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# Development and Validation of 3 Preliminary MRI Sacroiliac Joint Composite Structural Damage Scores in a 5-year Longitudinal Axial Spondyloarthritis Study

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***ABSTRACT.*** ***Objective.*** In axial spondyloarthritis (axSpA), sacroiliac joint (SIJ) erosion is often followed by fat metaplasia in an erosion cavity (backfill), and subsequently ankylosis. We aimed to combine the Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ structural score for erosion, backfill, and ankylosis into 3 versions of a novel preliminary axSpA magnetic resonance imaging (MRI) SIJ Composite Structural Damage Score (CSDS) and to test these.

***Methods.*** Thirty-three patients with axSpA, followed for 5 years after initiation of tumor necrosis factor inhibitor, had MRIs of the SIJs at baseline, and yearly thereafter. Three versions of CSDS were calculated based on different weightings of erosion, backfill, and ankylosis: (1) equal weighting: $CSDS_{equal}$ = (erosion × 0.5) + backfill + ankylosis; (2) advanced stages weighting more: $CSDS_{stepwise}$ = (erosion × 1) + (backfill × 4 ) + (ankylosis × 6); and (3) advanced stages overruling earlier stages ("hierarchical") with "<" meaning "overruled by": $CSDS_{hierarchical}$ = (erosion × 1) < (backfill × 4) < (ankylosis × 6).

***Results.*** At baseline, all CSDS correlated positively with SPARCC fat and ankylosis scores and modified New York radiography grading, and negatively with the Bath Ankylosing Spondylitis Disease Index and SPARCC SIJ inflammation scores. $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ (not $CSDS_{equal}$) correlated positively with symptom duration and the Bath Ankylosing Spondylitis Metrology Index, and closer with SPARCC ankylosis score and modified New York radiography grading than $CSDS_{equal}$. The adjusted annual progression rate for $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ (not $CSDS_{equal}$) was higher the first year compared with fourth year ($P = 0.04$ and $P = 0.01$). Standardized response mean (baseline to Week 46) was moderate for $CSDS_{hierarchical}$ (0.64) and $CSDS_{stepwise}$ (0.59) and small for $CSDS_{equal}$ (0.25).

***Conclusion.*** Particularly $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ showed construct validity and responsiveness, encouraging further validation in larger clinical trials. The potential clinical implication is assessment of SIJ damage progression by 1 composite score.

*Key Indexing Terms:* ankylosing spondylitis, magnetic resonance imaging, outcomes, prognosis, spondyloarthropathy

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Axial spondyloarthritis (axSpA) is a chronic inflammatory disease that causes inflammation and structural damage in the sacroiliac joints (SIJs) and spine.[1,2] Other characteristics include back and buttock pain and reduced physical function and spine mobility.[3] To date, conventional radiography of SIJs and spine has been the standard imaging method for assessing structural progression. However, definitive sacroiliitis on radiography is usually not present until after several years of disease activity and structural damage progression can only be reliably detected over 2 to 4 years.[4,5,6,7] Magnetic resonance imaging (MRI) of the SIJs captures structural lesions more accurately than conventional radiography when computed tomography (CT) is considered the standard reference.[8] MRI also reliably detects structural lesions such as fat lesions, erosion, backfill (i.e., fat metaplasia in an erosion cavity), and ankylosis in the SIJs,[9] and it can reliably display changes in fat, erosion, and backfill over time periods as short as 3 months.[10,11] In patients with ankylosing spondylitis (AS), several MRI studies have indicated an evolution of lesions in the SIJs where bone erosion[12] is often followed by new onset of fat metaplasia in the erosion cavity (backfill),[13] ultimately leading to ankylosis.[11,14,15] Based on the sequence of MRI lesions in the development of structural damage progression (erosion to backfill to ankylosis)[11,14,15] it could be relevant to combine these MRI pathologies by creating a composite score that would be able to capture the sequential development of structural lesions during the progression of the disease. Fat lesions (i.e., fat metaplasia inside the bone marrow) represent another construct, which is not a part of the development of erosion into backfill into ankylosis (i.e., all lesions located adjacent to or within the joint space) as described. Therefore, it would be most logical not to include fat lesions in the above-mentioned composite score of structural damage. Combining the individual structural lesions (i.e., erosion, backfill, and ankylosis) would make it possible to assess SIJ damage with a single outcome measure which can illustrate if there is structural progression or not, and would be a useful tool in clinical trials. One combined measure of overall SIJ damage progression may also increase sensitivity to change and potentially reduce the needed sample size and/or follow-up time in clinical trials.

The Spondyloarthritis Research Consortium of Canada (SPARCC) SIJ Structural Score (SSS)[9] is a reliable and validated method to assess structural lesions of the SIJs and it gives information on the amount of the individual structural lesions (i.e., fat lesion, erosion, backfill, and ankylosis). Therefore, SPARCC SSS could provide a basis for a SIJ composite structural damage score.

The aim of the study was to combine the SPARCC scores for erosion, backfill, and ankylosis into a composite score for SIJ structural damage, calculated with 3 different preliminary formulas. We tested these scores in a 5-year follow-up study of patients with axSpA treated with a tumor necrosis factor inhibitor (TNFi).

## METHODS

*Patients.* The Biomarkers in Spondylarthritis (BIOSPA; ClinicalTrials.gov: NCT00133315) study[16,17] was a prospective, investigator-initiated, open-label, observational, multicenter study of patients treated with a TNFi for the first time. The study was carried out from 2004 to 2012 as a collaboration among 9 departments of rheumatology in Denmark.

The study was approved by the regional scientific ethical committee (H-KF-02–050/04) and patients´ written informed consent were obtained. Patients were eligible if they fulfilled the European Spondyloarthropathy Study Group classification criteria for spondylarthritis[18]; had a Bath Ankylosing Spondylitis Disease Index (BASDAI) > 3.0 despite treatment with nonsteroidal antiinflammatory drugs (NSAIDs) at a maximum dose; had clinical indication for TNFi therapy as judged by the treating rheumatologist; and fulfilled the radiographic part of the modified New York (mNY) criteria[19] or had inflammation and/or structural lesions on MRI as evaluated by a musculoskeletal radiologist. Disease activity was evaluated repeatedly with BASDAI and C-reactive protein, and the Ankylosing Spondylitis Disease Activity Score (ASDAS) was calculated retrospectively. At Week 22, clinical responders, defined by 50% reduction in BASDAI or change of 2 (BASDAI range 0–10) since initiation of a TNFi, continued the original TNFi therapy, whereas the nonresponders changed TNFi at the discretion of the treating rheumatologist.

After 46 weeks, patients were invited to join an open-label extension of the study until Year 5. In the 5-year, open-label study, patients were treated according to the Assessment of SpondyloArthritis international Society (ASAS) recommendations.[20,21]

*Imaging.* MRIs of the SIJs and lower spine (T9–S1) were obtained on a 1.5T system with a 5-element phased-array spine coil with a slice thickness of 4 mm and a slice gap of 0.8 mm. SIJs were visualized with semicoronal T1-weighted turbo spin-echo images (repetition time: 550 msec; echo time: 14 msec; field of view: 300 × 270 mm; and matrix: 320 × 17) and short-tau inversion recovery (STIR) images (repetition time: 2500 msec; echo time: 60 msec; inversion time: 160 msec; field of view: 300 × 240 mm; matrix: 256 × 163). Images were obtained at Weeks 0 and 46 and Years 2, 3, 4, and 5 and were evaluated according to the SPARCC SSS for fat, erosion, backfill, and ankylosis. Radiographs of the SIJs were acquired at baseline, Week 46, and Years 3 and 5, and evaluated according to the mNY criteria. Images were anonymized and read by an experienced reader (UW) in known time order.

*SPARCC SSS.* The SPARCC SSS was applied according to the method as described by Maksymowych, *et al*.[9] In brief, the evaluation included 5 consecutive semicoronal slices through the cartilaginous portion of the SIJ on T1-weighted sequences. Lesions were scored dichotomously (present/absent) in SIJ quadrants (fat metaplasia, erosion) or halves (backfill, ankylosis). Erosion was scored 0–1 per joint quadrant (i.e., max score of 4 per SIJ per slice; total score range 0–40), fat metaplasia 0–1 per joint quadrant (i.e., max score of 4 per SIJ per slice; total score range 0–40), backfill 0–1 per joint half (i.e., max score of 2 per SIJ per slice; total score range 0–20), and ankylosis 0–1 per joint half (i.e., max score of 2 per SIJ per slice; total score range 0–20).[9] SPARCC SIJ inflammation was scored 0–1 per joint quadrant (i.e., max score of 4 per slice) on 6 consecutive semicoronal slices on STIR sequences. An additional 1 point was given per joint per slice if signal intensity was homogenous across the inflammatory lesion and if > 1 cm deep. Further, 1 point was given per joint per slice if signal intensity was as bright as the cerebrospinal fluid at the same horizontal level (i.e., max score of 12 per SIJ; total score range 0–72).[22]

Patients were subdivided into 2 groups: patients with almost complete bilateral ankylosis (baseline SPARCC SSS for ankylosis > 18) and patients with no-to-moderate ankylosis (baseline SPARCC SSS for ankylosis < 7). This was based on the assumption that patients with almost complete ankylosis at baseline would not progress further or would progress minimally during the 5 years of follow-up.

*Calculation of axSpA MRI SIJ Composite Structural Damage Score.* Based on the SPARCC scores for erosion, backfill, and ankylosis in the BIOSPA study, 3 different versions of a preliminary axSpA MRI SIJ Composite Structural Damage Score (CSDS) were calculated. Each of the 3 CSDS

had different weightings of erosion, backfill, and ankylosis as described below:

· Equal weighting:

$CSDS_{equal}$ = (erosion score × 0.5) + backfill score + ankylosis score; total score range of 0–60.

· Advanced stages weighing more:

$CSDS_{stepwise}$ = (erosion score × 1) + (backfill score × 4) + (ankylosis score × 6); total score range of 0–240.

· Advanced stages overruling earlier stages ("hierarchical"):

$CSDS_{hierarchical}$ = (erosion score × 1) < (backfill score × 4) < (ankylosis score × 6); total score range: 0–120.

The "<" indicates a hierarchical order, meaning that erosion was not included in the calculation if backfill was present in the same joint half, and erosion and backfill were not included in the calculation if ankylosis was present in the joint half. Rationales for selecting these algorithms are elaborated on as follows.

*Rationale for selection of the CSDS algorithms.* When combining erosion, backfill, and ankylosis into a composite score, the composite score may benefit from adjusting the weighting so the earliest changes (represented by erosion) will not be overweighted. Simple addition of scores for erosion, backfill, and ankylosis would not fulfill this, since a maximum score for erosion per joint half is 2 and the maximum score for backfill and ankylosis per joint half is 1. To adjust for this, the erosion score could be multiplied by 1/2 (as done in $CSDS_{equal}$). However, if erosion evolves to backfill or if backfill evolves to ankylosis, this approach would not result in an increased composite score. Since backfill is considered a more advanced lesion that often develops after erosion, it could be argued that it should count more in a composite score. Moreover, ankylosis often develops after backfill and since ankylosis is considered the ultimate structural damage lesion, ankylosis may deserve a higher weighting than backfill and erosion. To ensure that structural progression is expressed in the composite score, backfill could be weighted twice as much per joint half as the maximum erosion score per joint half, and ankylosis could be weighted 3 times as much per joint half as the maximum score for erosion per joint half. This gives weightings of 1, 4, and 6 for erosion, backfill, and ankylosis, respectively ($CSDS_{stepwise}$). Third, a further argument could be that more advanced lesions in the natural course (ankylosis > backfill > erosion) should "overrule" the earlier stages, that is as a hierarchical order ($CSDS_{hierarchical}$).

*Statistics.* The 2 groups were compared with the chi-square test and Fisher exact test for dichotomous variables and Mann-Whitney *U* test for continuous variables. The annual change in MRI was calculated as the change from baseline to Week 46, Week 46 to Year 2, Year 2 to 3, Year 3 to 4, and Year 4 to 5 and divided with the exact time interval (in yrs) between assessments. The change in scores from baseline to Week 46 were compared with the other time intervals (as mentioned above) using Wilcoxon signed-rank test. Erosion, backfill, and ankylosis scores for missing MRI scans were replaced by linear interpolation; for example, if an MRI from Year 3 was missing, MRIs from Years 2 and 4 were used for linear interpolation. To assess responsiveness of the measure, standardized response mean (SRM) was calculated as mean change divided by SD of the change and interpreted as follows: no < 0.20; small ≥ 0.20 and < 0.50; moderate ≥ 0.50 and < 0.80; and large ≥ 0.80.[23] Sensitivity analyses were performed for the annual progression rate with missing data replaced by using last observation carried forward. Statistical analyses were conducted in SPSS version 25.0 (IBM Corp.); $P < 0.05$ was considered statistically significant.

## RESULTS

*Study population.* Forty-two of the 60 patients included in the BIOSPA study were included in the 5-year, open-label extension of the study. All 42 patients fulfilled the ASAS criteria for axSpA. Thirty-three of the 42 patients were followed from initiation of a TNFi (baseline) to Year 5. Data from these 33 patients (infliximab, n = 21; etanercept, n = 8; and adalimumab, n = 4) were used for the analyses in this study (Supplementary Figure 1, available with the online version of this article). Ten patients had almost complete bilateral ankylosis (baseline SPARCC SSS for ankylosis > 18) and 23 patients had no-to-moderate ankylosis (baseline SPARCC SSS for ankylosis < 7). Nineteen of 198 MRI scans (9.6 %) for these 33 patients were missing. The proportions of missing MRIs in the group with no-to-moderate ankylosis (12/138, 8.7%) and in the group with almost complete ankylosis (7/60, 11.7%) were comparable.

*Baseline characteristics.* Twenty-nine of the 33 patients (88%) fulfilled the mNY criteria for AS. Patients with no-to-moderate ankylosis were statistically significantly younger, had shorter symptom duration, lower Bath Ankylosing Spondylitis Metrology Index (BASMI), higher SPARCC SIJ inflammation, lower SPARCC SSS for fat and ankylosis, and higher SPARCC SSS for erosion and backfill compared with patients with almost complete bilateral ankylosis (Table 1).

*Changes in SPARCC SSS and axSpA MRI SIJ CSDS over time.* Table 2 provides the mean (SD) SPARCC SSS scores for erosion, backfill, and ankylosis and the scores of $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ over the 5 years. The decrease in SPARCC scores for erosion was statistically significant from Week 46 and onwards, and SPARCC scores for backfill decreased numerically during the 5 years after initiation of a TNFi in the group of 33 patients ("all") as well as in the group with no-to-moderate ankylosis, whereas SPARCC scores for ankylosis increased significantly from Week 46 onwards. In the group with almost complete ankylosis, SPARCC scores for erosion and backfill were 0 and the ankylosis score did not change during the 5 years. Both $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ showed statistically significant increases from Week 46 and onwards for all patients and for patients with no-to-moderate ankylosis, whereas $CSDS_{equal}$ did not change.

Figure 1 shows the individual scores for each patient for SPARCC SSS for erosion (1A), backfill (1B), and ankylosis (1C) and for the $CSDS_{equal}$ (1D), $CSDS_{stepwise}$ (1E), and $CSDS_{hierarchical}$ (1F) at baseline and at Years 2–5 in each of the 23 patients with no-to-moderate ankylosis at baseline. Although large individual variation was seen, overall most erosion and backfill scores either decreased or remained unchanged, whereas the ankylosis scores either increased or remained unchanged over the 5 years. Figure 2 illustrates the structural SIJ damage progression on MRI in a patient with no-to-moderate ankylosis at baseline. Figure 3 shows the development over time for SPARCC SSS erosion, backfill, and ankylosis and $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$.

*Correlation between axSpA MRI SIJ CSDSs and clinical and MRI findings.* At baseline, $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ correlated positively with SPARCC scores for fat and ankylosis as well as with the mNY grading of SIJ radiography, and negatively with BASDAI and SPARCC SIJ inflammation (Table 3). $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ also correlated positively with symptom duration and BASMI.

In the group with no-to-moderate ankylosis, $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ correlated positively with

*Table 1*. Baseline characteristics for clinical/MRI variables and the $CSDS_{equal}$, $CSDS_{stepwise}$, $CSDS_{hierarchical}$ for all patients, patients with no-to-moderate ankylosis, and patients with almost complete ankylosis.

| | All, n = 33 | No-to-moderate ankylosis, n = 23 | Almost complete ankylosis, n = 10 |
|---|---|---|---|
| Sex, male | 26 (78.8) | 17 (73.0) | 9 (90.0) |
| Age, yrs | 40 (21, 62) | 35 (21, 62) | **46 (30, 62)*** |
| Symptom duration, yrs | 12.0 (1, 45) | 5.5 (1, 33) | **20.0 (12, 45)*** |
| HLA-B27 positivity | 26 (78.8) | 17 (73.9) | 9 (90.0) |
| ASDAS | 3.9 (2.0, 6.0) | 3.9 (2.1, 6) | 3.5 (2.0, 4.8) |
| BASDAI (0–10) | 5.1 (3.0, 9.8) | 5.4 (3.2, 9.8) | 4.8 (3, 8.1) |
| BASFI (0–10) | 4.6 (1.0, 9.9) | 4.5 (1.0, 8.3) | 5.0 (1.5, 9.9) |
| BASMI (0–10) | 3.0 (0.0, 6.0) | 3.0 (0.0, 6.0) | **4.0 (3.0, 6.0)*** |
| CRP (mg/L) | 18.0 (1.6, 149.0) | 18.0 (1.6, 149.0) | 18.5 (1.7, 107.0) |
| SPARCC SIJ Inflammation (0–72) | 0 (0, 37) | 4 (0, 37) | **0 (0, 4)**** |
| SPARCC SSS Fat (0–40) | 24 (0, 40) | 12 (0, 40) | **39 (0, 40)*** |
| SPARCC SSS Erosion (0–40) | 1 (0, 22) | 6 (0, 22) | **0 (0, 0)***** |
| SPARCC SSS Backfill (0–20) | 0 (0, 19) | 2 (0, 19) | **0 (0, 0)**** |
| SPARCC SSS Ankylosis (0–20) | 0 (0, 20) | 0 (0, 7) | **20 (18, 20)***** |
| mSASSS (0–72) | 8 (0, 46) | 4 (0, 29) | 17 (0, 46) |
| Total SIJ score (mNY grade 0-8) | 7.5 (0, 8) | 6.0 (0, 8) | **8.0 (8, 8)***** |
| SIJ score met mNY, n (%) | 29 (88) | 19 (83) | 10 (100) |
| $CSDS_{equal}$ (0–60) | 11.5 (0.0, 23.5) | 8.0 (0.0, 23.5) | **20.0 (18.0, 20.0)**** |
| $CSDS_{stepwise}$ (0–240) | 47.0 (0.0, 120.0) | 24.0 (0.0, 69.0) | **120.0 (108.0, 120.0)***** |
| $CSDS_{hierarchical}$ (0–120) | 41.0 (0.0, 120.0) | 24.0 (0.0, 76.0) | **120.0 (108.0, 120.0)***** |

Data are shown as n (%) or median (min, max). Values in bold are statistically significant. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$; all 2-tailed. Tests are chi-square test, Fisher exact test, Mann-Whitney *U* test. No-to-moderate ankylosis defined as a baseline SPARCC SSS for ankylosis < 7 and almost complete ankylosis defined as a baseline SPARCC SSS for ankylosis > 18. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Index; BASFI: Bath Ankylosing Spondylitis Functional Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CRP: C-reactive protein; CSDS: Composite Structural Damage Score; mNY: modified New York criteria; MRI: magnetic resonance imaging; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; SIJ: sacroiliac joint; SPARCC SIJ: Spondyloarthritis Research Consortium of Canada SIJ inflammation; SPARCC SSS: Spondyloarthritis Research Consortium of Canada SIJ Structural Score.

*Table 2*. SPARCC SSS for erosion, backfill, and ankylosis and $CSDS_{equal}$, $CSDS_{stepwise}$, $CSDS_{hierarchical}$ in all patients and patients with no-to-moderate ankylosis over time.

| | Baseline | Week 46 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|---|
| Erosion | | | | | | |
| All | 4.7 (6.0) | **3.8 (5.4)*** | **3.6 (5.2)**** | **3.1 (4.7)**** | **3.1 (5.2)*** | **3.0 (5.4)*** |
| No-to-moderate ankylosis | 6.7 (6.1) | **5.5 (5.7)*** | **5.2 (5.5)**** | **4.3 (5.1)**** | **4.5 (5.8)*** | **4.3 (6.0)*** |
| Backfill | | | | | | |
| All | 3.1 (5.2) | 3.1 (5.2) | 3.1 (4.9) | 2.6 (4.4) | **2.1 (3.7)*** | 2.1 (3.6) |
| No-to-moderate ankylosis | 4.5 (5.8) | 4.5 (5.8) | 4.4 (5.4) | 3.7 (4.9) | **3.0 (4.1)*** | 3.0 (4.0) |
| Ankylosis | | | | | | |
| All | 6.8 (8.9) | **7.4 (8.7)**** | **7.6 (8.7)**** | **8.2 (8.6)**** | **8.5 (8.6)**** | **8.8 (8.5)**** |
| No-to-moderate ankylosis | 1.1 (2.0) | **2.0 (3.1)*** | **2.3 (3.7)**** | **3.1 (4.5)**** | **3.6 (4.9)**** | **4.0 (5.1)**** |
| $CSDS_{equal}$ | | | | | | |
| All | 12.2 (8.1) | 12.4 (8.0) | 12.5 (7.9) | 12.3 (7.7) | 12.2 (7.5) | 12.4 (7.6) |
| No-to-moderate ankylosis | 8.9 (7.6) | 9.2 (7.5) | 9.3 (7.5) | 9.0 (7.0) | 8.9 (6.6) | 9.2 (7.0) |
| $CSDS_{stepwise}$ | | | | | | |
| All | 57.7 (47.0) | **60.6 (46.7)**** | **61.6 (46.7)**** | **62.4 (46.7)*** | **63.2 (45.6)*** | **64.1 (45.1)*** |
| No-to-moderate ankylosis | 31.2 (27.7) | **35.3 (30.9)**** | **36.7 (32.0)**** | **37.8 (33.0)*** | **39.0 (31.7)*** | **40.3 (33.6)*** |
| $CSDS_{hierarchical}$ | | | | | | |
| All | 55.4 (47.1) | **57.7 (46.4)**** | **58.5 (46.4)**** | **59.7 (46.3)*** | **60.6 (46.1)*** | **61.7 (46.2)*** |
| No-to-moderate ankylosis | 27.9 (24.4) | **31.1 (26.4)**** | **32.3 (27.6)**** | **34.0 (29.7)*** | **35.3 (29.7)*** | **36.8 (31.1)*** |

Data are shown as mean (SD). Values in bold are statistically significant. * $P < 0.05$, ** $P < 0.01$; all 2-tailed. Wilcoxon signed-rank test was applied to compare scores at baseline with scores at other timepoints. No-to-moderate ankylosis was defined as a baseline SPARCC SSS for ankylosis < 7. CSDS: Composite Structural Damage Score; SPARCC SSS: Spondyloarthritis Research Consortium of Canada Sacroiliac Structural Scores.

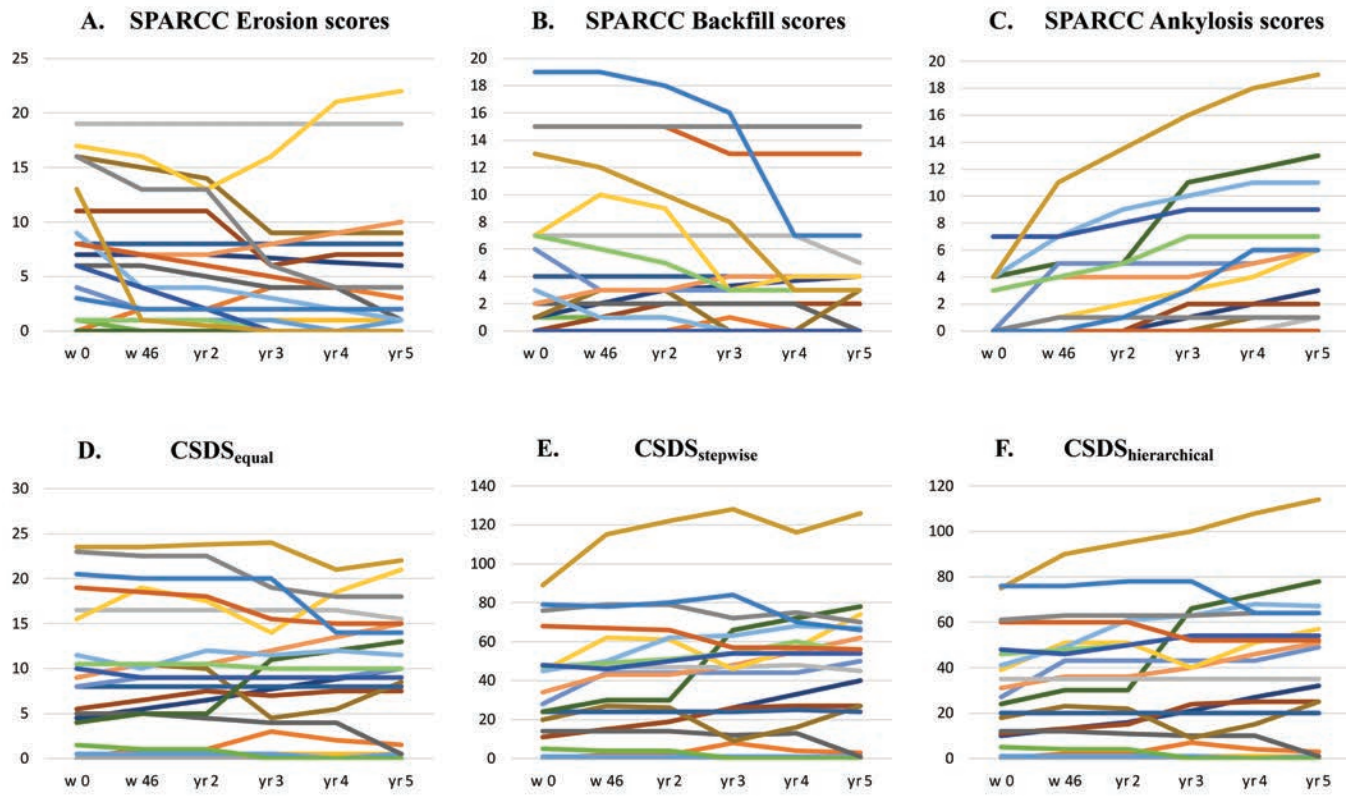


*Figure 1.* (A–C) Development in SPARCC SIJ Structural Scores for erosion, backfill, and ankylosis over 5 years after initiation of a TNFi for patients with no-to-moderate ankylosis. Each line represents 1 of the 23 patients, illustrating the diversity of the course of the structural damage progression. Erosion and backfill overall had a decreasing tendency whereas ankylosis tended to increase. (D–F) Change in the axSpA MRI SIJ CSDSs ($CSDS_{equal}$, $CSDS_{stepwise}$, $CSDS_{hierarchical}$) over the 5 years. $CSDS_{equal}$ generally seemed to increase less than $CSDS_{hierarchical}$ and $CSDS_{stepwise}$. axSpA: axial spondyloarthritis; CSDS: Composite Structural Damage Score; MRI: magnetic resonance imaging; SIJ: sacroiliac joint; SPARCC: Spondyloarthritis Research Consortium of Canada; TNFi: tumor necrosis factor inhibitor.

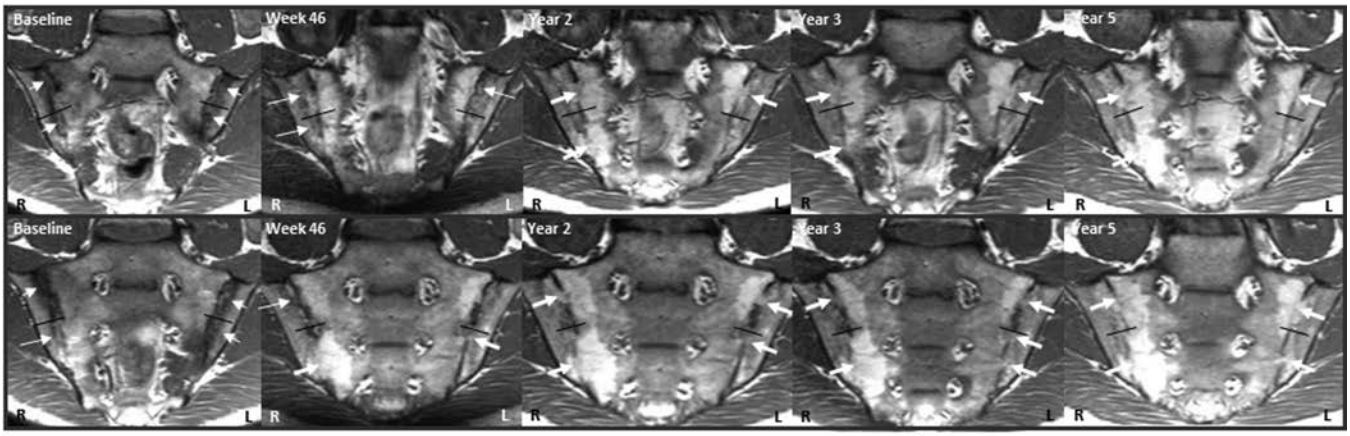


*Figure 2.* T1-weighted MRIs illustrating structural damage progression (i.e., change in erosion, backfill, and ankylosis) at baseline, Week 46, and Years 2, 3, and 5 in a patient initiating TNFi therapy. The images are from the same patient from the midsection (upper panel) and the posterior section (lower panel) of the cartilaginous part of the joint, and shown with the best possible slice match. Right upper SIJ: At baseline extensive erosion is seen in the mid and posterior section of the SIJ (short thin arrows) and at Week 46 backfill is seen in these areas (long thin arrows). From Year 2, ankylosis appears and progresses to Year 5 (thick arrows). Right lower SIJ: At baseline erosion is particularly seen in the midsection (short thin arrow) and backfill in the posterior section (long thin arrow). At Week 46 ankylosis is seen in the posterior section and at Year 2 in the mid sections (thick arrows), and the ankylosis progresses to Year 5. Left upper SIJ: At baseline erosion is seen in the mid and posterior section (short thin arrows) and at Week 46 backfill is seen in the midsection (long thin arrow). From Year 2 ankylosis is seen in both the mid and posterior sections (thick arrows). Left lower SIJ: At baseline a few small erosions are seen (short thin arrows). At Week 46 one ankylosing bone bridge is seen, and at Year 3 two ankylosing bone bridges is seen in the posterior section (thick arrows). MRI: magnetic resonance imaging; SIJ: sacroiliac joint; TNFi: tumor necrosis factor inhibitor.

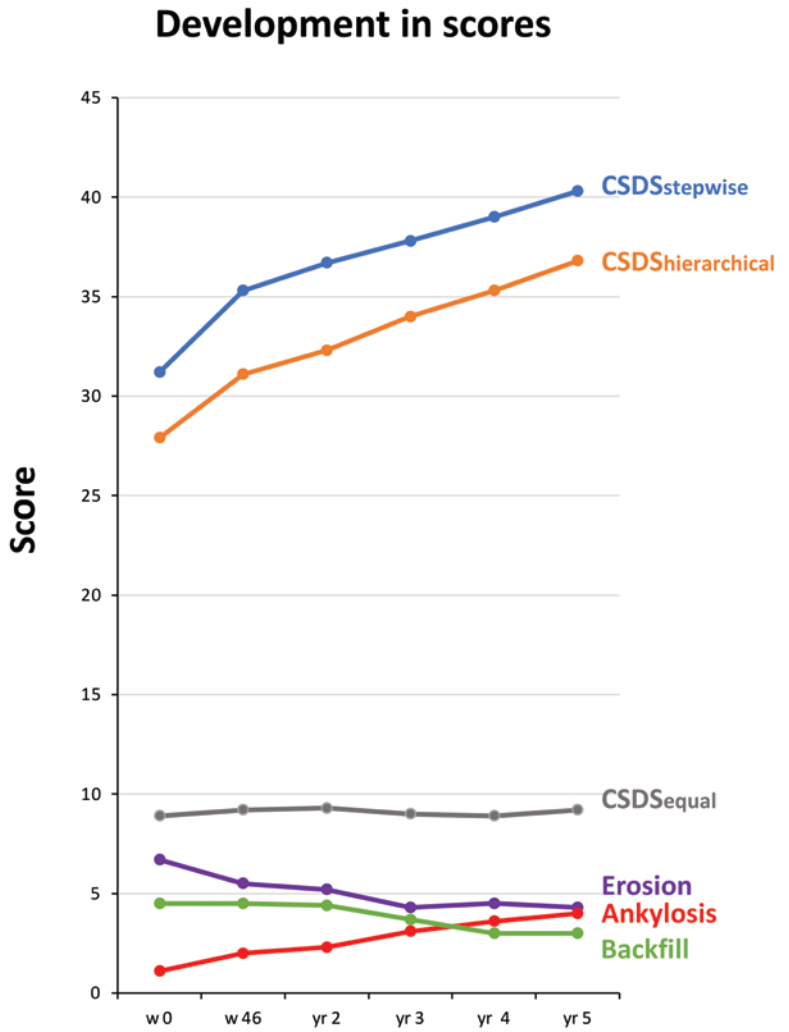


*Figure 3.* The development over time for SPARCC SSS erosion, backfill, and ankylosis, and $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ in the patients with no-to-moderate ankylosis. CSDS: Composite Structural Damage Score; SPARCC SSS: Spondyloarthritis Research Consortium of Canada Sacroiliac Joint Structural Score.

SPARCC scores for fat, erosion, and backfill and negatively with BASDAI at baseline. Further, $CSDS_{hierarchical}$ correlated positively with SPARCC ankylosis in this group. In the group of patients with almost complete bilateral ankylosis, $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ correlated negatively with SPARCC SIJ inflammation and positively with SPARCC ankylosis.

Changes in Years 0–5 in $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ in all 33 patients and in the group with no-to-moderate ankylosis correlated positively with change in SPARCC scores for fat. Change in $CSDS_{equal}$ also correlated positively with change in erosion and backfill, whereas $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ correlated positively with ankylosis and negatively with SPARCC SIJ inflammation.

*Annual changes in axSpA MRI SIJ CSDSs.* In the group of all 33 patients and in the group with no-to-moderate ankylosis, the more pronounced adjusted annual progression rate for $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ was statistically significant over the first year (baseline to Week 46) compared to the annual progression for the fourth year (Year 3 to 4) . The SRMs were highest for change at baseline to Week 46 for the group of patients with no-to-moderate ankylosis where $CSDS_{hierarchical}$ (0.64) was slightly higher than for $CSDS_{stepwise}$ (0.59), that is, both had moderate responsiveness. The SRM of $CSDS_{equal}$ (0.25) was lower than $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ (i.e., only had small responsiveness; Supplementary Table 1, available with the online version of this article). Results were comparable with missing data replaced by using last observation carried forward (Supplementary Table 2).

## DISCUSSION

This study introduces 3 novel preliminary composite scores of MRI SIJ structural damage (CSDS) that are based on the primary scores of the individual lesions from SPARCC SSS assessment of erosion, backfill, and ankylosis. A composite score of erosion, backfill, and ankylosis has, to our knowledge, not been reported previously. The 3 preliminary algorithms had various

*Table 3.* Correlation between clinical/MRI variables and $CSDS_{equal}$, $CSDS_{stepwise}$, and $CSDS_{hierarchical}$ at baseline and change Years 0–5 in all patients, patients with no-to-moderate ankylosis and patients with almost complete ankylosis at baseline.

| | $CSDS_{equal}$ | | | | | $CSDS_{stepwise}$ | | | | | $CSDS_{hierarchical}$ | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | | | Change 0–5 yrs | | Baseline | | | Change 0–5 yrs | | Baseline | | | Change 0–5 yrs | |
| | All | No-to-moderate ankylosis | Almost complete ankylosis | All | No-to-moderate ankylosis | All | No-to-moderate ankylosis | Almost complete ankylosis | All | No-to-moderate ankylosis | All | No-to-moderate ankylosis | Almost complete ankylosis | All | No-to-moderate ankylosis |
| Symptom duration, yrs | 0.40 | −0.01 | −0.40 | – | – | **0.59*** | −0.11 | −0.40 | – | – | **0.59*** | 0.11 | −0.40 | – | – |
| ASDAS | −0.29 | −0.16 | 0.06 | 0.10 | 0.05 | −0.21 | −0.17 | 0.06 | −0.17 | −0.08 | 0.21 | −0.16 | 0.06 | −0.17 | 0.06 |
| BASDAI (0–10) | **−0.40*** | **−0.46*** | −0.06 | −0.03 | −0.23 | **−0.37*** | **−0.50*** | −0.06 | 0.15 | −0.06 | **−0.35*** | **−0.46*** | −0.06 | −0.15 | −0.03 |
| BASMI (0–10) | 0.18 | −0.03 | −0.24 | 0.12 | 0.06 | **0.38**** | 0.09 | −0.24 | 0.13 | 0.19 | **0.38*** | 0.08 | −0.24 | 0.07 | 0.13 |
| SPARCC SIJ Inflammation (0–72) | **−0.37*** | −0.04 | **−1.00**** | −0.19 | −0.27 | **−0.47**** | −0.02 | **−1.00**** | **−0.55**** | **−0.54**** | **−0.47**** | −0.03 | **−1.00**** | **−0.57**** | **−0.53**** |
| SPARCC SSS Fat (0–40) | **0.56**** | **0.62**** | −0.31 | **0.48**** | **0.50*** | **0.57**** | **0.53**** | −0.31 | **0.55**** | **0.55**** | **0.56**** | **0.52*** | −0.31 | **0.52**** | **0.50*** |
| SPARCC SSS Erosion (0–40) | −0.02 | **0.74**** | – | **0.57**** | **0.55**** | −0.29 | **0.58**** | – | 0.02 | 0.06 | −0.31 | **0.55**** | – | −0.16 | −0.13 |
| SPARCC SSS Backfill (0–20) | 0.20 | **0.86**** | – | **0.47**** | **0.45*** | −0.08 | **0.81**** | – | 0.19 | 0.16 | −0.09 | **0.80**** | – | 0.14 | 0.11 |
| SPARCC SSS ankylosis (0–20) | **0.61**** | 0.29 | **1.00**** | 0.11 | 0.24 | **0.83**** | 0.43 | **1.00**** | **0.63**** | **0.69**** | **0.84**** | **0.45*** | **1.00**** | **0.75**** | **0.76**** |
| mSASSS (0–72) | 0.24 | 0.07 | 0.18 | −0.18 | −0.23 | 0.26 | 0.08 | 0.18 | −0.15 | −0.18 | 0.26 | 0.06 | 0.18 | −0.07 | −0.10 |
| Total SIJ score (mNY grade 0–8) | **0.61**** | 0.35 | – | 0.09 | 0.15 | **0.70**** | 0.39 | – | 0.18 | 0.13 | **0.70**** | 0.39 | – | 0.12 | 0.02 |

Values in bold are statistically significant. * $P < 0.05$, ** $P < 0.01$; all 2-tailed. Test is Spearman rank correlation analysis of baseline variables vs baseline CSDS and change in variables vs change in CSDS. No-to-moderate ankylosis defined as a baseline SPARCC SSS for ankylosis < 7 and almost complete ankylosis defined as a baseline SPARCC SSS for ankylosis > 18. ASDAS: Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Index; BASMI: Bath Ankylosing Spondylitis Metrology Index; CSDS: Composite Structural Damage Score; MRI: magnetic resonance imaging; mNY: modified New York criteria; mSASSS: modified Stoke Ankylosing Spondylitis Spine Score; SIJ: sacroiliac joint; SPARCC: Spondyloarthritis Research Consortium of Canada; SSS: SIJ Structural Score.

profiles to capture structural progression in the SIJ. $CSDS_{stepwise}$ and $CSDS_{hierarchical}$, in which backfill and ankylosis weighed more than erosion, showed a more pronounced progression in structural damage scores, a correlation with BASMI, a closer correlation with progression in ankylosis and radiographic SIJ damage, and finally a higher sensitivity to change than $CSDS_{equal}$.

The rationale for the selection of the 3 CSDS algorithms are described in the Methods section. $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ showed stronger correlation with ankylosis at baseline and over time compared to $CSDS_{equal}$. Further, the $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ performed similarly in terms of annual progression rate and correlation with SPARCC scores for ankylosis in contrast to $CSDS_{equal}$. SRM was, albeit mostly small, moderate for $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ over the first 46 weeks (up to 0.64), which was higher than for $CSDS_{equal}$. Thus, $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ seemed best suited as sensitive outcome measures for structural progression.

The responsiveness of $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ was also higher than previously reported for other MRI lesion scores in studies of patients with axSpA treated with a TNFi in 48 weeks (SRM range 0.19–0.48),[24] and over 2 years for the modified Stoke AS Spine Score[25,26] in studies of patients with AS (median 0.35, range 0.22–0.57).[27–34] This suggests that $CSDS_{stepwise}$ and $CSDS_{hierarchical}$ capture structural progression over relatively short time frames, in contrast to the traditional measures of structural progression in axSpA.

Methodological studies of SIJ radiography have all reported small changes in mNY scores over 1, 2, and 4 years and proposed that change should only be reported in studies of at least a 2-year duration and only as the percentage of patients with a change score > 0.[6,35,36] A lower sensitivity to change or responsiveness of SIJ radiography can partly be explained by 3-D anatomy being projected into 2 dimensions on radiographs.[37] In contrast, the MRI of the SIJs provides detailed tomographic images of the 3-D anatomy, making it possible to perform a slice-based (i.e., granular), lesion-based evaluation that is not possible with radiography.

To our knowledge, this is the first study to combine structural MRI scores into an overall combined structural score to describe the overall evolution of SIJ structural damage. To date, studies have only focused on single lesion scores. In the EMBARK trial, erosion scores decreased statistically significantly and backfill scores increased statistically significantly after 12 weeks' treatment with a TNFi compared with placebo, and the study reported that this may reflect an early healing process.[10] However, it could in principle, also be considered a progression in structural damage observed over a short time period. Other studies reported that erosion scores decreased significantly over 12 weeks in patients treated with adalimumab compared to placebo.[11] Development of new erosion was more often seen in patients treated with NSAIDs compared with a TNFi and a statistically significant higher proportion of patients treated with a TNFi developed new fat metaplasia,[15] associated with resolution of inflammation. Erosion is the first structural lesion that occurs following inflammation, whereas backfill and ankylosis occur at later stages. Combining the structural lesions (i.e., erosion, backfill, and ankylosis) into 1 outcome measure would allow comprehensive ascertainment of structural lesion progression in a single measurement, which may be useful in clinical trials. Bone erosion, backfill, and ankylosis represent different aspects in the disease development in axSpA, and the introduced combined CSDS assessment should be considered an addition to the current outcome measures; changes in the individual components of structural damage should, of course, still be analyzed. Future studies are needed to elucidate whether the individual components or a CSDS better reflect the outcomes that are most relevant to the patient and which are most useful in clinical trials for comparison of the amount of structural progression during different treatments.

Limitations of our study include the relatively small number of patients evaluated. Further, 10 patients had almost complete ankylosis at baseline, which meant that almost all change observed over time were derived from the 23 patients with no-to-moderate ankylosis at baseline. Most of the 23 patients had some ankylosis at baseline. In a patient group with less baseline ankylosis, more changes may have been observed over time. Moreover, all patients were treated with TNFi. Investigation of other populations (e.g., with less SIJ damage or receiving other treatments), are important for further validation and to clarify the most useful algorithm. Further, the weighting of scores was not evidence based, but the study should also be considered as exploratory, and the CSDS need further validation. CT could have been interesting as a reference standard, but this was not done due to the radiation exposure involved. Regarding MRI, it would have been optimal to have 2 readers, allowing assessment of interreader agreement. For statistical analyses, we did not correct for multiple comparisons. This was not done since the study was an exploratory, hypothesis-generating study.

In conclusion, we have developed 3 preliminary CSDS for MRI assessment of the SIJs in patients with axSpA that allow aggregate assessment of MRI progression from erosion through backfill to ankylosis. $CSDS_{stepwise}$ and $CSDS_{hierarchical}$, in which backfill and ankylosis weighed more than erosion, showed a more pronounced progression in structural damage scores and a clear correlation with changes in the individual structural lesions, and a higher sensitivity to change than $CSDS_{equal}$. The proposed novel approaches may be useful for monitoring and comparing structural progression in patients with axSpA receiving different therapies, but need further validation in observational cohorts and randomized controlled trials.

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## ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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