DETERMINANTS OF HYPERKYPHOSIS IN PATIENTS WITH ANKYLOSING SPONDYLITIS.
Category: extended report

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Abstract

Objective: To determine clinical and radiographic determinants of hyperkyphosis in patients with AS.

Methods: Of 135 patients with AS participating in the OASIS cohort spinal hyperkyphosis was assessed by the occiput-to-wall distance (OWD) and defined as OWD > 0. Disease activity was assessed by the BASDAI. Wedging of the vertebrae was calculated as the Ha / Hp ratio as described by Genant. Structural damage of the spine was assessed by the mSASSS. Hip involvement was assessed by the BASRI and defined as a score > 2. Data were analysed by multiple regression analysis on van der Waerden-normal OWD values, with mean Ha / Hp ratio, mSASSS, hip involvement and BASDAI as explanatory variables, and age, sex and disease duration after diagnosis as co-variates.

Results: 61 patients (45.2%) had an OWD > 0cm. Of these, 81% were male patients versus 57% in the group with normal OWD (p<0.001). Forty-two patients had wedged thoracic vertebrae. Of those 42 patients, 27 (44%) patients showed an increased OWD, as compared to 15 (20%) of the 74 AS patients with normal OWD (p=0.005). OWD was significantly correlated with mean wedging of the thoracic spine (ρ = -0.45, p= 0.01), mSASSS (ρ = 0.56, p= 0.01) and hip involvement (ρ=0.2, p=0.05). Multivariate analysis showed that mSASSS (standardised beta (stβ)= 0.52; p<0.001), wedging of the thoracic spine (stβ = -0.28; p= 0.01), and BASDAI (stβ = 0.15; p= 0.05) are independent determinants of OWD.

Conclusion: Radiological damage of the cervical and lumbar spine, thoracic wedging and actual disease activity are determinants of hyperkyphosis in patients with AS. These findings could be important in determining treatment goals in AS.

Key words: ankylosing spondylitis, disability, occiput–to–wall distance, osteoporosis, wedging and radiological damage
Introduction

Hyperkyphosis of the upper part of the spine is a frequent clinical problem among patients with ankylosing spondylitis (AS).\(^1\,2\,3\) In our prevalence cohort of patients with AS (Outcome in AS International Study (OASIS) cohort) with a mean disease duration of 9.4 years, 49\% of the patients have some degree of hyperkyphosis, if it is expressed as an Occiput-to-Wall Distance (OWD) of more than 0 cm.\(^\text{4}\) The prominent position of the head and neck may give functional and psychological impairments for the patients.\(^5\) They may be unable to see straight ahead, may have difficulties in activities of daily living. Further, severe hyperkyphosis could result in compression of the abdominal viscera.\(^6\)

The degree of hyperkyphosis in patients with AS is related to radiological damage.\(^7\) In general, hyperkyphosis is also associated with vertebral osteoporosis, and it is increasingly recognised that osteoporosis is a problem in patients with AS.\(^8\,9\,10\,11\,12\) Vertebral deformities are regarded as one of the classical hallmarks of vertebral osteoporosis. In a population-based study, the relative risk for vertebral morphometric deformities in patients with AS was 7.6 as compared to the control population.\(^13\) Other investigators found a prevalence of vertebral deformities in 10 to 17\% of the patients with AS seen in the clinic.\(^14\,15\,16\,17\) In a pilot study we have shown that thoracic vertebral deformities but not lumbar vertebral deformities are related to an increase of OWD in patients with AS.\(^17\) However, it is not known how all potentially contributory factors (such as disease activity, structural damage visible on radiographs, hip involvement and vertebral wedging) interrelate with respect to explaining increased OWD in patients with AS. Therefore we investigated the independent contribution of various factors that may explain hyperkyphosis in a cross-sectional study of patients with AS.

Patients and methods

We included 139 patients of the Outcome in AS International Study (OASIS) cohort, an international longitudinal, observational study on outcome in AS, with a male to female ratio of 2:1, a mean disease duration of 9.4 years (defined as years since diagnosis) and a mean duration of complaints of 17.9 years. Consecutive patients in four secondary and tertiary referral centres, fulfilling the modified New York criteria for AS were included.\(^18\) Patients were followed according to a fixed protocol.\(^4\) Data from the 4-year assessment were used in the present analysis and include Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)\(^19\), Bath Ankylosing Spondylitis Functional Index (BASFI)\(^20\), lateral radiographs of the cervical, thoracic, and lumbar spine and radiographs of the pelvis. To assess structural damage the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) was used.\(^21\) This method scores the anterior site of the lumbar (lower border T12 – upper border S1) and cervical (lower border C2 – upper border T1) spine at a lateral view. The anterior corners of each vertebra are examined and scored 1 for an erosion, sclerosis and / or squaring, 2 for a syndesmophyte and 3 for total bony bridging, giving a maximum possible score of 72. The mSASSS was applied by one observer (AW) (fig. 1). In a previous experiment we have determined that intra-observer (intraclass correlation coefficient (ICC) = 0.98) and inter-observer (ICC = 0.99) reliability on mSASSS status scores of this observer were excellent.\(^22\) Radiographic hip-involvement determined according to the Bath Ankylosing Spondylitis Radiology Index (BASRI)-hip\(^23\) was as follows: 0: no involvement; 1: (possible) focal joint space narrowing,.2: definite narrowing leaving a circumferential joint space > 2 mm; 3: narrowing with circumferential joint space ≤ 2 mm or bone-on-bone apposition of < 1 cm; 4: bone deformity or bone-on-bone apposition ≥ 1 cm. Grades 1 and 2 increase by one grade if two of the following bony changes are present: erosions, osteophytes, protrusion. Scores are applied to both hips. For the purpose of this article, hip involvement was defined as a BASRI-
Anterior (Ha) and posterior (Hp) height of the vertebrae was measured on lateral radiographs of the thoracic (T4-12) and lumbar spine (L1-5) in millimetres by one observer (DV) (fig.2). Imaging of the first three thoracic vertebrae mostly is inadequate so we omitted them in the analyses. Wedging of a vertebra was calculated as the Ha / Hp ratio. This was defined as mild if the Ha/Hp ratio was >0.75 and ≤0.80, as moderate if the Ha/Hp ratio was >0.60 and ≤0.75, and as severe if the Ha/Hp ratio was ≤0.60.24 We calculated the mean wedge (mean Ha/Hp ratio) of all thoracic and lumbar vertebrae per patient, as well as for the lumbar and thoracic spine separately.

To assess interobserver reliability of measuring anterior and posterior height two readers measured 70 vertebrae in 10 patients with AS. These vertebrae were chosen by an independent observer who tried to include the entire spectrum of deformities. The smallest detectable difference (SDD) calculated according to the limits of agreement method by Bland & Altman was 0.14 for Ha/Hp ratio. The ICC for mean vertebral wedging was 0.93 (95%CI: 0.85-0.96) for absolute heights and 0.84 (95%CI: 0.74-0.96) for Ha/Hp ratios.

To quantify hyperkyphosis the distance between occiput and wall (OWD) was assessed with the patient standing with the heels and back against the wall, with hips and knees as straight as possible. The chin was held at the usual carrying level and the patient undertook maximal effort to touch the head against the wall. The distance between the wall and the occiput was measured in centimetres with one decimal. The better of two tries was recorded.26,27 Patients were grouped as having a normal OWD (= 0 cm) or an increased OWD (> 0 cm).

**Statistical analysis**

Chi-square tests used to test differences is proportions. Spearman’s correlation coefficients were calculated to investigate univariate associations between OWD and mean wedging, mSASSS and BASDAI. Linear regression analysis was performed to investigate the independent contribution of BASDAI, mean wedging, hip involvement, and mSASSS to explain variation in the dependent variable OWD. Covariates in the analysis were age, disease duration and sex.

Not normally distributed variables were first normalised by the Van der Waerden technique.

**Results**

Of the 139 patients, four patients could not be included because of incomplete data. Table 1 presents some baseline characteristics of the patients. Of the 135 patients with complete data 50 of the 90 (56%) male patients and 11 of the 45 (24%) female patients had an OWD > 0 cm (p= 0.001). As compared to patients with a normal OWD, patients with an increased OWD were older, had a higher mean disease duration, and were more often of male gender. Disease activity (BASDAI) was similar in the two groups with a higher level of physical limitation (BASFI) and radiographic damage of the spine (mSASSS). In our cohort 12 patients (9%) had severe radiological hip involvement; eight of them had an OWD > 0 cm.

Overall, forty-two patients showed 89 vertebral wedgings defined as a Ha/Hp ratio ≤ 0.80. When comparing fracture rate in patients with normal OWD (n = 74) to increased OWD (n = 61), 15 (20%) patients in the normal OWD group had vertebral fractures compared to 27 (44%) patients with OWD > 0 cm. Of these 89 fractures 59 (66%) were mild, 29 (33%) moderate and 1 (1%) severe. All fractures were found in the thoracic spine except for four fractures (3 moderate and 1 mild) in the first lumbar vertebra and one mild fracture in the fourth lumbar vertebra (table 2). When comparing the number of fractures with OWD we found significant correlations, both analysing all fractures and analysing fracture groups (no, 1 or > 1 fracture and yes/ no fractures) versus OWD (p= 0.002, p= 0.01, p= 0.003).

Spearman’s correlation coefficients were calculated to investigate univariate associations between OWD and mean wedging in the thoracic and lumbar spine, mSASSS, hip...
involvement and BASDAI. Clearly, OWD showed significant correlations with all factors except with the mean lumbar wedging and with the BASDAI. (Table 3). In order to explore the independent contribution of different variables to explain variation in OWD (as a continuous measure), linear regression analysis was performed. Because age, sex and disease duration may spuriously be associated with OWD, these variables were included as co-variates. Table 4 shows the main results of this analysis. Variation in OWD was primarily explained by mSASSS. There was, however, an independent contribution of both mean thoracic wedging and cross-sectional assessed BASDAI. In this analysis severe hip involvement did not independently contribute to explaining variation in OWD, although a positive trend could be recognised.

OWD was merely associated with wedging of the thoracic part of the vertebral column. However, the mSASSS does not take the thoracic spine into account, but only the cervical and lumbar spine. We analysed the contribution of the mSASSS of the cervical spine and of the lumbar spine separately in explaining OWD by regression models, including the same variables as in the main model. The contribution of both site-specific mSASSSs in explaining variation in OWD was approximately similar (stβ = 0.62 for the cervical mSASSS and 0.57 for the lumbar mSASSS). This is not unexpected since the cervical and lumbar mSASSS were highly correlated (ρ= 0.64).
Table 1. Clinical and radiological data of all patients in relation to normal and increased occiput-to-wall distance

<table>
<thead>
<tr>
<th></th>
<th>Patients OWD = 0 (n=74)</th>
<th>Patients OWD &gt; 0 (n=61)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean ± SD)</strong></td>
<td>45.7 (10.5)</td>
<td>53.5 (11.9)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean disease duration after diagnosis, years (± SD)</strong></td>
<td>13.3 (9.7)</td>
<td>16.5 (9.6)</td>
<td>P=0.06</td>
</tr>
<tr>
<td><strong>Sex, % Males</strong></td>
<td>57%</td>
<td>81%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean BASDAI (± SD)</strong></td>
<td>3.3 (2.3)</td>
<td>3.6 (2.4)</td>
<td>p=0.28</td>
</tr>
<tr>
<td><strong>Mean BASFI (± SD)</strong></td>
<td>2.8 (2.3)</td>
<td>4.8 (2.5)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean mSASSS (± SD)</strong></td>
<td>8.0 (10.9)</td>
<td>28.5 (22.0)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean wedge Thoracic spine (± SD)</strong></td>
<td>0.94 (0.04)</td>
<td>0.90 (0.06)</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td><strong>Mean wedge Lumbar spine (± SD)</strong></td>
<td>1.03 (0.05)</td>
<td>1.05 (0.06)</td>
<td>P=0.013</td>
</tr>
<tr>
<td><strong>At least one wedged vertebra (Number of patients)</strong></td>
<td>15 (74)</td>
<td>27 (61)</td>
<td>P=0.005</td>
</tr>
<tr>
<td><strong>Severe hip involvement (Number of patients)</strong></td>
<td>4 / 70</td>
<td>8 / 53</td>
<td>P=0.12</td>
</tr>
</tbody>
</table>

* For the difference between patients with OWD=0 vs. patients with OWD>0

OWD: occiput-to-wall distance
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
BASFI: Bath Ankylosing Spondylitis Functional Index
mSASSS: modified Stoke Ankylosing Spondylitis Spine Score
SD: standard deviation
Table 2. Distribution of the number of vertebral fractures and rating of their severity.

<table>
<thead>
<tr>
<th></th>
<th>Number of fractures</th>
<th>Percentage of total fractures</th>
<th>Mild¹ fracture</th>
<th>Moderate² fracture</th>
<th>Severe³ fracture</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4</td>
<td>4</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T5</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>T6</td>
<td>13</td>
<td>10</td>
<td>6</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>T7</td>
<td>15</td>
<td>11</td>
<td>8</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>T8</td>
<td>14</td>
<td>10</td>
<td>6</td>
<td>8</td>
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<tr>
<td>T9</td>
<td>7</td>
<td>5</td>
<td>5</td>
<td>2</td>
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</tr>
<tr>
<td>T10</td>
<td>9</td>
<td>7</td>
<td>8</td>
<td>1</td>
<td></td>
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<tr>
<td>T11</td>
<td>12</td>
<td>9</td>
<td>9</td>
<td></td>
<td>3</td>
</tr>
<tr>
<td>T12</td>
<td>7</td>
<td>5</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td></td>
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<tr>
<td>L2</td>
<td></td>
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<tr>
<td>L3</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>L4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>L5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹: Ha / Hp ratio >0.75 and ≤ 0.80; ²: Ha / Hp ratio >0.60 and ≤ 0.75; ³: Ha/ Hp ratio ≤ 0.60.
Table 3. Univariate correlation coefficients between occiput-to-wall distance, wedging, disease activity, and radiological hip involvement.

<table>
<thead>
<tr>
<th></th>
<th>mSASSS</th>
<th>Mean wedging thoracic spine</th>
<th>Mean wedging lumbar spine</th>
<th>BASDAI</th>
<th>Hip score &gt; 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>OWD</td>
<td>0.56**</td>
<td>-0.45**</td>
<td>0.16</td>
<td>0.10</td>
<td>0.20*</td>
</tr>
<tr>
<td>mSASSS</td>
<td>1</td>
<td>-0.32**</td>
<td>0.05</td>
<td>0.05</td>
<td>0.16</td>
</tr>
<tr>
<td>Mean wedging thoracic spine</td>
<td>1</td>
<td>-0.10</td>
<td>0.10</td>
<td>-0.02</td>
<td></td>
</tr>
<tr>
<td>Mean wedging lumbar spine</td>
<td></td>
<td>1</td>
<td>-0.001</td>
<td>0.10</td>
<td></td>
</tr>
<tr>
<td>BASDAI</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>-0.03</td>
</tr>
</tbody>
</table>

** p = 0.01; * p = 0.05
Table 4. Multivariate analysis of variables determining occiput to wall distance in patients with ankylosing spondylitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardised beta</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>mSASSS</td>
<td>0.47</td>
<td>0.01</td>
</tr>
<tr>
<td>Mean wedging thoracic spine</td>
<td>0.28</td>
<td>0.01</td>
</tr>
<tr>
<td>BASDAI</td>
<td>0.15</td>
<td>0.05</td>
</tr>
<tr>
<td>Hip involvement</td>
<td>0.12</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Adjusted for age, sex and disease duration after diagnosis

Model $R^2 = 0.42$
Figure 1. Assessment of mSASSS
figure 2. Measurement of vertebral heights
Discussion

In the entire OASIS cohort spinal hyperkyphosis (OWD > 0) occurs in half of the patients. In our study we found a clear correlation between radiological damage assessed on the anterior site of the cervical and lumbar spine (mSASSS) and hyperkyphosis. Furthermore, the mean thoracic wedging was significantly and independently contributory to explaining OWD, while lumbar wedging deformities did not contribute to the OWD. Wedging was assessed in the thoracic spine as well as in the other parts, but mSASSS does not score thoracic spine. The reason is that radiographic changes in this particular area of the spine are difficult to score and reproducibility is not good. Braun et al published data on MRI changes in the thoracic spine and they found that the thoracic spine, as compared to the cervical and lumbar spine, was prominently involved. ^2^5^ Missing the thoracic spine scores would potentially have been critical if we had not found a correlation between mSASSS and OWD, since in such a scenario preferential thoracic spine damage could still be an explanation. But we found a correlation between radiological changes and OWD, even without including thoracic spine data, and we believe that if we had included the thoracic spine, these data would only have strengthened our findings.

In a multivariate analysis, in addition to mSASSS and mean thoracic wedging, disease activity (BASDAI) independently, although marginally, contributed to spinal hyperkyphosis. Considering the hip involvement in AS as a possible factor leading to limitation of movement, one can assume the influence of fixed flexion of the hips on the OWD. Therefore, we investigated the correlation between hip involvement and hyperkyphosis. We analysed this by comparing OWD in patients with severe hip involvement (BASRI > 2) versus no or mild hip involvement (BASRI ≤ 2). This analysis showed a trend, but did not reach statistical significance in both the univariate and multivariate analyses, possibly due to the low prevalence of hip involvement. It should be stressed that the variables that we have investigated here only in part explain hyperkyphosis. Other potentially contributory factors include inflammation of ligaments, muscles and entheses. And in a previous article we described the role of disc deformities in hyperkyphosis. In this study we did not analyse these soft tissues, as we focused on vertebral wedging and radiographic damage.

A shortcoming of our study is the cross-sectional design. It would be preferable to have a prospective follow-up of patients with AS in an early phase of their disease and to observe the development of the spine deformity. On the other hand, others could not find a relation between radiological damage and disease duration, age at diagnosis or acute phase response in such prospective studies. In previous analyses Boonen et al concluded that there was no change in self-reported health status over a period of 4 years. In a long-term follow-up study of the OASIS cohort, in which patients were followed every 2 months during the first 2 years and every year thereafter, mean BASDAI did not change (stβ = 0.007; 95%CI: –0.013 to 0.027), which is why we believe a cross-sectional approach is justified.

Possible confounders of the relationship between wedging and OWD are age and sex, since OWD may increase with age, and since AS is a predominantly male disease with a more serious course in male as compared to female patients. However, we did not find a relationship between age, sex and OWD, neither univariate, nor multivariate. In AS the burden of illness is a result of longstanding inflammation and its consequence. Further, cumulative inflammation results in radiological damage reflected in mSASSS scores. In our study we found an independent significant relation between these factors and hyperkyphosis.

In analogy with peri-articular bone loss in RA we hypothesise that vertebral wedging is the result of peri-articular bone loss in the spine. Inflammatory processes are found to be associated with increased bone loss and bone turnover. This results in reduced bone mineral density (BMD).
Osteoporosis is shown to be associated with inflammatory rheumatic diseases, such as RA\textsuperscript{31,32} and AS.\textsuperscript{11} Vertebral deformities are considered to be the main feature of osteoporosis. Our study confirmed an independent significant relation between wedging of (thoracic) vertebrae and hyperkyphosis.

In conclusion, we found three independent significant contributory factors to hyperkyphosis: structural damage of the spine, wedging of thoracic vertebrae and cross-sectional disease activity. In addition we found a significant higher BASFI in patients with an OWD > 0 cm. Therefore, in order to prevent or limit functional decline future studies on new therapies in the treatment of AS should include prevention, if possible, of the development of structural damage as well as prevention of the development of vertebral osteoporosis, and its effect on the development of hyperkyphosis.

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References


Figure 1

0  Normal
0  Erosion
1  Sclerosis
1  Squaring
2  Obvious
2  Syndesmophyte
3  Total bony
3  Bridge
figure 2. Measurement of vertebral heights
Determinants of hyperkyphosis in patients with ankylosing spondylitis

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