A Comparison of New Bone Formation in Patients With Ankylosing Spondylitis and Patients With Diffuse Idiopathic Skeletal Hyperostosis

A Retrospective Cohort Study Over Six Years

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Objective. Ankylosing spondylitis (AS) and diffuse idiopathic skeletal hyperostosis (DISH) are both characterized by new bone formation in the spine but presumably have a different pathogenesis. This study was undertaken to compare the natural course of new bone formation in AS and DISH.

Methods. Lateral radiographs of the cervical and lumbar spine from AS and DISH patients obtained at ≥2 time points within 6 years were analyzed to quantify osteophyte development. Radiographs were scored in a blinded manner by 2 readers using the modified Stoke AS Spine Score (mSASSS). Bone spurs were categorized as having an angle of <45° or >45°.

Results. AS patients (n = 146) were younger than DISH patients (n = 141) (mean ± SD 54.2 ± 12.3 years versus 60.3 ± 7.7 years). Symptom duration (mean ± SD) was 23.6 ± 11.2 years in AS patients and 21.6 ± 12.4 years in DISH patients. The mSASSS at baseline was lower in DISH patients (mean ± SD 14.3 ± 6.7) than in AS patients (20.5 ± 14.5) but had increased by a similar amount at followup (3.3 ± 4.2 versus 4.1 ± 9.5). The mean mSASSS progression rate per year (1.3 units) was also comparable. The mean ± SD number of syndesmophytes per patient was higher in AS (5.7 ± 5.5) than DISH (2.7 ± 2.8) patients (P < 0.001), while degenerative bone spurs (mean ± SD) were more frequent in DISH (1.4 ± 1.8) than AS (1.0 ± 1.4) patients. AS patients developed more new bone spurs with an angle of <45° than >45° per patient (mean ± SD 2.1 ± 2.7 versus 0.6 ± 0.9) (P < 0.001), while similar amounts of both types of bone formation were seen in DISH patients.

Conclusion. Our findings indicate that the rates of new bone formation in AS and DISH are largely similar. Both groups show osteophyte development, but as expected, syndesmophytes are more frequent in AS patients while DISH patients have more degenerative bone spurs. The nature of the different mechanisms of bone formation needs further study.

Diffuse idiopathic skeletal hyperostosis (DISH) and ankylosing spondylitis (AS) are the 2 most common diseases that are characterized by ossification of the ligaments and tendons in both the axial skeleton and peripheral sites (1–3). Formation of new bone in the spine is most typically seen at the anterior site of the vertebrae, but it does also occur at other sites in both diseases (4,5). The lower part of the thoracic spine and the upper part of the lumbar spine are the most frequently involved regions in both conditions (6–8). Osteophytes, commonly referred to as bone spurs, are bony projections that form along joint margins (9).

The radiographic appearance of both diseases is very similar, but the underlying pathology differs. Although there is no doubt that both spinal inflammation and new bone formation occur in AS, exactly how they are related is not so clear (10). Even less is known about DISH in this regard. While immune-mediated inflammatory rheumatic processes largely based on a genetic background are believed to occur in AS (11), DISH is

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most frequently assumed to be characterized by degenera
tive changes related to metabolic abnormalities (12,13). Other differences include the clinical character-
istics of the patients (14–16), such as an older age at
diagnosis in DISH patients. High rates of ossification at
entheses and ligaments are pathognomonic for DISH;
these are used to differentiate DISH from AS (17,18).
Importantly, Olivieri et al (19) have recently shown that
the clinical outcomes of DISH and AS are rather similar.

The classification criteria proposed by Resnick et
al (20) are often used to diagnose DISH. These require
hyperproliferative bony changes in ≥4 adjacent verte-
brae, preservation of the intervertebral disc space, and
absence of apophyseal joints or inflammatory sacroiliac
changes. The diagnosis of AS has frequently been made
using the 1984 New York classification criteria, which, in
addition to typical clinical symptoms, require structural
changes in the sacroiliac joints (21), while the typically
seen syndesmophytes, although not part of the New
York criteria, support a diagnosis of AS. Use of these
criteria has contributed to the well-established diagnos-
tic delay for axial spondyloarthritis of up to 10 years (22).

According to international recommendations (23), patients with AS who have persistent high disease
activity should be treated with tumor necrosis factor
(TNF) blockers (24–27). Although efficacy, including
positive effects on disease activity and function, has been
shown on a short- and a long-term basis, an inhibitory
effect on radiographic progression has not been docu-
mented to date. However, it should be noted that no
prospective placebo-controlled trial has been performed
because of ethical considerations. Thus, the radi-
ographic scoring results of the main anti-TNF trials have
been analyzed in comparison to the historical cohort of
the Outcome Assessments in AS International Study
(28–30).

In this study, we systematically evaluated radio-
graphs obtained in patients with DISH and AS at
baseline and followup, concentrating on new bone for-
amation. This allowed us to compare the rates of radi-
ographic progression in both diseases over several years.

PATIENTS AND METHODS

Patients. Overall, 141 patients who were diagnosed as
having DISH were retrospectively included in this study, and
146 patients with established AS from a historical cohort (31)
were included for comparison. All patients were hospitalized in
our clinic between 1993 and 2005 for different reasons despite
their primary diagnosis of DISH or AS. Patients were hospi-
talized mainly for increased back pain, functional decline, and
the need for intensive physical therapy. None of the AS
patients received any biologic agents during the time period
evaluated in this study. Inclusion criteria in the present study
were an established diagnosis of DISH (according to the
Resnick criteria [32]) or AS (according to the 1984 modified
New York criteria [21]) and the availability of complete sets of
radiographs of the cervical and the lumbar spine in the lateral
view for at least 2 different time points within 6 years.

Radiographic assessment of chronic spinal changes.
All radiographs were obtained using the standard protocol in
our hospital for the cervical and the lumbar spine, as previously
described (31). Two readers who were blinded with regard to
the diagnosis, the patient’s personal data, and the time order of
imaging analyzed the images independently in 2 different ways.

First, images were assessed for the presence of differ-
ent radiographic signs of bone formation. In the absence of any
other standardized definition, our practical approach for the
differentiation between AS-related changes and DISH-related
changes was to set a 45° angle as the cutoff. This is consistent
with previous proposals by our group (33,34). Measuring the
horizontal angle of new bone formation on lateral spinal
radiographs, AS-related changes (syndesmophytes) were as-
sumed to typically show a growth angle of ≤45° to the anterior
vertebral side, while a growth angle of >45° was assumed to
represent more DISH-related changes (spondylophytes).

The second method of analyzing the images consisted of
quantifying radiographic progression using the modified
Stoke AS Spine Score (mSASSS) (35) for all patients in this
study. Although the mSASSS has not been evaluated for use in
DISH patients, it was used for scoring both cohorts in this
study, since no other scoring system is available for DISH. The
mean mSASSS scores were used to analyze the rates of
radiographic progression. Similar to the approach used in a
recent study (30), “agreement” between readers was defined as
no difference between the 2 readers in the change in mSASSS
between time points. “Some disagreement” was defined as a
small difference of ≤2 mSASSS units, and “major disagree-
ment” was defined as a difference between the 2 readers of >2
units in the change in mSASSS between time points.

Statistical analysis. The association between the base-
line characteristics of the patients and the degree of radi-
ographic progression was assessed by the nonparametric
Jonckheere-Terpstra trend test. The paired Wilcoxon rank
sum test was used to compare scores between different time
points. Radiographic progression between time points was
analyzed by multivariate analysis after adjustment for baseline
radiographic status. The Mann-Whitney U test was used to
compare the subgroups of patients. Reliability and agreement
between readers was assessed by comparison of individual
radiographs and analysis of “agreement,” “some disagree-
ment,” and “major disagreement,” as described above.

RESULTS

Baseline characteristics. There were differences
between the 2 cohorts with respect to clinical character-
istics, mainly because of disease-specific parameters
(Table 1). The mean ± SD symptom duration was
23.6 ± 11.2 years in AS patients and 21.6 ± 12.4 years in DISH patients. The mean ± SD followup time was 3.0 ± 2.0 years in the DISH cohort and 3.8 ± 1.7 years in the AS cohort (range 1–6 years for both), while the mean number of followup visits with radiography was 2.9 in the DISH cohort and 2.7 in the AS cohort (range 2–6 for both).

Evaluation of radiographic progression by assessment of different types of osteophytes. At baseline, 126 of the 141 DISH patients (89.4%) and 132 of the 146 AS patients (90.4%) showed osteophyte formation. Bone spurs with an angle of <45° were seen in 107 of 141 DISH patients (75.9%) and in 121 of 146 AS patients (82.9%) (P = 0.148). At followup, spinal osteophytes were found in 128 of 141 DISH patients (90.8%) and in 136 of 144 AS patients (94.4%), while 112 of 141 DISH patients (79.4%) and 128 of 146 AS patients (87.7%) had bone spurs of <45° (P = 0.079).

In a more detailed analysis, the mean ± SD number of new osteophytes that developed between baseline and followup was higher in patients with AS (2.5 ± 2.8) (Figure 1) than in patients with DISH (1.1 ± 1.3) (Figure 2). This difference was statistically significant (P < 0.001) (Table 2). This was mainly due to the development of new bone spurs of <45° in AS patients. AS patients developed a mean ± SD of 2.1 ± 2.7 new bone spurs of <45° per patient and 0.4 ± 0.8 new bone spurs of >45° per patient (P < 0.001). DISH patients developed a mean ± SD of 0.6 ± 0.9 new bone spurs of <45° per patient and 0.5 ± 1.0 new bone spurs of >45° per patient (P = 0.332) (Table 2).

Quantification of spinal radiographic progression using the mSASSS. The mean ± SD mSASSS increased from 14.3 ± 6.7 to 17.6 ± 7.7 (mean change 3.3 ± 4.2 mSASSS units) in the DISH patients and from 20.5 ± 14.5 to 24.5 ± 16.1 (mean change 4.1 ± 9.5 mSASSS units) in the AS patients between baseline and followup (P < 0.001, baseline versus followup for both). However, after adjustment for baseline mSASSS, no significant differences were seen between the 2 diseases (P = 0.51). Furthermore, the mean ± SD radiographic progression rate per year was the same in both diseases, with 1.3 ± 1.0 mSASSS units per year in the DISH patients and 1.3 ± 2.5 mSASSS units per year in the AS patients.

Correlation between radiographic changes and clinical parameters. A significant correlation between age and the occurrence of bone spurs of >45° at baseline was found in AS patients (r = 0.33, P < 0.001), while this was not the case for bone spurs of <45° (r = 0.16, P = 0.06). There was no correlation between age and the occurrence of either bone spurs of >45° (spondylo-
Table 2. Within-group and between-group comparisons of the numbers of structural lesions and the radiographic scores in AS and DISH patients

<table>
<thead>
<tr>
<th></th>
<th>AS (n = 146)</th>
<th>DISH (n = 141)</th>
<th>P</th>
<th>AS versus DISH</th>
</tr>
</thead>
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<tr>
<td>Mean followup, years</td>
<td>3.8 ± 1.7</td>
<td>3.0 ± 2.0</td>
<td></td>
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<tr>
<td>Bone spurs of &gt;45°</td>
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</tr>
<tr>
<td>Baseline</td>
<td>1.0 ± 1.4</td>
<td>1.4 ± 1.8</td>
<td>0.047</td>
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<tr>
<td>Followup</td>
<td>1.2 ± 1.6</td>
<td>1.9 ± 2.1</td>
<td>&lt;0.001</td>
<td>0.017</td>
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<tr>
<td>Bone spurs of &lt;45°</td>
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<tr>
<td>Baseline</td>
<td>5.7 ± 5.5</td>
<td>2.7 ± 2.8</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Followup</td>
<td>7.8 ± 6.4</td>
<td>3.2 ± 2.9</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Any osteophyte</td>
<td></td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>6.7 ± 5.5</td>
<td>4.1 ± 3.2</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
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<tr>
<td>Followup</td>
<td>9.0 ± 6.3</td>
<td>5.0 ± 3.5</td>
<td>&lt;0.001</td>
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<td>New lesions per patient between baseline and followup</td>
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<tr>
<td>Bone spurs of &gt;45°</td>
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<td>0.5 ± 1.1</td>
<td>0.640</td>
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<tr>
<td>Bone spurs of &lt;45°</td>
<td>2.1 ± 2.7</td>
<td>0.6 ± 0.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Any osteophyte</td>
<td>2.5 ± 2.8</td>
<td>1.1 ± 1.3</td>
<td>&lt;0.001</td>
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<tr>
<td>mSASSS</td>
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<tr>
<td>Baseline</td>
<td>20.5 ± 14.5</td>
<td>14.3 ± 6.7</td>
<td>0.001</td>
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<tr>
<td>Followup</td>
<td>24.5 ± 16.1</td>
<td>17.6 ± 7.7</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Change</td>
<td>4.1 ± 9.5</td>
<td>3.3 ± 4.2</td>
<td>&lt;0.001</td>
<td>0.509</td>
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</table>

* Values are the mean ± SD. mSASSS = modified Stoke Ankylosing Spondylitis Spine Score.
† Versus ankylosing spondylitis (AS) patients at baseline.
‡ Versus diffuse idiopathic skeletal hyperostosis (DISH) patients at baseline.

phytes) (r = 0.02, P not significant [NS]) or bone spurs of <45° (r = 0.03, P NS) in DISH patients. No other clinical parameters, including sex, correlated with the occurrence or development of new bone spurs of any type in either group.

Reliability and agreement between readers. Both readers were in agreement with regard to the change in mSASSS in 83 of 146 patients with AS (56.8%) and in 75 of 141 patients with DISH (53.2%), while there was some disagreement with regard to the scores in 54 of 146 patients with AS (37%) and in 50 of 141 patients with DISH (35.5%) and major disagreement with regard to the scores in 9 of 146 patients with AS (6.2%) and in 16 of 141 patients with DISH (11.3%). Similar to previous findings (31), the agreement was higher in patients with an mSASSS of 0 at baseline as scored by both readers.

Prediction of radiographic progression. The presence of bone spurs with an angle of <45° at baseline was significantly predictive of higher numbers of new such spurs of <45° at followup in the AS group (mean ± SD 2.4 ± 2.7 new bone spurs of <45° per patient in patients with bone spurs of <45° at baseline versus 1.1 ± 2.7 new bone spurs of <45° per patient in patients with no bone spurs of <45° at baseline; P < 0.001) but not in the DISH group. The presence of bone spurs of >45° at baseline was significantly predictive of higher rates of new bone spurs of >45° in DISH patients (mean ± SD 0.9 ± 1.4 new bone spurs of >45° per patient in patients with bone spurs of >45° at baseline versus 0.3 ± 0.8 new bone spurs of >45° per patient in patients with no bone spurs of >45° at baseline; P < 0.001) but not in AS patients.

DISCUSSION

To our knowledge, this is the first study to compare the rates of radiographic progression in patients with AS and DISH in detail over a long followup period. Both diseases showed significant increases in the mean numbers of spinal osteophytes per disease and per patient after a mean followup period of 3 years (maximum 6 years). Surprisingly, the mean radiographic progression was similar in patients with AS and patients with DISH on both the group level (mSASSS progression per disease per year) and the individual level (mSASSS progression per patient per year). This was not really expected, since more radiographic progression was assumed to occur in AS.

However, since we performed not only quantitative, but also qualitative analyses, major differences between AS and DISH were also detected, and this is consistent with the content of current rheumatology textbooks. The mean number of bone spurs with an angle of <45° (almost equivalent to syndesmophytes) at baseline and at followup was higher in patients with AS than in patients with DISH, as expected, and the rates
were similar to those reported in other studies (36,37), while the mean rate of the development of new bone spurs of >45° of degenerative appearance was comparatively lower in AS patients (14.6%) than in DISH patients, and this was similar to the results of previous analyses (33). Indeed, the numbers of bone spurs of >45° in AS patients were recently shown not to change much over time, and their inclusion in mSASSS analyses had almost no influence on the final study results (33).

In contrast, the mean rates of new bone spurs of >45° and of <45° per patient with DISH per year were similar. This finding is not easy to interpret; it could indicate that different mechanisms play a role in DISH, but it could also call into question simple explanations for new bone formation, such as inflammation versus degeneration.

The underlying mechanisms of the development of new bone formation in both diseases are unclear to date. In AS, there is some evidence that inflammation precedes radiographic progression in the axial skeleton (11,38,39). However, there is also evidence of a disconnect (10), and other authors have suggested that the development of new syndesmophytes has to be considered mainly as a repair mechanism that is associated with a transformation of previously inflamed lesions to fatty degenerative changes (10). This special feature was not investigated in our study. In DISH patients, there is no data on the possible relationship between hyperproliferative changes and potentially preceding inflammatory lesions. Taking into account that DISH patients have a higher body mass index than patients with degenerative disc disease (14), an underlying inflammation cannot be excluded. Since the numbers of new spondylophytes at followup were rather similar in AS patients and DISH patients, biomechanical reasons for bone growth and other noninflammatory mechanisms may be assumed in patients >50 years of age in both groups.

Another interesting finding of this study is the predictive role of the presence of degenerative bone spurs at baseline with respect to the future development of such changes in patients with DISH. This is similar to what our group and others have previously reported for the development of syndesmophytes in AS (28,33), and it is a phenomenon that is widely recognized in rheumatic diseases (40).

The retrospective design of our study does not limit its scientific value, since data on the natural course of both diseases is scarce and since prospective trials to analyze the radiographic progression of AS patients receiving conventional therapy are unlikely to be performed in the near future. The data and radiographs collected in this study were obtained in patients who had been hospitalized in our center for different reasons, which were mainly, but not exclusively, related to disease activity. The demographic and clinical characteristics of our AS patients were similar to those of patient cohorts described in the literature. Since the patients had been admitted to inpatient care because of symptoms in the axial skeleton, it seems likely that they had more severe disease activity and radiographic damage. The percentage of radiographic AS-related changes at baseline supports this assumption. Nevertheless, our data represent the natural radiographic progression in 2 large cohorts of patients admitted to our hospital over several years.

In contrast to AS, the diagnosis of DISH is based on radiographic changes in the thoracic spine. However, the analyses in this study concentrated on cervical and lumbar radiographs. Indeed, the fact that the lower part of the thoracic spine and the upper part of the lumbar spine are the most frequently involved regions in both conditions (7,41) has implications for this study since, due to the well-known technical limitations of radiographic assessment of the thoracic spine because of the lung tissue, this part of the spine could not be subjected to scoring. This circumstance is likely to lead to a relative underestimation of new bone formation in both diseases. In any case, the evaluation of the cervical and lumbar radiographs in this study showed that syndesmophytes and osteophytes do also occur in patients with DISH. Studies using other imaging techniques, such as low-dose computed tomography or magnetic resonance imaging, are needed to assess the thoracic spine in both diseases.

For the quantification of spinal lesions in this study, a widely accepted scoring system established in AS, the mSASSS, was used. The mSASSS has not been evaluated for use in patients with DISH, and there is no other scoring method available for quantification of structural changes in this disease. However, the performance of this scoring system in assessing radiographic changes in patients with DISH was good in our study. This was expected because osteoproliferative bony changes are pathognomonic for both AS and DISH. Osteodestructive changes play only a minor role in the mSASSS (33). Furthermore, the differentiation between syndesmophytes and spondylophytes followed clear definitions (as described in Patients and Methods). Whether our proposal for a modification of the mSASSS, the Radiographic AS Spinal Score (RASSS) (8), which concentrates on bone formation and which
also includes the lower part of the thoracic spine, would be even more reliable to assess disease-related changes and differentiate between AS and DISH, needs further evaluation. We were unable to include the RASSS in the present study, since the thoracolumbar junction was not clearly visible in many of the radiographs.

In summary, we show that the overall rate of new bone formation in AS and DISH is similar. New bone formation of different types (syndesmophytes and degenerative osteophytes) does occur in both diseases, and it is possible to radiographically differentiate between AS and DISH. Disease-specific radiographic features at baseline were predictive of further and faster progression in both AS and DISH. Quantification of radiographic changes showed similar progression rates in AS and DISH, which supports the hypothesis that non-inflammatory mechanisms may play a role in both diseases. These findings are useful for future research in osteoproliferative inflammatory and noninflammatory rheumatic diseases.

AUTHOR CONTRIBUTIONS
All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Baraliakos had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Baraliakos, Listing, Buschmann, von der Recke, Braun.

Acquisition of data. Baraliakos, Listing, Buschmann, von der Recke, Braun.

Analysis and interpretation of data. Baraliakos, Listing, Buschmann, von der Recke, Braun.

REFERENCES


