [15]. In another study, radiographic spinal joint involvement with fusion was not associated with a history of peripheral

arthritis [6]. The previous studies provided equivocal findings and were limited by small sample size. The analysis of the data also had problems, ignoring the variation of radiographic assessment time and the fact that radiographic damage at baseline is a prognostic factor associated with continuing radiographic progression over time. In addition, prior studies did not focus on peripheral arthritis for radiographic spinal change in AS. To overcome these problems, we evaluated radiographic changes stratified by the presence or absence of peripheral arthritis. This cross-sectional approach showed that patients with a history of peripheral arthritis had lower radiographic damage scores than those without a history of peripheral arthritis. A history of peripheral arthritis was defined as having peripheral joint involvement at some time during the disease course. Therefore we collected available follow-up data of the patients with peripheral arthritis.

NSAIDs can reportedly retard new bone formation in AS patients [19]. However, NSAIDs did not affect the results in this study, as evidenced by comparable NSAID index scores between groups. Smoking status has been associated with radiographic severity [7, 15]. CRP level is an independent predictor for radiographic sacroiliitis and spinal progression in AS and axial SpA [4, 15]. However, there was no correlation between baseline CRP level and mSASSS change in our data ($r = 0.052$, $P = 0.393$). TNF inhibitors appear to reduce radiographic progression in AS [20]. However, we found no differences in mSASSS change between the TNF and non-TNF blocker groups ($P = 0.301$). Nonetheless, we analysed our data adjusting for these reported meaningful confounding parameters.

There are some limitations to this study. Although the assessment of enthesitis in AS patients could be quantified by scoring systems, it was not performed in this study. Hip involvement is an important feature of AS. Chen *et al.* [6] demonstrated that hip involvement is an important prognostic factor associated with radiographic damage in the spine. However, we did not evaluate hip joint involvement. Given the association between smoking status and radiographic progression, smoking burden should be assessed in detail by a pack-year tool. A history of peripheral arthritis could be a surrogate for the presence of PsA, IBD-associated arthritis or reactive arthritis, which might have sacroiliitis. However, reactive arthritis is usually self-limiting. Chronic sacroiliitis only occurs in some cases. Only 13 patients were found to have psoriasis and 7 patients were found to have IBD. Therefore these factors would only have a minor influence on the results.

Strengths of this study include the large, well-stratified sample and examination of data focusing on peripheral arthritis and radiographic progression. Nothing is known about the cause of the relationship between peripheral arthritis and radiographic severity in patients with AS. However, the median serum level of dickkopf-related protein 1 (DKK-1) in patients with current peripheral arthritis was higher than in patients without peripheral arthritis (346.8 pg/ml *vs* 247.7, $P = 0.038$). Given that DKK-1 is a major negative regulator of osteoblastogenesis, our result provides an interesting clue to understanding the mechanism of the relationships between peripheral arthritis and bone formation. Due to the small available sample tested, further research is necessary to ascertain whether the high level of DKK-1 can truly affect the slow progression of structural damage in patients with peripheral arthritis.

In conclusion, analysis after adjustment for confounding factors revealed that peripheral arthritis is an independent determinant of radiographic damage in the spine. Patients with a history of peripheral arthritis have slower radiographic spinal damage progression than those without peripheral arthritis.

**Rheumatology key messages**

- The unique feature in AS is syndesmophytes, leading to ankylosis and spinal fusion.
- This study focused on the association between peripheral arthritis and radiographic progression in AS.
- The presence of peripheral arthritis delays spinal radiographic progression in AS.

## Supplementary data

Supplementary data are available at *Rheumatology* Online.

## Acknowledgements

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