Association of Bone Morphogenetic Proteins with Spinal Fusion in Ankylosing Spondylitis

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ABSTRACT. ***Objective.*** To measure serum concentrations of bone morphogenetic proteins (BMP) in patients with ankylosing spondylitis (AS), and to investigate the relationship between BMP and clinical manifestations and radiographic changes.

Methods. We studied 60 consecutive AS patients with and 60 patients without spinal fusion. Spinal radiographs were assessed using the Bath Ankylosing Spondylitis Radiology Index (BASRI) and the modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS). Spinal fusion was defined as the presence of total bony bridging between 2 adjacent vertebral bodies in either the lumbar or cervical spine. Serum levels of BMP were determined by enzyme-linked immunosorbent assay.

Results. Patients with spinal fusion had higher serum levels of BMP-2 and BMP-4 than either the healthy controls or patients without spinal fusion ($p < 0.001$), but there was no difference between the latter 2 groups. Serum BMP-7, erythrocyte sedimentation rate, and C-reactive protein (CRP) levels were elevated in patients with spinal fusion compared with those without ($p < 0.05$). Serum BMP-4 and BMP-7 levels were higher in patients with hip involvement than in those without ($p < 0.05$). BMP-2 and BMP-4 levels had a significant correlation with spinal radiograph scores, especially for BASRI of the lumbar spine ($r = 0.356$ and 0.348, respectively, $p < 0.001$). CRP showed a significant correlation with spine BASRI and mSASSS scores ($r = 0.261$ and 0.260, respectively, $p < 0.05$).

Conclusion. Rising levels of BMP in AS patients with spinal fusion and the positive correlation between BMP and spinal radiograph scores indicate that BMP may play a role in the process of spinal ankylosis. Serum levels of BMP may reflect radiographic progression of the spine and hip joints. (First Release August 1 2010; J Rheumatol 2010;37:2126–32; doi:10.3899/jrheum.100200)

Key Indexing Terms:
ANKYLOSING SPONDYLITIS BONE MORPHOGENETIC PROTEIN SPINAL FUSION

Ankylosing spondylitis (AS), a form of spondyloarthritis (SpA), is a chronic inflammatory rheumatic disease that affects the axial skeleton, leading to structural damage and functional impairment[1]. The disease predominantly occurs in young people and has a strong genetic predisposition to human leukocyte antigen B27 (HLA-B27). There are 3 main musculoskeletal manifestations: spinal inflammation, peripheral arthritis, and enthesitis[1]. Definite AS is diagnosed if the radiological criterion of sacroiliitis (grade ≥ 2 bilaterally or grade 3–4 unilaterally) is present plus at least one clinical criterion[2]. Involvement of the axial skeleton usually starts in the sacroiliac joints and is followed by inflammation at different spinal sites. Imaging of the spine shows irregular erosion, sclerosis, and squaring of vertebral bodies. As the disease progresses, syndesmophytes grow from adjacent vertebrae and eventually meet to form a bony bridge. Widespread syndesmophyte bridging produces a radiographic appearance of "bamboo spine," which causes severe and permanent disability. The spinal ankylosis in AS is a slowly progressive process with much individual variation[3]. Development of bamboo spine can take years, but can also occur in early disease. Syndesmophytes can develop in the inflamed vertebral edges; however, syndesmophyte formation can be found at sites without evidence of inflammation on magnetic resonance imaging[4]. The relationship between inflammation and subsequent vertebral ankylosis remains unclear. Anti-tumor necrosis factor-α (TNF-α) agents can improve the inflammatory signs and symptoms of AS, but these treatments may be insufficient to halt radiographic progression of ankylosis[5]. Suppression of spinal inflammation only may not be enough to impede disease progression toward structural damage[6]. In addition to inflammation, other mechanisms may contribute to the pathogenesis of spinal fusion.

Bone morphogenetic proteins (BMP), members of the

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transforming growth factor-ß (TGF-ß) superfamily, play a crucial role in embryonic development, cell lineage determination, and osteoblastic differentiation and function. They are important for skeletal development and joint morphogenesis and appear to have a role in cartilage and bone homeostasis[7]. BMP are originally identified by their unique ability to induce ectopic cartilage and bone formation *in vivo*. BMP are also important in joint remodeling of arthritis, particularly in enthesophyte formation in SpA[8]. Most spinal pathological changes in SpA are related to enthesitis[9]. Enthesitis is a distinctive feature of SpA, and the enthesis, the insertion of ligaments or tendons into the underlying bone, is considered to be the primary site of inflammation[9,10]. Enthesitis is not only inflammation of the enthesis, but is associated with heterotopic cartilage and bone formation (enthesophyte). Different BMP are expressed in distinct stages of ankylosing enthesitis in mice[11]. Immunohistochemical staining revealed active BMP signaling in similar target cells in human SpA enthesitis. Recombinant human BMP were effective in inducing bone healing and enhancing spinal fusion in human trials[12]. Overproduction of BMP-2 and BMP-7 in patients with AS has been reported[13]. Although the mechanism of new bone formation is not fully defined in AS and related SpA, BMP are likely to play a significant role in spinal ankylosis and could be therapeutic targets[6].

AS is a common rheumatic disease in ethnic Chinese populations, with a prevalence ranging from 0.19% to 0.54%[14]. Fusion of the spine can cause chronic functional impairment. We investigated the serum levels of BMP in Chinese AS patients with and without spinal fusion. We also evaluated the relationship between BMP and inflammatory indicators, disease activity, functional ability, physical mobility, and radiographic severity.

MATERIALS AND METHODS

Patients and clinical assessments. We consecutively enrolled 120 patients (60 with spinal fusion; 60 without spinal fusion) from our outpatient clinic. All patients met the 1984 modified New York criteria for definite AS[2]. No biological agents had been used in these patients. For each patient, we recorded age, sex, disease duration, clinical manifestations, and treatment. Medical records were reviewed for information related to the clinical manifestations of patients, including uveitis, enthesitis, and peripheral arthritis. To assess disease activity, functional ability, spinal mobility, and global assessment, we used the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Functional Index (BASFI), Metrology Index (BASMI), and Patient Global Score (BAS-G), respectively[15,16,17,18]. All clinical assessments were evaluated by well trained nurses and rheumatologists. The control group consisted of 40 healthy volunteers who had no known diseases; they were matched by age and sex to the 120 patients with AS. This research was approved by the local medical ethical committee and written informed consent was obtained from all participants.

Radiological evaluations. The sacroiliac joints were scored using the modified New York criteria. The severity of radiological change in the hip joints, lumbar spine, and cervical spine was assessed separately by the Bath Ankylosing Spondylitis Radiology Index (BASRI) and modified Stoke Ankylosing Spondylitis Spinal Score (mSASSS)[19,20]. The total BASRI score included BASRI-hip (range 0–4) and BASRI-spine (range 2–12), which combined the scores of the sacroiliac joints (range 0–4), lumbar spine (range 0–4), and cervical spine (range 0–4). The mSASSS (range 0–72) was the sum of the lumbar and cervical spine scores. All radiographs were scored randomly and blindly by 2 experienced rheumatologists. Spinal fusion was defined as the presence of total bony bridging between 2 adjacent vertebral bodies (i.e., mSASSS score 3 at each site) in either the lumbar or cervical spine (Figure 1). Hip involvement was based on the BASRI-hip scoring system.

Measurement of BMP. Serum samples were collected from all subjects in the study population as they entered the study, and were kept frozen at –80˚C until use. We used commercial ELISA for BMP (Human BMP-2 and BMP-7, R&D Systems Inc., Minneapolis, MN, USA; BMP-4, RayBiotech Inc., Norcross, GA, USA), according to the manufacturer's instructions and carried out tests in duplicate. The minimum detectable dose of BMP-2 ranged from 4.3 to 29 pg/ml, and that of BMP-7 ranged from 0.79 to 7.83 pg/ml. The minimum detectable dose of BMP-4 was typically < 15 pg/ml. Laboratory evidence for inflammation in these AS patients was assessed by the erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Statistical analysis. Nonparametric statistics were adopted, since most continuous variables in the study were skewed in distribution. The differences in the continuous data were evaluated by Mann-Whitney U test for 2 independent group comparisons, and the Kruskal-Wallis H test for 3 independent group comparisons, with post-hoc multiple comparisons (Dunn's test). Correlation between 2 continuous or ordinal variables was expressed by Spearman's correlation coefficient. The chi-square test or Fisher's exact test was performed to compare categorical data, when appropriate. A p value < 0.05 was considered statistically significant, if not addressed, while the type I error in post-hoc comparisons was corrected by the Bonferroni rule. Data analysis was done by SPSS for Windows, version 17.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

Patient characteristics. Table 1 describes the disease-related characteristics of the AS patients and the differences between patients with and without spinal fusion. The control subjects consisted of 36 men and 4 women, mean age 34.8 ± 9.4 (± standard deviation) years. A male predominance was noted in these AS patients. No differences were found in the percentage of the sexes, HLA-B27, use of nonsteroidal antiinflammatory drug or sulfasalazine treatment, or cumulative history of enthesitis, uveitis and peripheral arthritis between the 2 patient groups. In contrast, patients with radiographic spinal fusion were significantly associated with older age, longer disease duration, and higher spinal BASRI, mSASSS, BASFI and BASMI scores. Patients with spinal fusion also had significantly elevated ESR, CRP, and BMP levels. There were no differences in the BASDAI and BAS-G assessments.

BMP levels among subjects. Patients with AS showed higher serum BMP-2 levels than the controls, but the difference was not statistically significant (92.3 ± 164.0 vs 49.4 ± 20.3 pg/ml, respectively; p = 0.07). Patients with spinal fusion had higher levels of BMP-2 than either controls (98.0 ± 188.5 vs 49.4 ± 20.3 pg/ml; p < 0.001) or patients without spinal fusion (98.0 ± 188.5 vs 86.6 ± 136.5 pg/ml; p < 0.001), but there was no difference between the latter 2 groups (Figure 2A). Serum BMP-4 levels of AS patients were significantly higher than those of the controls (129.4 ± 327.6 vs 22.2 ± 24.0 pg/ml; p = 0.001). Patients with spinal fusion also had higher levels of BMP-4 than either the con-

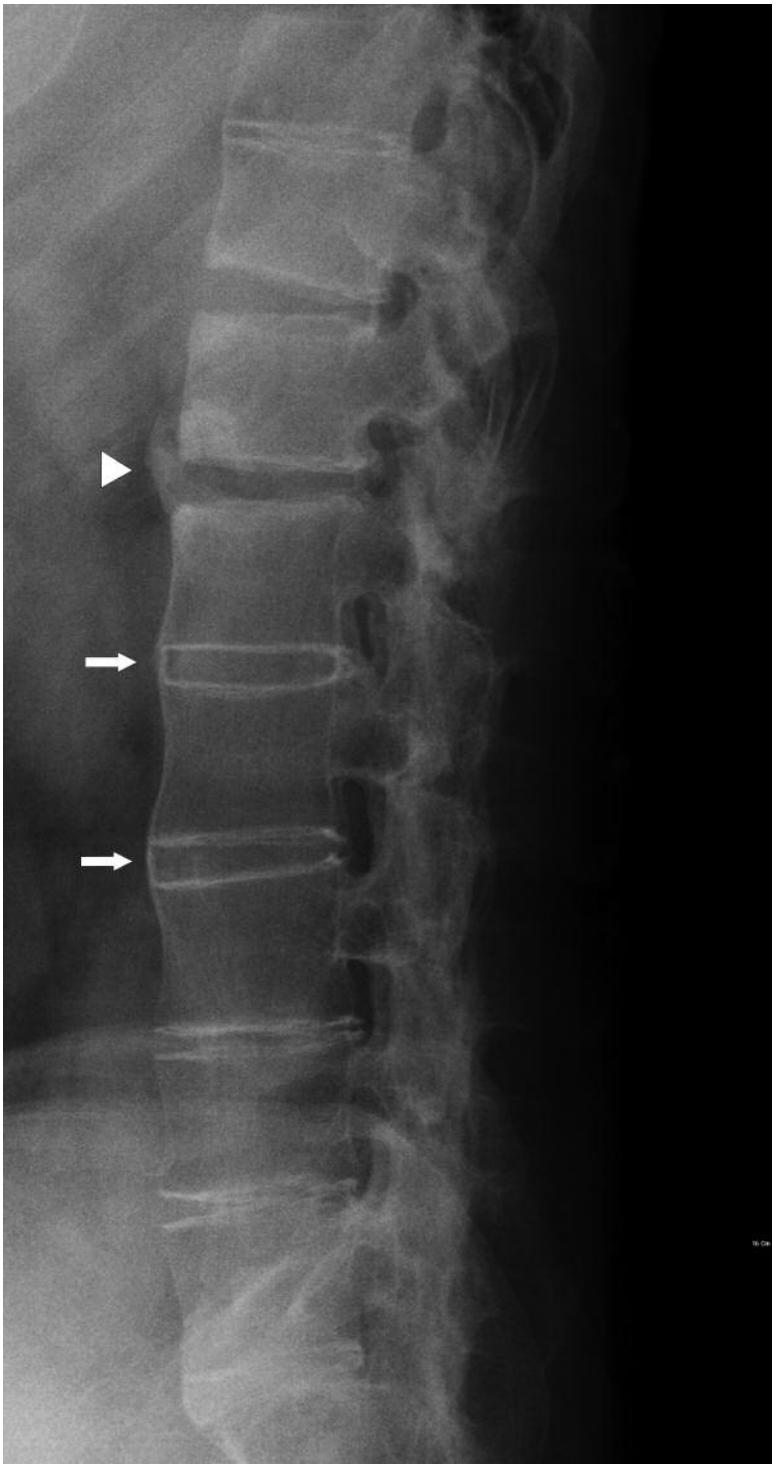

Figure 1. Lateral lumbar radiograph from one of our patients shows total bony bridging from the lower border of first lumbar vertebra to the upper border of third lumbar vertebra (arrows) and bony sclerosis without fusion between the 12th thoracic vertebra and first lumbar vertebra (arrowhead).

trols (133.6 ± 129.4 vs 22.2 ± 24.0 pg/ml; $p < 0.001$) or the patients without spinal fusion (133.6 ± 129.4 vs 125.2 ± 446.9 pg/ml; $p < 0.001$), but there was no difference between the latter 2 groups (Figure 2B). AS patients had higher serum BMP-7 levels than controls, but the difference did not reach statistical significance (44.0 ± 81.6 vs 22.0 ± 10.9 pg/ml; $p = 0.3$). Serum BMP-7 levels of patients with spinal fusion were significantly elevated compared with

Table 1. Comparison of clinical, laboratory and radiographic data between patients with AS with and without spinal fusion. Values are mean ± standard deviation, unless indicated otherwise.

Characteristic	With Spinal Fusion, n = 60	Without Spinal Fusion, n = 60	p
Men, %	85.0	76.7	0.354
Age, yrs	41.6 ± 12.6	29.7 ± 8.3	< 0.01*
Age at onset, yrs	26.8 ± 11.3	23.4 ± 7.0	0.115
Disease duration, yrs	14.8 ± 8.5	6.0 ± 5.9	< 0.001*
Enthesitis, %	43.3	31.7	0.258
Uveitis, %	13.3	10.0	0.777
Peripheral arthritis, %	60.0	66.7	0.570
HLA-B27, %	96.7	86.7	0.095
NSAID, %	76.7	70	0.536
Sulfasalazine, %	43.3	40	0.853
BASRI-spine	9.5 ± 3.0	3.0 ± 1.2	< 0.001*
mSASSS	36.2 ± 23.2	0.8 ± 2.7	< 0.001*
BASDAI	4.5 ± 2.1	4.7 ± 2.1	0.791
BASFI	4.1 ± 2.5	2.6 ± 2.5	0.001*
BASMI	6.0 ± 1.8	2.0 ± 1.8	< 0.001*
BAS-G	5.9 ± 2.8	5.7 ± 2.7	0.625
BMP-2	98.0 ± 188.5	86.6 ± 136.5	< 0.001*
BMP-4	133.6 ± 129.4	125.2 ± 446.9	< 0.001*
BMP-7	51.2 ± 96.0	36.7 ± 64.2	0.005*
ESR, mm/h	31.8 ± 25.3	23.0 ± 21.0	0.041*
CRP, mg/dl	2.2 ± 2.1	1.5 ± 1.6	0.027*

* Statistically significant. p values calculated by Mann-Whitney U test, except sex, enthesitis, uveitis, peripheral arthritis, NSAID, and sulfasalazine by chi-square test, and HLA-B27 by Fisher exact test. See text for definitions.

those of the patients without spinal fusion (51.2 ± 96.0 vs 36.7 ± 64.2 pg/ml; p = 0.005), but the difference was not statistically significant compared with the control group (51.2 ± 96.0 vs 22.0 ± 10.9 pg/ml; p = 0.028, more than 0.0167; Figure 2C). When the 3 groups were compared, a value of p less than 0.0167 was considered statistically significant by Bonferroni adjustment. Hip joint disease was identified radiographically in 18 patients (15%). Serum BMP-4 and BMP-7 levels were higher in patients with radiological hip involvement than in those without (174.0 ± 156.7 vs 119.6 ± 352.7 pg/ml for BMP-4, p = 0.006; 105.0 ± 153.3 vs 55.5 ± 130.8 pg/ml for BMP-7, p = 0.014). We also found that serum BMP-2 and BMP-4 levels were higher in patients with a history of enthesitis than in those without such a history (90.2 ± 106.5 vs 62.8 ± 35.3 pg/ml for BMP-2, p = 0.003; 156.5 ± 157.2 vs 132.1 ± 426.9 pg/ml for BMP-4, p = 0.01), and that the BMP-2 level was significantly elevated in patients with a uveitis history compared to patients without uveitis (86.8 ± 40.4 vs 82.0 ± 112.6 pg/ml; p = 0.011). There were no significant differences in serum BMP levels between male and female patients. No significant difference was found in BMP levels depending on HLA-B27 status. In the patient group without spinal fusion, there were no significant differences in serum BMP levels between patients with and those without syndesmophytes, but the former had higher CRP levels (2.6 ± 2.2 vs 1.2 ± 1.3 mg/dl, respectively; p = 0.015).

Correlations of BMP levels with clinical and radiological assessments. Correlations between serum BMP and clinical and radiographic features are given in Table 2. BMP-2, BMP-4, and BMP-7 had a significant association with the radiographic severity of the spine. The correlations to radiological damage were more obvious at the lumbar spine for BMP-2 and BMP-4. Serum BMP levels also correlated significantly with the number of fused vertebrae. In addition, BMP-2 and BMP-4 levels had an association with BASMI scores, especially BMP-2 with measurement of lumbar flexion (r = –0.350, p < 0.001) and BMP-4 with measurement of lumbar side flexion (r = –0.314, p = 0.001). We also found the BASRI hip score had an association with levels of serum BMP-4 and BMP-7. These BMP did not have a correlation with inflammatory markers such as ESR or CRP. Serum BMP levels showed no significant correlation with current age, age of disease onset, and disease duration in AS patients using Spearman rank correlation. CRP had a significant correlation with the BASRI of the spine (r = 0.261, p = 0.015) and the mSASSS (r = 0.260, p = 0.016), while ESR did not.

DISCUSSION

We found serum levels of BMP-2, BMP-4, and BMP-7 were higher in patients with AS than in healthy controls; but the elevation of BMP-2 and BMP-7 did not reach statistical significance. Serum BMP levels were significantly elevated in AS patients with spinal fusion, compared to patients without spinal fusion. AS patients with spinal fusion also were of

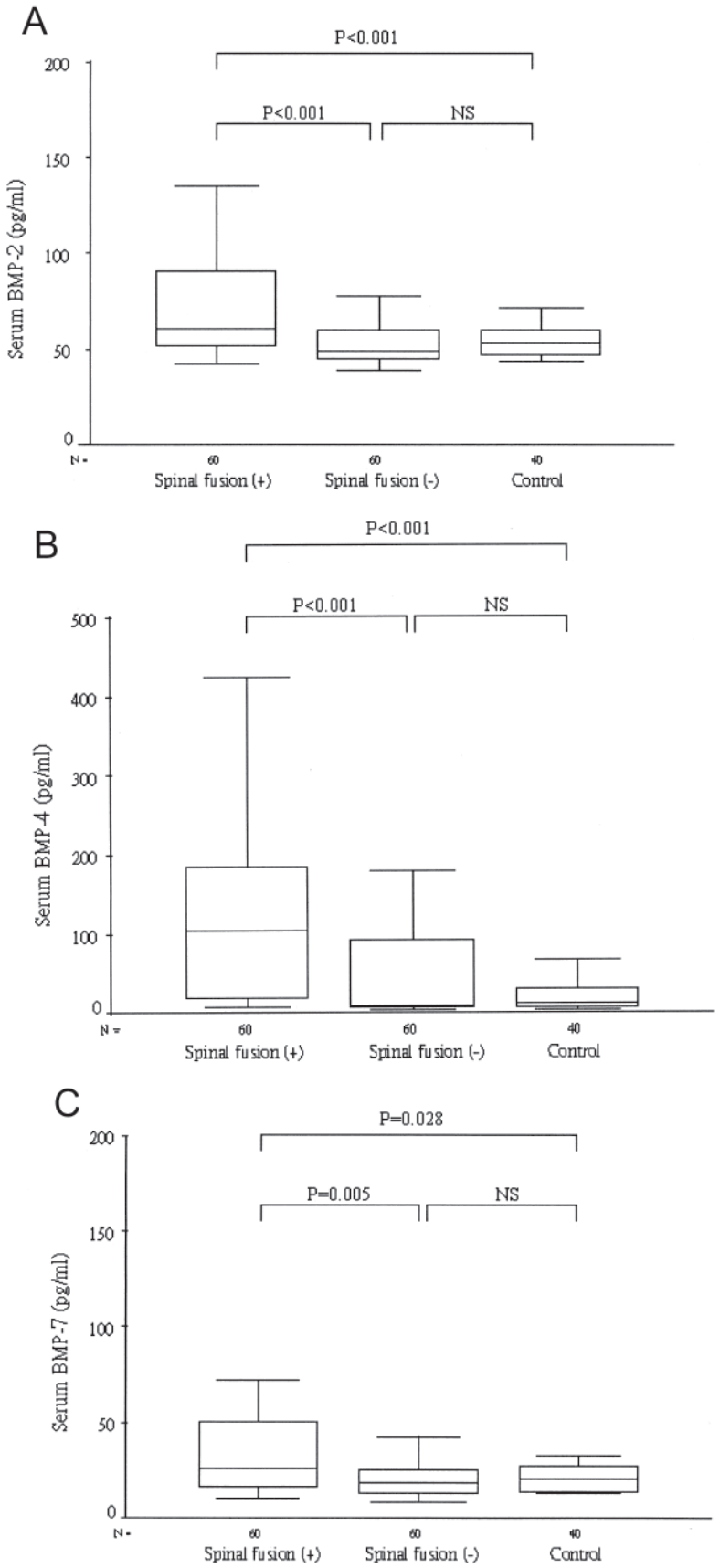

Figure 2. Comparisons of concentrations of BMP-2 (A), BMP-4 (B), and BMP-7 (C) in patients with and without spinal fusion and healthy controls. Horizontal lines indicate medians; edges of the boxes indicate lower and upper quartiles. Data compared by Kruskal-Wallis H test, followed by Dunn's tests for pairwise post-hoc comparisons. A p value < 0.0167 is considered significant after Bonferroni correction for multiple comparisons. NS: nonsignificant.

Table 2. Correlations between BMP and clinical and radiographic variables.

Factor	BMP-2		BMP-4		BMP-7	
	r	p	r	p	r	p
ESR	0.115	0.249	0.073	0.463	–0.088	0.380
CRP	0.160	0.108	0.095	0.342	–0.021	0.831
BASDAI	0.025	0.789	0.044	0.635	–0.132	0.15
BASFI	0.215	0.018*	0.081	0.379	0.066	0.475
BASMI	0.303	0.001*	0.255	0.007*	0.164	0.083
BASG	0.036	0.694	0.052	0.572	0.004	0.968
BASRI total	0.311	0.002*	0.213	0.034*	0.167	0.098
BASRI hip joint	0.131	0.161	0.255	0.005*	0.219	0.018*
BASRI spine	0.320	0.001*	0.207	0.040*	0.150	0.139
Sacroiliitis grade	0.206	0.025*	0.110	0.235	0.001	0.991
BASRI cervical spine	0.251	0.011*	0.204	0.004*	0.210	0.034*
BASRI lumbar spine	0.356	< 0.001*	0.348	< 0.001*	0.256	0.006*
mSASSS total	0.285	0.004*	0.278	0.005*	0.210	0.024*
mSASSS cervical spine	0.221	0.026*	0.209	0.035*	0.234	0.018*
mSASSS lumbar spine	0.344	< 0.001*	0.314	< 0.001*	0.190	0.041*
No. fused vertebrae**	0.261	0.009*	0.258	0.009*	0.225	0.024*

* Statistically significant. ** Determined by assessing cervical spine from the lower border of the second cervical vertebra to the upper border of the first thoracic vertebra, and lumbar spine from the lower border of the 12th thoracic vertebra to the upper border of the sacrum. r: Spearman correlation coefficient.

older age and had longer disease duration. However, serum BMP levels showed no significant correlations with age and disease duration, as reported by Park, *et al*[13]. Park, *et al* have reported that serum BMP-2 and BMP-7 levels were elevated in AS patients, while BMP-4 was not. Other studies found no significant serum BMP-7 elevation in patients with AS compared to controls[21,22]. Patients with early disease in Park's study had a mean symptom duration of 1.6 ± SD 1.8 years. The inconsistent results from our investigation and others may be due to the enrollment of patient populations with different disease stages or different spinal severity. BMP levels, especially BMP-2 and BMP-4, correlated with spinal dysmobility and radiographic scores in our study. The correlations were more obvious at the lumbar spine for both radiological and clinical measurements. Park, *et al* reported a correlation between BMP-2 and BASDAI, and BMP-7 was associated with spinal BASRI and BASMI scores[13]. We did not find any association between BMP and BASDAI. BMP-7 had a correlation with the mSASSS, but not with the BASMI score. Different BMP may have different effects on AS patients as the disease progresses.

In our study, serum BMP-2 and BMP-4 levels were elevated in patients with a history of enthesitis. Enthesitis is associated with entheseal cell proliferation and heterotopic cartilage and bone formation (enthesophyte), leading to ankylosis. The process is called ankylosing enthesitis, which is a prominent feature of SpA[11]. It is characterized by accumulation of fibroblast cells, chondrogenic differentiation, chondrocyte hypertrophy, and replacement of the cartilage by bone[8]. Different BMP have been involved in this process. BMP-2 is found in proliferating and early chondrogenic cells, and BMP-7 was found in prehypertrophic chondrocytes in ankylosing enthesitis in mice[11]. Similarly, activation of BMP signaling is found on enthesitis lesions in patients with SpA. Gene transfer of the BMP antagonist, noggin, is effective in inhibiting the onset and progression of ankylosing enthesitis in the mouse model[11]. These findings suggest that BMP can be involved in the pathogenesis of enthesitis and contribute to the formation of enthesophytes in SpA.

Serum BMP-4 and BMP-7 levels showed significant correlations with hip joint involvement in this study. BMP-2 is expressed in synovial biopsies obtained from patients with rheumatoid arthritis and SpA, and is upregulated by proinflammatory cytokines of interleukin 1 (IL-1) and TNF-α[23]. BMP-7 can increase the expression of mRNA for IL-17, a proinflammatory cytokine similar to TNF-α, in the cell lines of mice[24]. BMP can act as pleiotropic cytokines or growth factors in the skeletal system and may be involved in synovium homeostasis and pathology in arthritis.

The pathogenesis of spinal fusion in AS is not very clear. In the assessment of inflammatory change by magnetic resonance imaging, syndesmophytes occur almost 3-fold more often at edges of inflamed vertebrae, but most newly developed syndesmophytes occur in regions without inflammation[4]. Currently, inhibition of TNF-α is the most effective strategy for controlling the painful symptoms and improving vertebral joint inflammation in AS patients. Anti-TNF-α agents did not affect the incidence and severity of joint ankylosis in a mouse model of SpA[25]. Similarly, anti-TNF-α therapy appeared to be ineffective in inhibiting the process of spinal ankylosis in cohort studies[5,26]. Serum BMP-7 levels remained unchanged during anti-TNF-α therapy in AS patients, while inflammatory measures and disease

activity decreased[22]. BMP may have activity on related cells, affecting bone ankylosis when inflammation has been sufficiently suppressed by TNF-α blockers. In our study, both BMP and the inflammatory measures (ESR, CRP) were higher in patients with spinal fusion than in those without spinal fusion, but they did not have any correlation. This suggests that part of the regulation of BMP is inflammation-independent. Spine radiograph scores had an association with serum BMP and CRP. Inflammation and bone formation may be linked in some way in patients with AS; however, they can be independent phenomena[6]. Ankylosis of the axial spine is a major cause of disability in human AS and related SpA. The abnormal bone formation in AS may be not only an ossification phenomenon of involved tissues, but may be considered part of the pathogenetic cascade of the disease.

In our study, elevation of BMP in serum of AS patients with spinal fusion and the positive correlation between BMP and spine BASRI and mSASSS scores support the notion of BMP playing an important role in the pathogenesis of spinal ankylosis in these patients. The serum BMP levels may reflect radiographic progression of the spine and hip joints. In established AS, both spinal inflammation and ankylosis can cause spinal disability and functional impairment. Controlling abnormal bone formation is as important as controlling inflammation to prevent structural damage in AS. Our study may offer an alternative and complementary approach to prevent development of axial ankylosis in such patients. Larger studies or longitudinal observation of cohorts of patients are needed to confirm this finding.

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REFERENCES

1. Braun J, Sieper J. Ankylosing spondylitis. Lancet 2007;369: 1379-90.
2. van der Linden S, Valkenburg HA, Cats A. Evaluation of diagnostic criteria for ankylosing spondylitis. A proposal for modification of the New York criteria. Arthritis Rheum 1984;27:361-8.
3. Baraliakos X, Listing J, von der Recke A, Braun J. The natural course of radiographic progression in ankylosing spondylitis — evidence for major individual variations in a large proportion of patients. J Rheumatol 2009;36:997-1002.
4. Baraliakos X, Listing J, Rudwaleit M, Sieper J, Braun J. The relationship between inflammation and new bone formation in patients with ankylosing spondylitis. Arthritis Res Ther 2008;10:R104.
5. Baraliakos X, Listing J, Brandt J, Haibel H, Rudwaleit M, Sieper J, et al. Radiographic progression in patients with ankylosing spondylitis after 4 yrs of treatment with the anti-TNF-alpha antibody infliximab. Rheumatology 2007;46:1450-3.
6. Lories RJ, Luyten FP, de Vlam K. Progress in spondylarthritis. Mechanisms of new bone formation in spondyloarthritis. Arthritis Res Ther 2009;11:221.
7. Lories RJ, Luyten FP. Bone morphogenetic protein signaling in joint homeostasis and disease. Cytokine Growth Factor Rev 2005;16:287-98.
8. Lories RJ, Luyten FP. Bone morphogenetic proteins in destructive and remodeling arthritis. Arthritis Res Ther 2007;9:207.
9. Benjamin M, McGonagle D. The anatomical basis for disease localisation in seronegative spondyloarthropathy at entheses and related sites. J Anat 2001;199:503-26.
10. Marzo-Ortega H, Emery P, McGonagle D. The concept of disease modification in spondyloarthropathy. J Rheumatol 2002;29:1583-5.
11. Lories RJ, Derese I, Luyten FP. Modulation of bone morphogenetic protein signaling inhibits the onset and progression of ankylosing enthesitis. J Clin Invest 2005;115:1571-9.
12. Hsu WK, Wang JC. The use of bone morphogenetic protein in spine fusion. Spine J 2008;8:419-25.
13. Park MC, Park YB, Lee SK. Relationship of bone morphogenetic proteins to disease activity and radiographic damage in patients with ankylosing spondylitis. Scand J Rheumatol 2008;37:200-4.
14. Chou CT, Pei L, Chang DM, Lee CF, Schumacher HR, Liang MH. Prevalence of rheumatic diseases in Taiwan: a population study of urban, suburban, rural differences. J Rheumatol 1994;21:302-6.
15. Garrett S, Jenkinson T, Kennedy LG, Whitelock H, Gaisford P, Calin A. A new approach to defining disease status in ankylosing spondylitis: the Bath Ankylosing Spondylitis Disease Activity Index. J Rheumatol 1994;21:2286-91.
16. Calin A, Garrett S, Whitelock H, Kennedy LG, O'Hea J, Mallorie P, et al. A new approach to defining functional ability in ankylosing spondylitis: the development of the Bath Ankylosing Spondylitis Functional Index. J Rheumatol 1994;21:2281-5.
17. Jenkinson TR, Mallorie PA, Whitelock HC, Kennedy LG, Garrett SL, Calin A. Defining spinal mobility in ankylosing spondylitis (AS). The Bath AS Metrology Index. J Rheumatol 1994;21:1694-8.
18. Jones SD, Steiner A, Garrett SL, Calin A. The Bath Ankylosing Spondylitis Patient Global Score (BAS-G). Br J Rheumatol 1996;35:66-71.
19. Calin A, Mackay K, Santos H, Brophy S. A new dimension to outcome: application of the Bath Ankylosing Spondylitis Radiology Index. J Rheumatol 1999;26:988-92.
20. Creemers MC, Franssen MJ, van 't Hof MA, Gribnau FW, van de Putte LB, van Riel PL. Assessment of outcome in ankylosing spondylitis: an extended radiographic scoring system. Ann Rheum Dis 2005;64:127-9.
21. Wendling D, Cedoz JP, Racadot E, Dumoulin G. Serum IL-17, BMP-7, and bone turnover markers in patients with ankylosing spondylitis. Joint Bone Spine 2007;74:304-5.
22. Wendling D, Cedoz JP, Racadot E. Serum levels of MMP-3 and cathepsin K in patients with ankylosing spondylitis: effect of TNF alpha antagonist therapy. Joint Bone Spine 2008;75:559-62.
23. Lories RJ, Derese I, Ceuppens JL, Luyten FP. Bone morphogenetic proteins 2 and 6, expressed in arthritic synovium, are regulated by proinflammatory cytokines and differentially modulate fibroblast-like synoviocyte apoptosis. Arthritis Rheum 2003;48:2807-18.
24. You Z, DuRaine G, Tien JY, Lee C, Moseley TA, Reddi AH. Expression of interleukin-17B in mouse embryonic limb buds and regulation by BMP-7 and bFGF. Biochem Biophys Res Commun 2005;326:624-31.
25. Lories RJ, Derese I, de Bari C, Luyten FP. Evidence for uncoupling of inflammation and joint remodeling in a mouse model of spondylarthritis. Arthritis Rheum 2007;56:489-97.
26. van der Heijde D, Landewé R, Einstein S, Ory P, Vosse D, Ni L, et al. Radiographic progression of ankylosing spondylitis after up to two years of treatment with etanercept. Arthritis Rheum 2008;58:1324-31.