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Quantitation of Circumferential Syndesmophyte Height along the Vertebral Rim in Ankylosing Spondylitis Using Computed Tomography

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Abstract

Objective.—Using the 3-D imaging capability of computed tomography (CT), we developed an algorithm quantitating syndesmophyte height along the entire vertebral rim. We investigated its reliability and sensitivity to change, performed a 2-year longitudinal study, and compared it to CT measures of syndesmophyte volume.

Methods.—We performed thoracolumbar spine CT scans on 33 patients at baseline, Year 1, and Year 2, and computed syndesmophyte height in 4 intervertebral disc spaces (IDS). Height was computed every 5° (72 angular sectors) along the vertebral rim. These 72 measures were summed to form the circumferential height per IDS, and results from 4 IDS were summed to provide results per patient. To assess reliability, we compared results between 2 scans performed on the same day in 9 patients. Validity was assessed by associations with spinal flexibility.

Results.—Coefficient of variation for circumferential syndesmophyte height was 0.893% per patient, indicating excellent reliability. Based on the Bland-Altman analysis, an increase in circumferential height of more than 3.44% per patient represented a change greater than measurement error. At years 1 and 2, mean (SD) circumferential syndesmophyte height increases were 10.2% (11.7%) and 16.1% (14.0%), respectively. Sensitivity to change was 0.72 and 0.87 at years 1 and 2, respectively. Circumferential syndesmophyte height correlated with the Schober test ($r = -0.56$, $p = 0.0003$) and lateral thoracolumbar flexion ($r = -0.73$, $p < 0.0001$).

Conclusion.—CT-based circumferential syndesmophyte height had excellent reliability and good sensitivity to change. It was more highly correlated with spine flexibility than

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syndesmophyte volume. The algorithm shows promise for longitudinal studies of syndesmophyte growth.

Key Indexing Terms:

ANKYLOSING SPONDYLITIS; SYNDESMOPHYTE; COMPUTED TOMOGRAPHY

Spinal fusion in ankylosing spondylitis (AS) results from the fusion of apophyseal joints and bridging syndesmophytes[1]. Progression toward fusion is best monitored by the examination of syndesmophyte growth because it is more visible than the fusion of the apophyseal joints. The ability to track the development of syndesmophytes is essential for many types of AS studies, especially investigations of the effect of medications on syndesmophyte growth[2,3,4] and the search for biomarkers of bone formation[5,6,7]. The current standard method for the evaluation of syndesmophyte growth is the reading of radiographs using the modified Stoke AS Spinal Score (mSASSS), but this method[8] has some limitations. Poor visualization caused by the reliance on a 2-dimensional technique to assess a complex 3-D structure, combined with the use of a coarse semiquantitative scoring system, limits the validity and the sensitivity to change of this method[9].

To improve the assessment of syndesmophyte growth, we developed a computer algorithm that measures syndesmophytes on thoracolumbar computed tomography (CT) scans, exploiting the 3-D imaging capability of this modality[10,11]. The algorithm can measure the total syndesmophyte volume along the entire vertebral rim of an intervertebral disc space (IDS). We previously showed that the method had excellent reliability and very good validity compared to the readings of physicians[12]. In a 2-year longitudinal study, we also demonstrated that this method was much more sensitive to change than radiography and had very good longitudinal validity[13]. In addition to syndesmophyte volume, the algorithm can also evaluate syndesmophyte height. In our previous studies, we computed the maximal syndesmophyte height in each IDS, recording the height measurement at 1 single point along the entire vertebral rim. Circumferential syndesmophyte height, summing height measures taken all along the vertebral rim, is likely to be a much more informative and relevant measure for studies of drug efficacy or biomarkers of bone formation. Circumferential height also holds additional information compared to total syndesmophyte volume. When an increase in syndesmophyte volume is recorded, it is not known whether this is because of an increase in width (thickening), an increase in height, or both. An increase in height has special importance because it adds bone in the direction of fusion, whereas increases in width only do not contribute to fusion. Circumferential syndesmophyte height may, therefore, be related more to measurement of patient flexibility impairment and more useful in evaluating treatments that seek to preserve spine flexibility.

The objectives of our study were to assess the reliability of circumferential syndesmophyte height measurement, present a 2-year longitudinal study, evaluate its sensitivity to change, and examine its relation with measurements of spinal flexibility compared to previous CT quantitation of syndesmophytes.

MATERIALS AND METHODS

Patients.

Patients were enrolled at the US National Institutes of Health or Johns Hopkins Medical Institutions using the following inclusion criteria: age ≥ 18 years, diagnosis of AS by the modified New York criteria[14], and a Bath AS Radiology Index (BASRI) lumbar spine score of 0, 1, 2, or 3 (i.e., excluding patients with completely fused lumbar spines)[15]. To have representation of patients with different degrees of syndesmophytes, we enrolled at least 5 patients in each BASRI category. The study protocol was approved by the institutional review boards of both centers, and all patients provided written informed consent.

Study protocol.

Patients had a clinical evaluation and completed questionnaires, including the Bath AS Functional Index (BASFI; range 0–100 with higher scores representing greater limitations)[16]. Lumbar motion was evaluated using the modified Schober test and lateral thoracolumbar flexion, with examinations performed by 1 physician. Patients had antero-posterior and lateral radiographs of the thoracolumbar spine and thoracolumbar spine CT scans at study entry, 1 year, and 2 years.

CT scanning.

Patients were scanned on a Philips Brilliance 64 (slice thickness 1.5 mm, Philips) or a GE Lightspeed Ultra scanner (slice thickness 1.25 mm, GE Medical Systems). Spacing between slices was 0.7 and 0.625 mm for the Philips and GE, respectively. Voltage was 120 kVp and current was 300 mAs for both scanners. Scans were performed from T10 to L4, providing 4 IDS for processing: T11–T12, T12–L1, L1–L2, and L2–L3. The thoracolumbar junction was chosen because syndesmophytes have been shown to be most prevalent in this region[17,18]. The estimated equivalent radiation dose from the CT scan was 8.01 mSv (0.801 rem).

Reliability study.

A subsample of patients who had syndesmophytes at 1 or more levels agreed to undergo 2 thoracolumbar CT scans on the same day. After the first scan, patients stood up before lying down again for the second scan. This ensured that they did not lie in the same position and that the variation between scans was in the range expected in a longitudinal study.

CT image analysis.

We developed a semiautomated computer algorithm that detected syndesmophytes as bone projecting beyond the vertebral endplates in each IDS[10,11]. To compute circumferential syndesmophyte height, we divided the 360° of the vertebral endplate rim into 72 angular sectors of 5° each (Figure 1). We used 72 angular sectors, rather than more or fewer sectors, because this number provided measures that had good sensitivity to change and yet retained high reliability. Finer angular divisions resulted in measurements with lower reliability.

For each angular sector, we computed the height of all syndesmophyte voxels. Height is computed as distance to the endplate along the direction of the normal to the endplate. From the list of all heights, we recorded the maximum. This height was divided by the local disc height so that a value of 1 meant bridging and a value of 0 represented no syndesmophyte in the sector. If an angular sector had 2 syndesmophytes, 1 ascending and 1 descending, their heights were added (both heights were positive because the syndesmophytes were measured from the endplates from which they originate). Heights in the 72 angular sectors were added to provide the circumferential height per IDS (maximum of 72, which would represent a completely fused IDS). Further, circumferential height measures in 4 IDS were added to provide a total per patient (maximum of 288).

Radiography reading.

The 4 IDS processed by the algorithm were also scored on radiographs using mSASSS by 2 readers (MMW and LY). Scores of 1 were excluded because these do not represent syndesmophytes. We called this mSASSS, reduced to be comparable to the computed measurements, the “adapted mSASSS”. The agreement between the 2 readers was excellent, with intraclass correlations of 0.94 for IDS and 0.98 for patients.

Statistical analysis.

We assessed reliability by the difference in measured circumferential syndesmophyte height between paired scans done on the same day, their coefficients of variation (CV), and their intraclass correlation coefficients (ICC). We evaluated the 95% limits of agreement between paired measurements using the Bland-Altman analysis[19]. We applied a log-transformation to measurements that were found to be heteroskedastic. For such measurements, the limits of agreement were expressed in percentage terms[20].

Using Spearman correlations, we also tested the strength of the association between circumferential syndesmophyte height per patient and the duration of AS, Schober test, lateral thoracolumbar flexion (using the lower of right- and left-side values), and BASFI.

We measured the sensitivity to change at 1 year and 2 years using standardized response means (SRM)[21]. The SRM is the ratio of mean change to the SD of change. Larger values of SRM indicate greater sensitivity to change. CI for the SRM were derived using bootstrapping with 200 random samples. For comparison, we also computed the SRM for volume measures. To linearize the values and improve normality, a cube root function was applied to volumes. In addition, for the longitudinal study, cumulative probability plots of changes in circumferential syndesmophyte height over 1 year and 2 years were constructed. These plots can be used to assess whether measured heights agree with the accepted observations that syndesmophyte growth is progressive and irreversible.

Statistical analyses were performed using SAS software (version 9.2, SAS Institute Inc.).

RESULTS

Patients.

We enrolled 38 patients, 31 men and 7 women, with AS: mean (SD) age 46.1 years (11.5) and mean disease duration 20.0 years (11.8). Their mean Schober test was 3.3 cm (1.2), mean lateral thoracolumbar flexion was 11.1 cm(4.8), and mean BASFI was 25.7 (23.0). The mean circumferential height was 41.1 (51.0) per patient. Mean circumferential heights per patient were higher in those with higher mSASSS scores (Appendix 1).

Of these 38 patients, 33 participated in the longitudinal study and had additional CT scans at years 1 and 2. Twenty-four of the 33 patients (73%) were found by the CT algorithm to have existing syndesmophytes at baseline. The algorithm detected syndesmophytes in 81 IDS at baseline (61%). For those 33 patients, the mean circumferential height was 11.0 (17.1) per IDS and 44.0 (53.7) per patient.

Reliability study.

Nine patients (36 IDS) were enrolled in the reliability study. Reliability was evaluated for both circumferential height per IDS and per patient. The means and SD of circumferential syndesmophyte height measurements on the paired scans were very similar with small absolute differences (Table 1). Very high reliability was also reflected by the low CV values and high ICC. Reliability was higher for the sum of 4 IDS than for individual IDS. Circumferential height measures were heteroskedastic with larger interscan differences for IDS with higher circumferential height. The Bland-Altman analysis on log transformed values exhibited narrow 95% limits of agreement and few outliers, indicating very good reliability (Appendix 2). Based on the Bland-Altman plot, a difference of more than 5.6% represents change beyond those expected by measurement error for circumferential syndesmophyte height in an individual IDS. For summed values of the 4 IDS in an individual patient, the threshold was reduced to 3.4%.

In preliminary analyses, measurements with finer angular divisions were less reliable. For example, with 120 angular sectors of 3° each, the 95% limits of agreement for interscan differences per patient was ± 5.84%. For comparison, the 95% limits of agreement for syndesmophyte volumes per patient was ± 3%.

Associations with patient flexibility, BASFI, and disease duration.

Tests of association were performed using circumferential heights per patient. Among the 38 patients, circumferential syndesmophyte height had high correlations with physical measures of patient flexibility (the higher the syndesmophyte height, the lower the range of motion). Additionally, circumferential height was correlated with longer disease duration and higher BASFI scores (Table 2). In Table 2, for comparison, we also listed the correlation scores obtained with syndesmophyte volumes and maximal syndesmophyte height from a previous study[12]. Circumferential height had higher correlations with flexibility measures than measures of syndesmophyte volume or maximal height.

Sensitivity to change and longitudinal study.

Circumferential syndesmophyte height per patient was more sensitive to change at 1 year and 2 years than maximal syndesmophyte height and the adapted mSASSS, but less sensitive to change than syndesmophyte volume (Table 3).

The mean percentage progression (computable only for IDS and patients with baseline syndesmophyte measure larger than 0) of circumferential height for individual IDS was

10.7% at Year 1 and 17.4% at Year 2 (Table 4). Results were similar for this measure when aggregated by patient.

The cumulative probability plots (Figure 2) showed that circumferential heights increased for most IDS and patients. A small number of IDS exhibited negative changes at Year 1 (17%) and Year 2 (9.8%), but when summed per patient, there were no negative height changes at Year 2. As expected, the increases from baseline to Year 2 were visibly larger than from baseline to Year 1. The gap between the 2 curves was clear especially for circumferential heights per patient.

DISCUSSION

The ability to monitor syndesmophyte change is essential for understanding the processes that regulate syndesmophyte growth and for evaluating the effects of treatments on the progression of spinal fusion. For a method to be useful, it has to be accurate, reliable, and sensitive to change. We previously tested a new CT-based method for evaluating syndesmophytes in 3-D space. The method was fully quantitative, and measured syndesmophyte volume and maximal height in each IDS. Both volumes and maximal height had very good validity and reliability[12]. We have now extended the height measure from maximal height, measured at only 1 point along the vertebral rim, to circumferential height, measured in 72 angular sectors along the vertebral rim. Circumferential height clearly offers a more complete description of each IDS and represents a better reflection of the state of the disease in patients. In our present study, we found that circumferential height per patient had a higher sensitivity to change than maximal height, and correlated better with disease duration and objective measures of patient flexibility.

Circumferential height also had excellent reliability. However, error measures were heteroskedastic, which was not the case for maximal height. That is because if the algorithm makes a mistake for maximal height, it will be counted only once, while for circumferential height, it will be counted in all the angular sectors where syndesmophyte is detected. Reliability still remained very high with any change of 3.44% or more per patient exceeding the expected measurement error. We tested reliability by scanning patients twice on the same day. Measurement variability caused by differences in patient positioning on the scanner table was thus integrated into the error estimate. We measured height in 72 angular sectors of 5°. It afforded good sensitivity to change and good correlation with spinal flexibility. When we further increased the fineness of the angular division, measurement reliability dropped considerably compared to our previous methods.

In our previous work, syndesmophyte volumes were also computed all along the vertebral rim. Like circumferential syndesmophyte height, volumes also offer a complete description of each IDS. In fact, volumes exhibited better sensitivity to change while retaining similar reliability. That is probably because while circumferential height can only be added in 2 dimensions (in the z direction and along the vertebral rim), volumes can also grow in 1 additional dimension (they can thicken). For instance, an IDS that is completely fused can no longer progress in height, but it can still add volume by thickening. However, syndesmophyte volume thickening may be less relevant to patient movement than growth in height. Our tests of association indicate that circumferential syndesmophyte height per patient correlated better with measures of flexibility than volumes. This was particularly true for lateral thoracolumbar flexion (−0.73 for height, −0.60 for volume). In our longitudinal study, circumferential syndesmophyte heights increased in most IDS, but a small number of IDS exhibited decreases larger than the expected measurement error. These decreases could still represent measurement errors, because the Bland-Altman limits of agreement do not entail a certainty, but a 95% chance of not being an error. However, at this early stage of research using CT to image syndesmophytes, we cannot discount the possibility that these decreases may be real. Our study was limited by the relatively small number of patients examined, particularly in the reliability study. Recruitment for the reliability study is difficult because the 1-day repeated CT scan entails additional radiation exposure that advances knowledge but offers no clinical benefit.

We have presented a method that shows promise for use in characterizing the development and progression of syndesmophytes over time in research studies. It will permit the study of the modes of growth of syndesmophytes and help answer questions such as whether syndesmophytes preferentially grow in height or width. The method is particularly adapted to the study of the role of syndesmophytes in limiting patient flexibility and the evaluation of the effects of treatment on flexibility.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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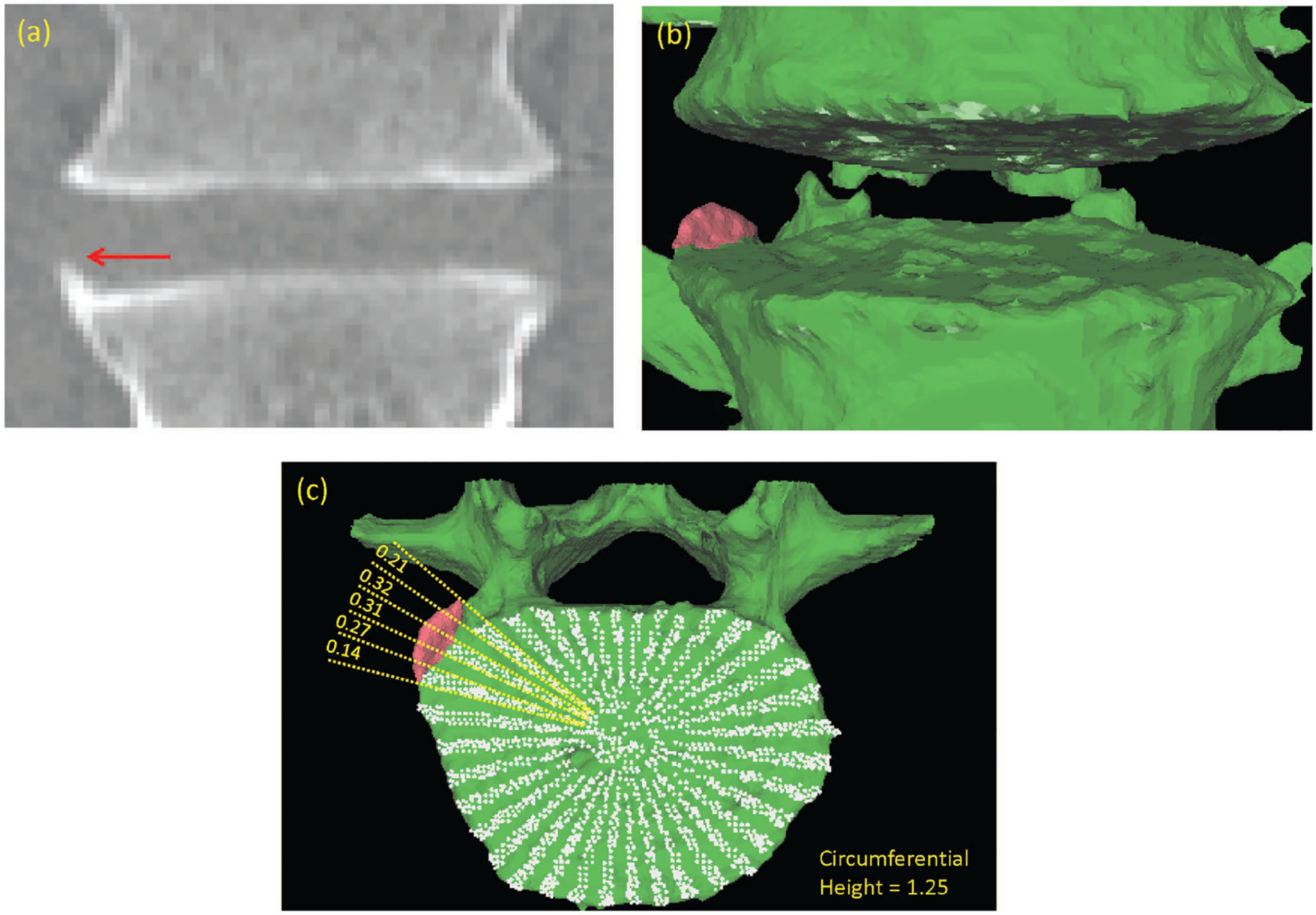

Figure 1.

Syndesmophyte height measurement along the vertebral rim. A. Coronal CT slice showing an IDS with a syndesmophyte (arrow). B. Three-D reconstruction of the same IDS with the same syndesmophyte in red. C. Top view of (B) showing the division of the vertebral rim into 72 angular sectors of 5° each (36 green and 36 white). The top left numbers indicate the relative syndesmophyte height (maximum syndesmophyte divided by the local IDS height) in each angular sector where the syndesmophyte was detected. These numbers are summed to form the circumferential height (bottom right). CT: computed tomography; IDS: intervertebral disc space.

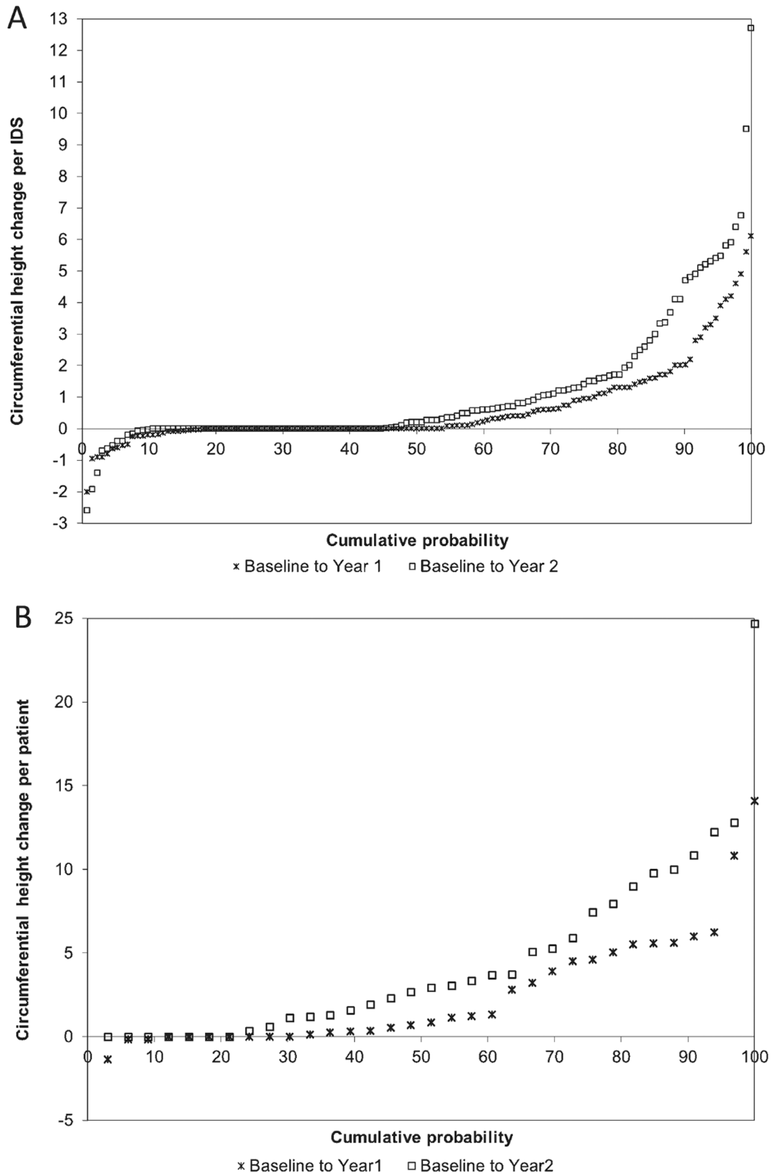

Figure 2.

Cumulative probability plots for changes in circumferential height measures (A) per IDS and (B) per patient. IDS: intervertebral disc space.

Table 1.

Reliability of circumferential height measures. Values are mean ± SD unless otherwise specified.

Height	First Scan	Second Scan	InterScan Difference*	ICC	CV, %	Limits of Agreement, %
Height per IDS, n = 36	12.6 ± 18.8	12.6 ± 18.7	0.28 ± 0.44	0.99	2.92	−5.64–5.64
Height per patient, n = 9	50.5 ± 65.9	50.4 ± 65.5	0.46 ± 0.46	1	0.893	−3.44–3.44

* Interscan difference in absolute positive value. ICC: intraclass correlation coefficient; CV: coefficient of variation; IDS: intervertebral disc space.

Table 2.

Association between quantitative measures of syndesmophytes per patient and disease duration and measures of patient flexibility and functionality.

Characteristics	Circumferential Height		Maximal Height		Volume	
	r	p	r	p	r	p
Disease duration	0.38	0.02	0.34	0.04	0.35	0.03
Schober test	−0.56	0.0003	−0.55	0.0003	−0.48	0.0003
Lateral thoracolumbar flexion	−0.73	< 0.0001	−0.60	< 0.0001	−0.60	< 0.0001
BASFI	0.34	0.04	0.38	0.02	0.32	0.02

BASFI: Bath Ankylosing Spondylitis Functional Index.

Table 3.

Standardized response means for circumferential height, maximal height, and volumes of syndesmophytes and mSASSS per patient. Values are mean (95% CI).

Characteristics	Baseline to Yr 1	Baseline to Yr 2
Circumferential height	0.72 (0.71–0.74)	0.87 (0.85–0.89)
Maximal height	0.54 (0.53–0.55)	0.68 (0.68–0.69)
Volume	1.10 (1.08–1.13)	1.29 (1.27–1.32)
Adapted mSASSS, reader 1	0.26 (0.25–0.27)	0.23 (0.21–0.24)
Adapted mSASSS, reader 2	0.25 (0.23–0.26)	0.21 (0.20–0.22)

mSASSS: modified Stoke Ankylosing Spondylitis Spine Score.

Table 4.

Mean (SD) changes in syndesmophyte circumferential height over 1 and 2 years in absolute and percentage terms. Values are mean (SD) unless otherwise specified.

Characteristics	Per IDS			Per Patient		
	n	**Baseline to Yr 1**	**Baseline to Yr 2**	**n**	**Baseline to Yr 1**	**Baseline to Yr 2**
Original unit	132	0.63 (1.32)	1.14 (2.16)	33	2.52 (3.46)	4.57 (5.35)
Percentage*	81	10.7 (26.1)	17.4 (30.8)	24	10.2 (11.7)	16.1 (14.0)

*Percentage change can only be computed for IDS and patients with baseline syndesmophyte measures larger than 0. IDS: intervertebral disc space.