Bone formation in ankylosing spondylitis

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Abstract

Introduction
Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder with unclear pathogenesis. Bone formation is a hallmark feature of AS, precise mechanisms of which are unknown. The aim of this review was to summarize the current knowledge regarding both clinical significance and pathogenesis of bone formation in AS.

Materials and methods
Articles, published in the medical literature and chapters in textbooks related to the discussed topic, were critically reviewed and relevant data were selected, collated and organized for the purpose of this manuscript.

Results
Conventional radiography is the most valuable classical tool for identification of structural changes in AS. The typical manifestations of bone formation in AS usually involve the axial skeleton, including spine, sacroiliac and hip joints, and, if properly recognized, have an important role in diagnosing, classifying and monitoring patients. Molecular pathways leading to bone formation in AS have not been elucidated sufficiently. Abnormally active signalling by wingless-type (wnt)-like and bone morphogenetic protein (BMP)-mediated pathways have been suggested as major contributors to disease-related ossification in AS. The only medicines, shown currently to delay the process of bone formation in AS patients, are nonsteroidal anti-inflammatory drugs.

Conclusion
Better understanding and prediction of structural damage would help to improve and individualize management of patients suffering from AS.

Introduction
Ankylosing spondylitis (AS) is a chronic inflammatory rheumatic disorder with unclear pathogenesis. The prevalence of AS in the general population is estimated at 0.5%, and its prominent features include sacroiliitis, spondylitis, asymmetric peripheral arthritis, enthesitis and an association with the histocompatibility allele HLA-B27. AS disease activity can be appreciated by clinical and laboratory measures, such as the severity of the inflammatory back pain, presence of synovial or enthesal inflammation, acute uveitis, constitutional symptoms and elevated indices of inflammation in the blood such as erythrocyte sedimentation rate and/or serum levels of C-reactive protein (CRP). The pathologic progression of AS is measured by new bone formation, appearance of syndesmophytes at vertebral body margins and, eventually, ankylosis of the sacroiliac joints and vertebral column. The presence of inflammation at the areas of subsequent osseous proliferation is considered to be a necessary trigger; but, on the other hand, the rate of new bone formation in AS does not seem to be a simple function of the inflammatory activity of the disease, and the precise mechanisms of the progressive ankylosis are unknown. It is also well appreciated that the rate and course of new bone formation can be individually determined, with some AS patients having radiographic ankylosis already upon first clinical presentation, while others do not develop ankylosis even after longstanding disease. The factors influencing this significant variability in both rate and magnitude of new bone formation in individuals with AS have not been elaborated. The aim of this review was to summarize the current knowledge regarding both clinical significance and pathogenesis of bone formation in AS.

Materials and methods
A literature search of the PUBMED database using the crossover of keywords ‘bone formation’ and ‘ankylosing spondylitis’ was conducted, with 227 papers listed. These manuscripts, as well as other articles published in the medical literature and chapters in textbooks related to the discussed topic, were critically reviewed and relevant data were selected, collated and organized for the purpose of this article.

Results
Radiographic features of bone formation in AS
Bone formation is a characteristic feature of AS, which, if properly recognized, has an important role in diagnosing, classifying and monitoring patients suffering from the disease. Conventional radiography, while unable to visualize active inflammation, is the most valuable classical tool for identification of structural changes in AS. The typical manifestations of bone formation in AS usually involve the axial skeleton, including spine, sacroiliac and hip joints, while ossification of the entheses may occur also peripherally.

The characteristic radiographic changes in AS, related to bone formation, include:

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• osseous fusion (ankylosis) of sacroiliac joints (Figure 1);
• formation of syndesmophytes and the resulting appearance of ‘bamboo spine’ in advanced disease (Figures 2–4);
• ankylosis of vertebral apophyseal joints (Figure 4);
• ankylosis of costovertebral joints (Figure 3);
• ossifying enthesopathy of posterior spinal ligaments and pelvic entheses, particularly at ischial tuberosities and iliac crests (Figure 1);
• osteophyte formation on the margins of femoral head with collar-like appearance about the femoral neck (Figure 1).

Computed tomography, superior to conventional radiography by depicting layer-by-layer changes, has additional value in disclosing bony growth particularly in locations where x-ray imaging is difficult, such as within sacroiliac joints or posterior spinal elements (Figure 5). Magnetic resonance imaging, on the contrary, is more useful in demonstrating signs of active inflammation about joints, while changes related to bone formation may be missed due to the magnetic properties of calcium compounds within new bone.

Bone formation per se is not pathognomonic for AS, as it is also a feature of other spondyloarthopathies, as well as of osteoarthritis, diffuse idiopathic skeletal hyperostosis, alkaptonuria and other disorders. The pattern of bone formation in each of these diseases, however, is unique, allowing for proper differentiation in the majority of cases.

Of note, bone formation is not only a diagnostic feature of AS, but is also a measure of the pathologic progression of the disease. Standard quantitative assessment of this new bone formation, used in clinical trials and research of AS, is focused mainly on the cervical and lumbar segments of the spine. Four methods, developed to score structural changes in AS, include the Bath AS Radiology Index (BASRI), the Stoke AS Spinal Score (SASSS), modified SASSS (mSASSS)...

Figure 1: Pelvic radiogram of a patient with established AS.
1, complete ankylosis of both sacroiliac joints; 2, ossification of posterior spinal ligaments; 3, ‘star’ sign (ossification of the ligaments in the posterosuperior portion of sacroiliac joints); 4, osteophyte formation on the margin of the femoral head with appearance of a collar about the femoral neck (arrowhead); significant narrowing of the right hip joint space is evident, the left hip joint is replaced; 5, enthesopathy of the ischial tuberosity and iliac bone.

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and Radiographic AS Spinal Score (RASSS). The last three methods are primarily based on scoring the presence of ‘squaring’ of vertebral bodies, characteristic sclerosis of bone, bony erosions and, particularly, syndesmophytes and bridging ankylosis along the spine, while the BASRI also scores sacroiliac joints and, in its modified form, hip joints (BASRI-hip). mSASSS is currently considered the best method for scoring the radiographic progression of AS, while BASRI remains useful as an instrument for the staging of AS.

Pathogenesis of bone formation in AS
Histological data available from studies conducted on biopsies and/or autopsies of patients with AS suggest that an active inflammatory process, probably originating in the subchondral bone marrow, precedes new bone formation. As such, early sacroilitis is characterized mainly by infiltration of the synovium, the cartilage and the bone with large number of macrophages, as well as lymphocytes and plasmacytes. Mild osteoblastic activity is already seen at the edges of bone trabeculae at this early stage. More advanced sacroilitis manifests by osteoclastic resorption of the subchondral bone, the ongoing presence of a dense inflammatory infiltrate and appearance of abundant, loose extracellular matrix with many active osteoblasts seen. At a later stage, the sacroiliac joints are filled by granulation tissue: with islands of metaplastic cartilage, and fibroblasts, chondrocytes and chondroblasts, some of them hypertrophic and calcified, present; while osteoblasts synthesize endochondral bone around vascular buds. This endochondral type of bone formation, with formation of cartilage skeleton which is eventually replaced by bone, has been also shown to be the leading mechanism of the formation of syndesmophytes in patients with AS. Evidence of membranous type of bone formation, with mesenchymal stem cells differentiating directly into osteoblasts, omitting the chondrocyte intermediate state, has also been seen occasionally in patients with AS.

Figure 2: Syndesmophyte formation in a patient with AS. Syndesmophyte formation (ossification within the annulus fibrosus) is seen at the upper anterior vertebral corner of second lumbar vertebrae (arrow).

Figure 3: Radiogram of the thoracolumbar spine of a patient with AS. Undulating vertebral contour due to extensive syndesmophytosis, named ‘bamboo spine’ (black arrows); ankylosis of costovertebral junctions (white arrows).
Figure 4: Radiogram of cervical spine of a patient with long-standing AS. Extensive syndesmophytosis of cervical spine (arrows) and osteopenia of the vertebral bodies are evident. There is also ankylosis of apophyseal joints and fusion of posterior spinal elements (hollow arrows).

Figure 5: Computed tomography of pelvis in a patient with active AS. Sacroiliitis with eroded sacroiliac joint (black arrows) and adjacent osseous sclerosis. Formation of a single bony bridge between iliac and sacral bones can be observed (white arrow).

Major contributors to disease-related ossification in AS. In the normal bone, BMPs are critical in the triggering of endochondral bone formation in its early stages, and wnt-related proteins stimulate new bone formation by direct effect on osteoblasts. Studies on animal models of arthritis have found that blocking of Dickkopf-1 (Dkk-1), which is a natural inhibitor of wnt pathway, leads to the formation of osteophytes and ankylosis of sacroiliac joints in tumour necrosis factor-α (TNF-α) transgenic mouse model. Similarly, higher levels of noggin, an inhibitor of BMP signalling, were protective against ankylosis in DBA/1 mice prone to ankylosing spondespathy.

Additional clinical studies have found some evidence that Dkk-1 is dysfunctional in AS patients, while reports on correlation of serum levels of sclerostin, another inhibitor of wnt pathway, or various proteins of the BMP pathway, with radiographic damage in AS, have not been consistent.

The conundrum of bone formation in AS is further complicated by the concurrence of local ossification resulting in the development of syndesmophytes and ankylosis, on the one hand, and generalized bone loss and osteoporosis, on the other hand, in the same patients (Figure 4). These simultaneous phenomena are considered by most authorities to be related, at least partially, to the inflammation of AS; thus, the speculation that osteoporosis may be related primarily to the systemic effects of inflammation while bony growth is a function of its local effects seems justified. In this context, the potential local effects of transforming growth factor-β1 (TGF-β1) on AS-related bone formation may be of interest. TGF-β1 was detected in sacroiliac biopsies in patients with advanced AS, as well as in the synovial fluid of patients with spondyloarthritides in increased concentrations as compared with other rheumatic disorders. The literature suggests that TGF-β1 is heavily involved in the pathogenesis of osteoarthritis, osteophyte formation and ossification of spinal ligaments, supporting the hypothesis that TGF-β1 may be a central cytokine-regulating bone formation in a variety of conditions. Convincing evidence for the
involvement of TGF-β1 in AS bone formation is, however, still lacking at this point.

The link between inflammation of AS and radiographic disease progression is not linear nor simple, however. While the above noted histological data, as well as experiments on the HLA-B27 transgenic animal models, suggest that inflammation and bone formation are strongly coupled in AS, more recent data have demonstrated that new bone formation may progress independently of the inflammatory process, and may even be accelerated by the resolution of inflammation. These observations have spawned the proposition of a hypothesis of a disconnect between inflammation and bone formation in AS. According to this hypothesis, some aetiological trigger simultaneously induces inflammatory reaction and endochondral bone formation, but two of these pathways remain uncoupled during disease development. MRI-based studies conducted on AS patients treated with anti-TNF-α agents have suggested that early suppression of inflammation may prevent future bone formation, and yet a long-standing inflammatory process, even if eventually effectively treated, may proceed, independently of inflammation, to progressive bone formation.

Clinical aspects of bone formation in AS

Radiographic damage in AS is associated with the impairment of spinal mobility and correlates long term with interference in functioning. The clinical measurements of spinal mobility, reflecting the structural damage in AS patients, are of particular significance in the later stages of the disease, while in the earlier disease, spinal mobility may be more influenced by the reversible inflammatory process.

The pattern of spinal damage in AS is unpredictable, with the possibility of cervical, thoracic or lumbar involvement dominant in different persons. Thus, clinical evaluation of spinal mobility in these patients should cover all spinal segments. The measurements of tragus-to-wall, occiput-to-wall distances and cervical rotation can be used for determining limitations of cervical spine mobility; chest expansion measurement allows to detect limitations in movement of thoracic spine/costovertebral joints, while fingers-to-floor distance, lumbar flexion (Schober test) and lateral lumbar flexion can assess restriction in lumbar spine motion. Maximal inter-malleolar distance is used for the assessment of hip joint involvement.

Of relevance, the rate of new bone formation differs among individuals and is rather slow, with an estimated follow-up duration of at least 2 years necessary to show measurable progression in clinical studies. Some of the patients with AS will not develop new syndesmophytes at all during the disease course. A recent study on 132 patients with established AS showed that only 60% of patients had syndesmophytes at the baseline, and about 50% developed new syndesmophytes during a 4-year period of follow-up. Of importance, only the presence of existing syndesmophytes was a significant predictor of new bone formation in this study. Similarly, in other studies performed on patients with AS or axial spondyloarthritis, the presence of pre-existing syndesmophytes has always been found to be the most powerful predictor of future structural damage. Elevated CRP and smoking also seem to drive new syndesmophyte growth in AS patients. Worthy of note, bone formation occurs faster in males with AS as compared with females. The localization of new syndesmophyte growth may also differ between genders, with females developing more cervical, and males developing predominantly lumbar, syndesmophytes.

The negative long-term consequences of bone formation in AS patients reflected in radiographic damage make this an important target for therapeutic intervention. Anti-TNF-α agents, widely used nowadays in the treatment of AS, while highly effective in the alleviation of clinical, laboratory and imaging signs of the inflammatory process related to AS, have failed to prevent or slow the radiographic damage in a series of trials. The only medicines, shown currently to delay the process of bone formation in AS patients, are nonsteroidal anti-inflammatory drugs (NSAIDs), medications traditionally used in AS for many decades. Two studies have demonstrated the dose-dependent efficacy of NSAIDs in slowing syndesmophyte growth in AS patients, purportedly through their anti-prostaglandin action. Physical therapy and intense exercising, while never examined for their propensity to influence the rate of new bone formation in AS, can improve spinal mobility and functional status of patients, thus diminishing the negative clinical consequences of structural damage related to bone formation in AS. Thus, management combining both pharmacological and nonpharmacological approaches to deal with the long-term consequences of AS should be advocated for all patients diagnosed with the disease.

Discussion

Beyond amelioration of signs and symptoms of arthritis, disease course modification has become a goal in modern rheumatology in the last decade. The recognized ability of the biologic agents to virtually shut down the process of erosion formation in rheumatoid arthritis (RA) has revolutionized the approach to the management of RA patients, fundamentally changed the outcomes of their treatment and led to the anticipation that a similar approach will result in disease modification.
of other rheumatic disorders, primarily AS. The expectation that new bone formation in AS patients will be inhibited by anti-TNF-α medicines, founded on the superb clinical efficacy of these medicines with respect to pain and stiffness control, was not confirmed in several 2-year long clinical trials. The failure of these biologics to slow radiographic progression of AS has, however, triggered new intense basic research in the field of AS-related bone formation. It has also put to question our ability to recognize, calculate and evaluate the significance of this bone formation in both clinical trials and individual patients. While the recognition of new AS-related ossification is still primarily based on traditional radiography, new more sensitive scoring systems, such as mSASSS, have been proposed; and experience in clinical research, learning both the natural history of AS progression and ways to intervene in it, has been gained. Finally, the discoveries in the field gained by basic research open new horizons and inspire hope for ferreting out the mystery of AS-related bone formation in the near future.

**Conclusion**

Bone formation is a hallmark pathological feature of AS and the primary cause of long-term disability in these patients. Radiographic features of bone formation in AS are well known, and conventional radiography represents a convenient tool for the measurement of disease progression. The pathogenesis of bone formation, as well as its relation to the inflammatory process, is poorly understood, but the disease-related breakdown in pathways regulating bone remodelling may play a role. As the rates and severity of bone formation vary significantly among AS patients, biomarkers for bone formation and prediction of structural damage would help to improve and individualize management of patients suffering from AS.

**Abbreviations list**

AS, ankylosing spondylitis; BMP, bone morphogenic protein; CRP, C-reactive protein; NSAID, nonsteroidal anti-inflammatory drug; RA, rheumatoid arthritis; TGF-β1, transforming growth factor-β1; TNF-α, tumour necrosis factor-α; wnt, wingless-type

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