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REVIEW

Biomechanics in the onset and severity of spondyloarthritis: a force to be reckoned with

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ABSTRACT
Increasing evidence suggests that there is a pivotal role for physical force (mechanotransduction) in the initiation and/or the perpetuation of spondyloarthritis; the review contained herein examines that evidence. Furthermore, we know that damage and inflammation can limit spinal mobility, but is there a cycle created by altered spinal mobility leading to additional damage and inflammation? Over the past several years, mechanotransduction, the mechanism by which mechanical perturbation influences gene expression and cellular behaviour, has recently gained popularity because of emerging data from both animal models and human studies of the pathogenesis of ankylosing spondylitis (AS). In this review, we provide evidence towards an appreciation of the unsolved paradigm of how biomechanical forces may play a role in the initiation and propagation of AS.

INTRODUCTION
The unique classically defined clinical features (males, spine predominant, lower extremity involvement) of ankylosing spondylitis (AS) have traditionally struck investigators as having an undefined mechanism that cannot be explained entirely by genetic background or intestinal triggering. As the definition of AS has been expanded to spondyloarthritis (SpA) and now includes almost equal gender representation and more diverse phenotypes observed in children as well as adults who may not carry the HLA-B27 genotype, the conundrum of clinical disease expression remains an unsolved mystery. With the explosion of studies using animal models, thoughtful epidemiological investigations from countries around the world, and advanced imaging applications, we now have a glimpse into the potential reasons for this unique phenotype based on the mechanotransduction hypothesis. The evidence is presented herein.

The concept of critical biomechanical stresses affecting the localisation of inflammatory response in SpA, and the role of the multihit model for immune activation have

WHAT IS ALREADY KNOWN ON THIS TOPIC
⇒ Animal models have previously provided evidence that sustained biomechanical stress may initiate and potentiate enthesitis—one of the main sites of pathology in spondyloarthritis (SpA).

WHAT THIS STUDY ADDS
⇒ Our study provides a comprehensive review regarding the results of studies focusing on the impact of movement and physical forces in SpA particularly with respect to causation and progression of disease in SpA.
⇒ We provide data from occupational studies, investigations in juvenile SpA, extra-articular manifestations, obesity and research on impact of medications on bone growth and radiographic progression in SpA.
⇒ Anatomic differences in the SI joint, the spine and consequent biomechanical changes in force transmission may contribute to clinical heterogeneity between the genders in SpA.
⇒ The unique features of facet joint involvement and ankylosis over thoracolumbar spine, heterogeneity in growth of syndesmophytes and the location extra-articular manifestations in SpA—all support the distinctive role of mechanical stress in the pathogenesis of SpA.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ Our review highlights the relationship between mechanical stress, HLAB27 positivity, SI joint, lumbar spine, peripheral arthritis and extra-articular manifestations and will serve as an updated guide for further studies in the realm of biomechanical stress in SpA.

both been pioneered by the work of McGonagle *et al* particularly from the sentinel paper in 2001.[1] The authors report that shear stress as a consequence of biomechanical loading activates a number of genes, leading to upregulation of transcription factors and other genes to play a crucial role in the inflammatory cascade and subsequently highlight the unique anatomic features of extraspinal

involvement in AS.[1] Much complementary work has been done in this area to support these pivotal observations and to highlight the innovative work by McGonagle *et al*.

ANIMAL MODELS OF ENTHESITIS AND TENDONITIS

Although animal models cannot exactly replicate human disease, they can examine disease pathogenesis with a sharp focus on certain mechanisms which can be isolated and studied with precision.[2 3] Entheses (attachments of the ligaments and tendons to the adjacent bone) are one of the main sites of pathology and clinical symptoms in SpA. Enthesitis is associated with inflammation in the adjoining bone marrow, and these changes may represent the early stages of periostitis and new bone formation, typical of SpA.[4]

As early as 1959, Cava postulated mechanical stress may contribute to enthesitis.[5] In 'Enthesitis: traumatic disease of insertions', he wrote that the enthesis was a location where 'continually recurring concentration of muscle stress at these points provokes a reaction of inflammation with a strong tendency to the formation of fibrosis and calcification'.[5]

Recent work has revealed that sustained biomechanical stress over enthesis sites may result in microtrauma.[6] Shear stress alone may activate the transcription of genes including platelet-derived growth factor, tissue plasminogen activator, and a variety of adhesion molecules. These changes in gene expression contribute to the upregulation of several molecules and nuclear transcription factors that play crucial roles in the inflammatory cascade.[6] In addition, loss of mechanotransduction signalling in entheseal tenocytes may promote apoptosis and contribute to damage resulting from ineffective repair.[6 7]

The role of mechanical stress in SpA using animal models has been investigated using the TNF TNFΔARE mice model[8] and the DBA/1 mouse model,[9] both of which have been reported as translational models best suited to study SpA. Braem *et al*[10] studied the effect of aggressive behaviour in an ageing DBA/1 mouse model of ankylosing enthesitis and postulated that stimulating aggressive behaviour can contribute to stress-induced inflammation. These investigators reported that poor housing conditions and other sensory factors may have significantly contributed to the spontaneous development of arthritis.

Jacques *et al*[11] investigated the outcomes of mechanical unloading of the hindlimbs in TNFΔARE mice. Mechanical unloading by tail suspension for 14 days prevented induction of clinical signs of Achilles enthesitis and peripheral arthritis of ankles and hind paws, and histological examination revealed only mild inflammatory cell infiltration compared with controls. ERK-1/2, the well-known mechanoreceptor signalling pathway in Achilles' tendon lysates, was inhibited by hindlimb unloading and quickly reactivated after reintroduction of mechanical strain in previously unloaded limbs.

When a collagen-antibody-induced arthritis model was in susceptible DBA/1 mice, those that were tail suspended had significantly smaller osteophytes, and osteophyte size correlated with the severity of inflammation. These results suggest that mechanical unloading alleviates deregulated TNF-induced enthesitis and arthritis in this mouse model.

Cambré *et al*[12] studied the contribution of biomechanical loading on site-specific localisation of inflammation. These investigators combined high-resolution micro-CT with histological microanatomy studies in a collagen-induced arthritis (CIA) model examining the location of bone surface erosions in early phases of arthritis, and most importantly, whether biomechanical forces modulate this pattern. The authors observed that increased loading (by running) resulted in a tendency towards more bone erosions over calcaneus-cuboid-MTV (CCM) joints in the lateral region while unloading prohibited development of erosions in the midfoot and hindfoot. Histological evaluation of joints under different loading regimens focusing on the midfoot and hindfoot in CIA revealed that the lateral side of the hind paw is the most commonly and most severely inflamed region.

To further highlight the role of biomechanical forces in determining the site-specific origin of human arthritis, these investigators performed high-resolution peripheral quantitative CT investigations of the feet in patients with SpA. The authors noted preferential involvement (compared with healthy controls) of the CCM region, the cuneiformI-MT1 region and the Achilles tendon. SpA patients had significantly larger enthesophytes at cuneiform and cuboid bone areas compared with controls.[12]

To substantiate these findings, Cambré *et al*[13] also performed an additional in-depth evaluation of joints in a CIA arthritis model where mice were evaluated clinically and histologically under different loading conditions. Voluntary running impaired the resolution phase of CIA, leading to persistent inflammation and bone surface porosity, as observed by micro-CT. The authors also observed that the transition to disease chronicity caused by voluntary running was unrelated (and possibly not linked) to systemic inflammatory responses as no differences were noted based on CCL2, CXCL1, IL6, TNF and IL1β blood stream levels.

An abstract presented at ACR 2022 showed preliminary findings suggesting the presence of a novel force-induced gene (BHLHE40) that was upregulated in the synovial tissue of patients with SpA. BHLHE40 strongly promoted joint inflammation in murine models of arthritis and uncoupled systemic autoimmunity from joint tissue inflammation.[14]

HUMAN OCCUPATIONAL AND WORK-PLACE STUDIES

Recent investigations have suggested that work activities may affect functional or radiographic outcomes. Ramiro *et al* have proposed the concept of 'constitutive radiographic progression' which could be independent

of inflammation.[15] They studied the effect of job type, smoking and socioeconomic status on radiographic progression in AS, and investigated whether 'job type' was directly or indirectly associated with the course of radiographic progression. Patients were divided into two job types based on self-reported occupational information—'blue-collar', or manual labour jobs that imply more physical labour, and 'white-collar', or sedentary jobs implying less physical activity. Radiographic progression (using the modified Stoke Ankylosing Spondylitis Spine Score (mSASSS)) was slightly but statistically significantly higher in blue-collar (2.18 mSASSS-units/2 years (95% CI 1.52 to 2.84)) compared with white-collar workers (1.82 mSASSS-units/2 years (95% CI 1.54 to 2.11) (p=0.05). However, in subgroup analysis by sex, this difference lost statistical significance. Examining the indirect role of Ankylosing Spondylitis Disease Activity Score (ASDAS) regarding radiographic progression, blue-collar work amplified the effect of ASDAS on radiographic progression in comparison with white-collar work. The authors postulated that lifetime mechanical stress, with job type as the surrogate measure, may contribute to radiographic progression in AS.

The same investigators examined an early disease patient collection (called the 'DESIR cohort') for the potential role of mechanical stress as an effect modifier, using 5-year data obtained from 406 axial SpA (axSPA) patients.[16] Smoking was independently associated with greater MRI-sacroiliac joint (SIJ) inflammation at each visit over the 5 years, and this effect was present only among the 64 blue-collar patients that were included (β (95% CI) 5.41 (1.35 to 9.48)). The authors concluded that mechanical stress likely amplified the effects of smoking on inflammation in axSpA SIJ.

In an earlier study of 402 patients with AS, greater functional limitation (with higher Bath Ankylosing Spondylitis Functional Index (BASFI) and Health Assessment Questionnaire modified for the spondylarthropathies (HAQ-S) scores) and more radiologic damage (higher BASRI scores) were noted among workers who had jobs with higher dynamic flexibility, particularly those with repeated bending, stretching, or twisting without adequate rest.[17] The authors also observed more severe radiographic damage in patients with higher exposure to whole body vibration (subjects who drove trucks, tractors or operated heavy equipment). They postulated that the osteogenic effect of low-magnitude whole body vibration may play a role resulting in this clinical observation.[18–20]

These data suggest that there may be an inflammation-independent mechanism responsible for the impact of physically demanding job types on the pre-existing inflamed axial skeleton (figure 1). While the above studies were cross-sectional, association only, and were unable to establish causal connections, they clearly justify initiating prospective studies to confirm a biomechanical basis for AS.

- Patients with blue collar jobs have increased radiographic progression
- Higher functional limitation in patients who have jobs with higher dynamic flexibility

Figure 1 Physically demanding occupations in patients with SpA. SpA, spondyloarthritis.

JUVENILE SPA

The impact of biomechanical forces has been underexplored in juvenile SpA (jSpA).[21] Several unanswered questions remain, including whether walking with adult-like velocity with immature lower limbs[22] and aberrant tendon stiffening amidst increasing body mass during childhood[23] apply increased forces on the entheses of susceptible children and hence favour disease development.

A recent review suggested that children may have a lower threshold for developing enthesitis than adults and also identified age-related differences in skeletal anatomy as well as kinematic forces of biomechanical stress that are essentially unexplored in jSpA.[21] Studies show that children with immature lower limbs or those who exercise with increasing body mass during childhood may have increased forces to contend with that might favour disease development.[22 23] This important area of biomechanical trigger for jSpA requires attention.

MEDICATION EFFECT ON INFLAMMATION AND BONE GROWTH

Studies on the effects of non steroidal anti inflammatory drugs (NSAIDs), Tumor necrosis factor inhibitors (TNFi) and IL-17 inhibitors on radiographic changes and axial damage accrual have been inconsistent and conflicting. From a mechanistic standpoint, elevated prostaglandin E2 levels may promote osteoblastic activity, and hence, it is presumed that blocking prostaglandin (especially prostaglandin E2) synthesis by COX-2 inhibitors might inhibit new bone formation.[24 25]

TNF may promote osteoclastogenic activity, which contributes to bone resorption.[26] TNF itself may lead to the production of DKK-1, and subsequent pharmacological blocking of TNF may actually stimulate new bone formation by decreasing this repressor.[27] Through the induction of RANKL, which can increase osteoclastogenicity, IL-17 may influence bone loss. Additionally, it may inhibit the WNT pathway by promoting osteoblast activity. Studies in mesenchymal stem cells show that IL17 stimulates the production of new bone by decreasing RANKL levels. As above, the impact of targeted medications (Il-17

and TNF) on bone loss and bone growth in AS is varied, complex and possibly bidirectional.

Multiple effects of these agents, particularly those related to TNFi which may be bidirectional, may make it difficult to show differences between groups within the framework of clinical trials.

Another potential challenge to demonstrate the effect of NSAID administration on the development of syndesmophytes in AS clinical trials may relate to the known circadian rhythm of bone biology, where formation occurs during the resting period, or night-time, and resorption occurs during the active period, or the day time.[28] All bone cells express clock genes that influence their expression at different times; NSAID drugs exert a strong anti-inflammatory effect when administered for clinical reasons during the morning or early afternoon while their administration in the evening creates adverse effects such as renal or GI toxicities. In a murine tibia fracture surgical model, investigators demonstrated that pain, inflammation and tissue resorption occur during the day when the drugs are most effective in promoting healing; however, if the drugs are administered during the resting period at night, there is severe bone healing impairment and suppression of bone formation growth factors.[28] Therefore, the usual administration of NSAIDs during the daytime for clinical reasons in trials may promote bone growth, and hence syndesmophytes, in the AxSpA patient. A clinical trial where these agents were administered during the resting phase is warranted.

A Mayo Clinic-based meta-analysis[29] examining the impact of different therapies on radiographic progression in axSpA suggested that treatment duration may be critical. NSAIDs did not significantly inhibit radiographic progression in the AS spine at 2 years or the SIJ at >2 years (mSASSS difference=−0.30, 95% CI=−2.62 to 1.31, I^2=71%). These investigators demonstrated that TNFi may slow radiographic progression at the AS spine at ≥4 years when only studies judged to have a low risk of bias were included (mSASSS difference=−2.03, 95% CI −4.63 to 0.72, I^2=63%) but not at 2 years (mSASSS difference=−0.73, 95% CI −1.52 to 0.12, I^2=28%).

A study of 314 patients from the Alberta Prospective cohort disclosed that TNFi treatment was directly associated with less mSASSS progression and partially separate from the effects of TNFi on inflammation.[30] After 2 years, those who were receiving TNFi at the start of that interval had 0.85 units lower on the mSASSS which may be independent of their effects on inflammation as measured by the ASDAS score. An important effect of TNFi therapy duration and timing of treatment initiation was also noted in another study of 334 patients.[31]

Fewer studies have investigated the effect of IL-17 inhibitors on radiographic progression in SpA. A study with secukinumab did not show a significant difference in radiographic progression at 2 years (mSASSS difference=−0.34, 95% CI −0.85 to 0.17).[32] Phase III data from secukinumab showed no increase in spinal radiographic damage in 80% of AS patients at 2 and 4 years[33 34], but

these data need to be interpreted with caution in the absence of a control group. A study evaluating the long-term effect of Ixekizumab on radiographic changes of the spine revealed that the majority of the patients (89.6% vs 75.7%) had minimal (mSASSS change from baseline <2) or no radiographic progression (mSASSS change >0) through 2 years of treatment.[35]

In almost all studies on radiographic progression, the presence of baseline syndesmophytes has been associated with a subsequent high likelihood of structural progression.[36 37] However, given the slow rate of syndesmophyte development, short-clinical trials of ≤2 years using radiographic endpoints might not be able to capture differences in syndesmophyte growth.[27]

GENDER DIFFERENCES AND THE HETEROGENEITY OF DISEASE

Previous studies have reported significant SpA clinical heterogeneity to occur between the genders (men and women) attributable to hormonal, immunological and genetic factors.[38–40] Oestrogen, by virtue of inhibiting TNF alpha production, was thought to have anti-inflammatory properties, but its effect on SpA has been controversial.[41–44] Some studies have noted that male gender is associated with more severe radiographic damage,[45] greater spinal radiographic progression, greater syndesmophyte formation, decreased chest wall expansion,[44] worse radiographic sacroiliitis and MRIs with inflammatory lesions of the SI joints.[46]

A 5-year prospective study reported differential effects of risk factors on disease progression in both the sexes—with smoking being an important predictor in men and bisphosphonate therapy being more important in women.[47] Enthesitis and dactylitis are more common and severe in female patients, and studies report that males have acute anterior uveitis more frequently.[48] There have also been investigations reporting a lower response rate to TNFi therapy in women compared with men.[48] Older literature had suggested cervical vertebral involvement is more common[49 50] in women while other studies[51 52] have reported contradictory findings. Studies have proposed that there are gender differences in the activation status of the immune system, with several emphasising the differences on the TH17 axis (gene regulation of IL17 RA and, blood levels of IL17A and Th17 cells).[53]

A prospective cohort study by Webers *et al* found no gender-attributable differences in disease activity (measured with ASDAS) or physical function over time.[54] It is possible that case selection may have a significant impact on reports showing differences between the genders; for example, if studies only include those with modified NY criteria, then only women with these criteria would be included and it would be likely that no differences would be found between the genders.

A recent study demonstrated the effect of expert judgement bias on the classification of axial SpA using the concept of latent class analysis.[55] From two independent cohorts of early onset inflammatory back pain, subjects

were grouped into meaningful diagnostic classes based on the best fit of most prominent features: pure axial SpA, axial SpA with peripheral signs, and axial SpA at risk. The second category, axial SpA with peripheral signs, was not captured well by the ASAS axSpA criteria and hence not likely to be included in axSpA clinical trials. This specific group, compared with the pure axial SpA group had a greater representation of women and was more likely to be B-27 negative. Hence, gender differences found in clinical studies may be powerfully explained by how the inclusion criteria are constructed. Another possible explanation is that the axSpA with peripheral signs group is largely B-27 negative and has negative imaging results, their exclusion from the major phase-3 registration trials of anti-TNF agents has created an artificial distinction that this phenotype is less responsive to these agents because they were not tested in the first place.

Insights into gender differences in human disease has been provided by CT scan technology allowing the tomographic technique to display wide anatomic variability commonly present in sacroiliac (SI) joints. A study examining the role of anatomic variants in the SI joint in symptomatic patients with mechanical joint disease (MJD) and axial SpA noted that these anatomic variants were more likely to occur in women than in men (65.0% vs 17.8%; p<0.001) and that the highest rate of atypical joint forms was found in females with MJD, with 92.7% of patients exhibiting an atypical joint.[56] In males, these atypical joint forms (particularly ilio-sacral complexes and crescent-shaped ilii) were most likely to contribute to symptomatic joint disease in both the axSpA and MJD groups (32.2% in axSpA and 55.0% in MJD vs 13.9% in controls; p≤0.001). As a possible explanation, the authors postulated that these variants may lead to supra-physiological biomechanical stress, inducing microtrauma at the cartilage level. In another study of degenerative changes in the SI joints of patients without known SI joint disease, the authors noted that the spatial distribution of SIJ degeneration differed between men and women: female sex was associated with only a fifth of the risk of male sex exhibiting ventral osteophytes (OR 0.2) but with more than a fourfold risk of exhibiting dorsal osteophytes.[57]

A longer diagnostic delay for females compared with men has been traditionally attributed to differences in clinical symptoms reported by female patients, such as a lower frequency of typical inflammatory back pain[44] as a presenting complaint, the presence of more prominent upper thoracic and neck or widespread pain[44] coupled with observations that there is less severe or slower progression of radiographic damage in women.[58] A higher disease burden measured by patient-reported outcomes and disease activity scores in women has also been observed in many studies, which has been attributed to longer delays in diagnosis and potential differences in the expression and response to proinflammatory cytokines, resulting in higher disease activity.[39]

Alternatively, much of this difference may not necessarily be due to anatomic distinctions in disease phenotypes. A recent study examining differences in early diagnostic coding and specialty doctor visits between men and women on their journey to a final diagnosis of AS in a commercial research database revealed marked divergences.[47] An alternate explanation for not only these recent findings, but potentially for many of the prior studies that allegedly demonstrated dissimilarities in disease phenotypes between men and women, can be explained by a cognitive bias whereby healthcare practitioners use different tools and testing mechanisms when approaching the diagnosis of AS in women versus men. We postulate that differences between the genders in SpA disease severity may be only partially linked to differences in anatomy between the two genders; however, the literature focusing on this area needs greater exploration.

ANATOMIC FEATURES OF THE HUMAN PELVIS AND SPINE
The human pelvis
The SIJ absorbs and transmits forces from the spine to the pelvis, allowing the transfer of loads from the spine to the lower extremities.[59] It has limited range of motion, and further movement is restricted by the presence of a firm capsule, multiple stabilising ligaments and strong muscles of the pelvic floor.[60] The SI joints act as shock absorbers and can transfer large bending and compression loads; but however, they do not have much stability against shear loads. It is well known that the SI joint undergoes a decrease in joint width and increasing sclerosis with increasing age.

Inherent differences in SIJ anatomy (table 1) between men and women contribute to sexual dimorphism and potentially many of the findings under discussion as differences in disease expression between men and women.

With the centre-of-gravity location difference between women and men, men would subsequently have a greater lever arm than women perhaps accounting for higher loads and stronger SI joints in males. This also contributes to restricted mobility at the SI joints in men (approximately 40% less than that of women). Women have a greater pubic angle and a less pronounced curvature of the SIJ surface, contributing to increased mobility. This increased mobility could contribute to SIJ misalignment effects in young women. Men also have almost twice the amount of lumbar isometric strength so therefore require significantly more load transfers through the SIJs.[60]

The shape and the presence of anatomic variants of the SI joint have gained much attention in recent times and may play a role in degenerative disease of the joint in both genders. Among 800 asymptomatic patients, Ziegeler et al observed a significant association between joint sclerosis and the presence of accessory joint facets (OR 2.7).[61] Sclerosis was noted in the dorsal and caudal aspects of the joints, indicating pathological bony contact. Among those joints with an ilio-sacral complex pattern, sclerosis in the ventral and dorsal joint aspect was less common, but the risk of ventral osteophytes increased

Table 1 Differences in sacroiliac joint in men and women[103 104]

Biomechanical unit	Women	Men
Sacral base articular facet for fifth lumber vertebra	Less than 1/3 width of sacral base	More than 1/3 width of sacral base
Sacrum	Wider, more uneven, less curved, more backward tilted	Narrower, more curved
Sacral cartilage	Thicker	Thinner
Pelvis	Wider, shorter	Narrower, longer, more conical
SIJ surface area	Less	Greater
Angular range of motion	Higher	Lower
SIJ motions	More rotational	More translational
Anterior and posterior sacroiliac ligaments	Larger	Smaller
Centre of gravity	Passes in front of or through the SIJ	More ventral compared with women

SIJ, sacroiliac joint.

more than threefold (OR 3.6). The authors postulate that joint shape alteration differences may cause atypical biomechanical loading in the joint and thereby change the natural history of degeneration and contribute to mechanically induced bone marrow oedema (BME)—which may mimic inflammatory osteitis adjacent to the joint.[61] Finally, a comparison of the relationship between lumbar spine and pelvic CT scans was performed in 719 subjects without back pain.[62] Results revealed parallel processes of degeneration in both anatomic areas for men, but the processes were unrelated in women, again suggesting that important differences in normal anatomy between the genders can lead to strikingly different clinical consequences.[62]

This emerging line of research, as well as clinical observations, suggests that the atypical SI joint may represent a normal anatomical variation but is not necessarily causative when it comes to pathogenesis of axSpA. The role of these anatomical variants deserves greater scientific attention. Nevertheless and as noted above, the divergence in mechanical forces between the two genders as well as the differences in the prevalence of anatomic variants between them may likely contribute to degenerative changes[57] and hence variance in symptoms between the two genders. A result could be the creation of clinical conundrums resulting in misclassification when it comes to relying on imaging emphasis as the key part of the diagnostic and classification process.

Pregnancy and women

As a consequence of hormonal and biomechanical changes during pregnancy, hormones such as relaxin loosen the SIJ fibrous apparatus further and increase SIJ mobility.[63] During pregnancy, an increase in mass of the uterus and breasts can cause anterior displacement of the centre of gravity. Both of these effects heighten joint loads, increase the risk of injury, and contribute to SIJ and pelvic girdle pain which may persist after delivery.[64]

BME over the SI joints as a consequence of mechanical stress and peripartum strain may simulate sacroiliitis during pregnancy and the postpartum period.[65] In a study of 103 primigravida mothers evaluated using serial MRI scans during and after pregnancy, BME was noted as long as 12 months post partum.[66] BME peaked at 3 months postpartum, and 41% of the women met the current ASAS sacroiliitis definition at 12 months. The virtual absence of erosions and topographical BME distribution (involvement of anterior middle portions of the cartilaginous SIJ without a widespread lesion distribution) can help distinguish between the two entities. Finally, another consequence of BME may be osteitis condensans ilii (OCI), typically seen in middle-aged women and detected on imaging revealing sclerotic areas, mainly in the iliac bone, with relatively normal joint spaces.[67] OCI is usually bilateral, symmetric and more frequent in multiparous women.

The human spine

Sexual dimorphism also exists at the level of the spine. Men experienced more absolute spinal compression than women in a biodynamic examination of spinal loading.[68] Men have larger vertebral dimensions than woman; these are summarised in table 2.

In the cervical spine, dimorphism persists; women's cervical vertebral dimensions are smaller,[69] and their cervical geometries differ[70] from those of men. Additionally, it has been noted that women's neck muscular moment-producing capacity is lower (approximately 40%–60% of men's).[71] Because of these spinal geometrical variations, women may be less able to actively stabilise their cervical spines, which increases the risk of traumatic injury in the region and results in larger movements during physiologic and dynamic stress. According to one study, women are more likely to have radiographic progression of axSpA in the cervical vertebrae than males,[49] and we hypothesise that this result may also be influenced by biomechanical variables.

As shown in table 2, there are several differences between the genders in the spine, potentially producing effects at different stages of a person's life cycle depending on the mechanical pressures placed on the spine from physical activities for either recreation or from work requirements. Further, each gender is subject to spine stresses that are not going to be the same (childbearing is one) but the differences in gender specific sports and the work environment would play a role. Finally, progressive spine deterioration in today's world has almost

Table 2 Differences at the spine in men and women[103]

Spinal unit	Differences between the genders
Lumbar body heights and width, size and cross-sectional areas	Larger in men, considering age, stature and total body mass
Lumbar ligaments	Women have decreased collagen and increased elastin
Vertebral width, disc-to-facet depth, segmental support area*	Greater in men
Pedicle width, height, length, axis length, medial and sagittal offsets, and transverse and sagittal angulations	Greater in men
Dorsal cartilage gap†	Greater in women
Mean facet cartilage thickness	Greater in women

*Vertebral width is the distance between most lateral extents of right and left articular masses. Disc-to-depth is distance between the most anterior vertebral body extent and the most posterior articular mass extent. Segmental support area is the triangular area formed by the interfacet width and disc-to-facet depth which is the distance between the posterior extents of the right and left articular masses.
†Cartilage gap is the distance from the most ventral or most dorsal region of the facet joint to the location where the cartilage begins to appear.

Figure 2 Higher disease activity scores have been observed in obese patients with SpA. BMI, body mass index; DAS, Disease activity score; SpA, spondyloarthritis.

reached epidemic proportions with the frequency of spine surgery and other interventions for spinal pain and spinal stenosis affecting most adults. More work needs to be done in this area.

Obesity, muscle tone and its role in AxSpA

Recent studies have explored the significance of high body mass index (BMI) and obesity in the persistence of symptoms and radiographic progression in SpA. Whether the presence of obesity leads to differences in the location of syndesmophytes over the spine (because of a displaced centre of gravity) or to progression of disease in AxSpA because of its proinflammatory effects is still under investigation (figure 2).

Overweight and obese individuals reported worse disease activity scores and spine stiffness in a survey study involving 509 participants.[72] A systematic review that examined the relationship between BMI and imaging-defined inflammation and injury in SpA found that a higher BMI was closely related to new bone formation including syndesmophytes, enthesophytes, and a higher mSASSS score.[73]

Masi *et al* proposed a hypothesis based on innate axial spinal myofascial hypertonicity in order to explain the biomechanical stress concept.[74] A stiffer axial myofascial system noted in AS may exaggerate tensional force and stress, and transmit greater stresses to tendons, ligaments or bony entheses sites leading to greater micro-damage and potentiate an
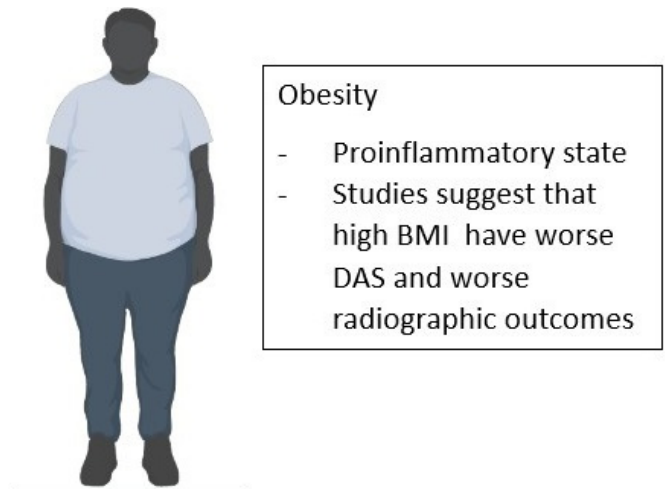
abnormal tissue response.[75] In a biomechanical study of myofascial tissues in patients with AS compared to healthy controls, increased disease duration was associated with myofascial degradation.[76] More work needs to be done in this intriguing area to sort out whether these observations are potentially bi-directional in scope and concept.

IMAGING OF HUMAN DISEASE: NEW AND EMERGING DATA

Syndesmophytes are one of the pathognomonic signature features of AS; extensive bridging of syndesmophytes across multiple vertebrae are typically seen in advanced disease leading to ankylosis. These lesions consist of cortical bone outgrowths from the vertebral rim or face of the vertebral body that extend vertically along or close to the annulus fibrosus. The intervertebral disc space (IDS) can be bridged by the growth of syndesmophytes, joining two contiguous vertebral bodies together with eventual spinal fusion creating the classical imaging finding of a 'bamboo spine'.

The legendary theory that AS begins in the SI joints and progresses up the spine from caudal to cranial because of syndesmophyte progression with eventual ankylosis has not been substantially validated. A radiographic progression study by Tubergen *et al* using serial X-rays at diagnosis, 2-year and 4-year follow-up, failed to identify a specific predilection site and revealed no particular order for occurrence and development of syndesmophytes.[77] The authors noted that syndesmophytes occurred more frequently in the cervical spine and bridged more frequently in the lumbar spine.

If the initiation and progression of SpA was solely related to inflammation from enthesitis (and independent of the effects of biomechanics), the involvement of the spine, growth of syndesmophytes and subsequent bridging would be expected to occur in a random fashion around the rim of any individual vertebral body.

Therefore, systemic factors acting alone should produce a slow linear evolution of spinal fusion within the same IDS or among IDSs of a single patient. However, this view was not supported by observations of Tan and Ward.[78]

Tan *et al* continued this line of inquiry (where does AS begin and how does it progress) and mapped the location of syndesmophytes in thoracolumbar IDSs of 50 patients with AS using a CT scan computer algorithm to measure syndesmophyte heights, volume and location. They provided evidence that syndesmophyte formation in AS is preferentially localised to the posterolateral vertebral rim of the IDS—an area of significant mechanical stress.[79] They observed that this area had the tallest syndesmophytes with most of the bridging; the anterior rim was often either less involved or involved much later. Syndesmophytes were generally noted on superior vertebral endplates and gradually increased in height particularly in the anterolateral regions and descended from the opposing vertebral endplate. The posterolateral rim subsequently experienced focal bridging initially, followed by the development of discontinuous bridges in other areas of the IDS. The IDS was surrounded by bridges that expanded circumferentially and united, eventually enclosing it. The middle column of the spine, or the posterior portions of the vertebral bodies accompanied by the base of the pedicles, are the well-known locations where mechanical stress is concentrated.[80] The finding that early development of syndesmophytes occurs in this area suggests that syndesmophytes may arise in response to mechanical stress and that mechanical stress could possibly contribute to localised osteitis.

To identify the earliest location and distribution of syndesmophytes in the spine, Tan *et al* studied thoracic and lumbar syndesmophytes with the aim of determining whether thoracic involvement correlated with lumbar involvement and which the level of initial spinal damage.[81] The thoracic spine had slightly more syndesmophytes than the lumbar spine, and bridging was substantially more frequent. Results revealed lumbar syndesmophytes often develop following the development of thoracic syndesmophytes.

The thoracolumbar spine has unique biomechanics.[82] There is a 40% and 60% increase in cross-sectional area and load-carrying capacity, respectively, in the mid-thoracic and lower thoracic regions compared with the upper thoracic regions.[83] Unlike other thoracic vertebrae, T11 and 12 have free floating ribs whose costovertebral joints directly oppose the vertebral body. This transition between a rigid (normally kyphotic) T-spine and a mobile (normally lordotic) L-spine provides a fulcrum for flexion-extension and induces additional load at the thoracolumbar junction spine. The intervertebral disks in the thoracic spine are thinner and shorter compared with the lumbar spine.[84] These unique features in loading pattern and the distinctive mechanics at the thoracolumbar junction may also contribute to the early development of syndesmophytes noted in this area (figure 3).
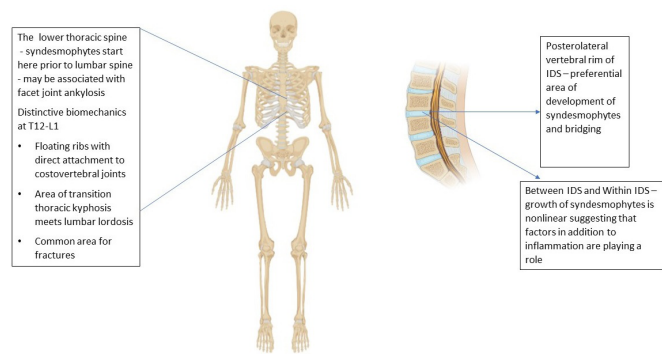

Figure 3 Biomechanics of the thoracolumbar spine. IDS, intervertebral disc space.

Most studies assessing structural progression in axSpA have focused on the vertebral bodies themselves with less attention given to the role of the facet joint, which may also ankylose. Facet or zygapophyseal joints are synovial-lined joints posterior to the vertebral columns. Stal *et al* conducted a study to evaluate the occurrence and progression of facet joint ankylosis in the whole spine using low-dose CT; they compared progression of facet joint ankylosis with syndesmophytes over a 2-year period.[85] Facet joint ankylosis, and new development of vertebral ankylosis over 2 years, was detected in all spinal segments but was most common in the thoracic segment (T2-L1).[85]

A report from Tan *et al* using full dose CT to study a limited part of the thoracolumbar spine (T10–L4) reported a high degree of correlation between syndesmophytes and facet joint ankylosis.[86] To address the same question, DeVlam and Mielants noted that about two-thirds of vertebral levels with facet joint ankylosis were not accompanied by bridging of syndesmophytes, and that bridging syndesmophytes rarely occurred without facet joint ankylosis on X-rays.[87]

The above studies suggest that the thoracic spine location and the facet joints themselves throughout the spine may play a much more important role in the initiation and progression of AS than previously thought. Both syndesmophytes and facet joint ankylosis have been observed most in the thoracic spine, even out of proportion to the lumbar spine. Based on the above findings, several additional topics need to be addressed. Do facet joints, which are synovial-lined joints that allow spinal mobility (rotation, bending), have a different pathophysiologic mechanism for disease progression and ankylosis than the immovable vertebral bodies? Does motion matter, or does the synovial lining's component of inflammation provide a separate mechanism for the advancement of the disease? Does control of inflammation where motion occurs or where there is synovium have a differential effect on bone formation compared with areas that do not move (the vertebral body)? Are bidirectional effects present—where one opposes the other? To address these questions, additional research must take place.

Investigations of long-term radiographic change in AS have revealed a slow trend towards spinal fusion with wide variability in syndesmophyte growth. Studies employing the modified Stoke AS Spine Score (mSASSS; potential range 0–72) have consistently indicated mean increases of 1 mSASSS unit/year.[27] Even though the mean rates of progression are low generally, there are substantial differences in rates among patients, with some experiencing no progression for years on end, and up to one-third experiencing rapid progression with increments of 55 mSASSS units/year. There is also evidence of within-patient and between-patient variation, with periods of faster syndesmophyte growth occasionally occurring before or after periods of stability in certain patients.[88 89] When using growth-mixture modelling, investigators have found longitudinal endotypes (ie, subgroups) of syndesmophyte progression in cohort studies.[90] Nevertheless, recent research focusing on dynamics of syndesmophyte growth in individual patients demonstrates that there is a significant variation in the growth of syndesmophytes within individual IDSs and between IDSs in individual patients.[88] Only 11 of 60 IDSs throughout a 2-year period were found to have a new syndesmophyte in a study of 24 individuals who had at least two IDSs with syndesmophytes at baseline. Most of the growth was noted in pre-existing syndesmophytes. Within the same IDS, the authors discovered a striking heterogeneity in the proliferation of syndesmophytes. Both bridged and non-bridged syndesmophytes exhibited this pattern. Similar patterns were seen within patients where syndesmophytes in some IDSs grew explosively whereas some grew slowly or not at all.

These results suggest that syndesmophytes may have growth spurts interspersed with periods of relative stagnation. This temporal non-uniform growth heterogeneity suggests that syndesmophyte growth is impacted by local factors in the surrounding area. In addition to anatomic location playing a key role in the perpetuation of disease, we hypothesise that differences in motion, force transmission and biomechanics may also contribute to these regional changes noted within the spine.

Syndesmophyte formation, vertebral bone loss and vertebral fractures: a vicious perpetuating cycle?

Recently, there has been increased interest in the interactions between bone mineral density (BMD), syndesmophyte development and the opposing processes of bone growth and bone loss in AS.

A recent study by Tan *et al* evaluating the role of vertebral bone loss and syndesmophyte formation in AS, suggests close relationships among bone strength, BMD, and syndesmophyte formation and differences between bridged and non-bridged vertebrae.[91] The authors conclude that bridging is essential for altering the spinal fusion process, often contributing to bone thinning in AS, and propose a model to link the growth of syndesmophytes and vertebral bone loss consistent with Wolff's law and concepts of bone adaptation. Extensive bridging may

serve as a scaffold that distributes compressive pressures away from trabecular bone and onto the cortical shells of the adjacent vertebrae. Trabecular bone is destroyed faster when there is less compressive force present. Additionally, this might create a vicious self-perpetuating cycle between bridging and low vertebral tBMD. This work is quite suggestive that bridging, as a mechanical force, exerts feedback that will generate more trabecular bone loss over time contributing to the fragility of the spine in AS, making it subject to fractures. It is well known that the AS patient experiences more spinal fractures compared with age and gender matched control subjects.[92]

OTHER SPA FEATURES RELATED TO MECHANICAL FORCES: THE EYE, THE SKIN, AORTIC ROOT

The biological mechanism origin for triggering entheseal inflammation in SpA is consistent with a conceptual model which involves a threshold effect; a lower severity of stimulus may trigger, in a genetically susceptible individual, a substantially exaggerated response.[14] Entheseal microtrauma may perpetuate TNF and IL 17 overexpression and maintain enthesitis.[4] This leads to an overexuberant response contributing to ectopic bone formation and eventual ankylosis. This is further supported by early MRI studies demonstrating that entheseal sites with prior inflammation tend to have an increased frequency of bony appositions.[37 93]

McGonagle proposed the concepts of 'synovio-entheseal complexes' which consists of an enthesis-related fibrocartilage (which is usually an immune devoid area) that is critically dependent on immediately adjacent synovium for lubrication and nourishment.[94] As an effect of aberrant tissue responses, biomechanical microtrauma at the entheses is dissipated and there is secretion of proinflammatory factors from focal bony attachment sites; this may trigger simultaneous secondary osteitis and synovitis. In an ultrasound and microanatomic guided study of the Achilles tendon in early SpA by McGonagle *et al*,[95] the authors observed that spur formation happens when tensile pressures are more likely to be present and erosions would necessarily develop in areas of high compression.

Because mechanical overloading contributes significantly to the pathogenesis of enthesitis, it would take place more commonly in lower extremities as a result of increased mechanical forces.[96] It has also been postulated that HLA B27 could modulate responses to microtrauma by recognising tissue specific antigens, and then initiating and perpetuating autoimmunity based on molecular mimicry.[7 97] Proof for this role for HLA-B27, however, is lacking.

Tendons and ligaments in the human body are subjected to wide differences in loading, mechanical impact forces and hence mobility.[98] Not all entheseal sites and soft tissues may adapt equally to these heightened forces, making certain areas increasingly prone to microtrauma. This key concept provides a basis for differences

in damage noted in certain anatomic locations compared with others.[7] This potential concept is also postulated as an explanation for the extra-articular manifestations noted in SpA at the gut (terminal ileum, near the ileocecal valve), the aortic root and the eye.[99] The aortic root is subjected to repetitive stretching forces between systole and diastole. At the ileocecal valve (a sphincter designed to prevent reflux of bowel contents into the colon), intraluminal content may accumulate proximal to the valve and thus cause stretching of the wall. These sites share several anatomic features including repetitive mechanical stress, similar resident immune cell populations and tissue repair responses[1 99]

HLA-B27 positivity has been associated with worse radiographic damage overall, more typical marginal syndesmophytes and an increased frequency of syndesmophyte symmetry in SpA patients. This concept relates HLA-B27 to disease severity rather than to susceptibility. The first line of evidence in this direction comes from the observation that HLA-B27+ individuals appear predisposed to exaggerated bone formation regardless of SpA disease status; Aschermann *et al* noted that changes in key regulators of endochondral ossification are found in HLA-B27 carriers, independent if they were healthy or affected by uveitis or SpA.[100] Contrary to the previously discussed literature, another study argues against a direct role of HLA-B27 in mediating new bone formation in axial SpA.[21] HLA-B27 overexpression in various in vitro mouse and human differentiation systems mimicking endochondral ossification did not result in differences in bone formation when compared with the HLA-B7 overexpression controls. While the experimental set-up was deliberately reductionist to exclude the influence of possibly intervening variables (eg, proinflammatory cytokines, immune cells), its oversimplicity may render the study's conclusions premature.

How heritability and genetics (not just limited to HLA-B27) contribute to disease severity remains an area that requires further work. Support for this concept comes from a variety of recent studies that relate HLA-B27 positivity more directly to SIJ and lumbar spine pathology as opposed to peripheral arthritis. Further, these recent studies indicate that our longstanding clinical observations of SpA disease heterogeneity in women with largely non-radiographic SpA that now can be partially explained by a reduced frequency of HLA-B27 positivity as well as a lower polygenetic risk score.[101] This is additionally demonstrated in recent findings from specialised cohorts of SpA subjects where there was an absence of an association between HLA-B27 positivity and peripheral structural damage in a collection of dominant peripheral disease SpA patients.[102] This concept goes along with similar findings in the latent class analysis study from two independent cohorts of early-onset chronic back pain where patients with axSpA (mostly female) had back pain but were unlikely to be positive for sacroiliitis on imaging or possess HLA-B27 positivity.[55] The future identification of additional genotypes with other SpA clinical
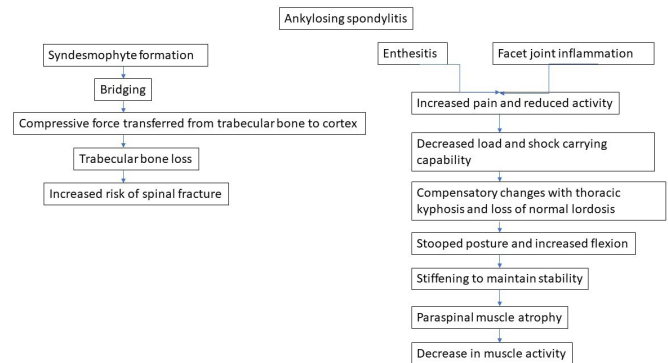

Figure 4 The role of biomechanical forces in the pathogenesis of SpA. SpA, spondyloarthritis.

manifestations might add to the picture that the authors are trying to present in this review—biomechanical forces are part of multiple contributions to the complexity of SpA.

CONCLUSION

Axial SpA is a distinct disease that is substantially influenced by biomechanical forces (figure 4). Evidence supporting the role of mechanotransduction in SpA pathogenesis, either as initiating or perpetuating the disease, is accumulating at a rapid pace. Animal model experiments, human occupational studies, gender differences in spinal anatomy, atypical SI joint variability between the genders, the unique biomechanics of certain targeted SpA areas of involvement, and advanced imaging studies of the location and features of syndesmophyte formation clearly support the role of mechanotransduction perhaps even at the earliest stages of the disease. The location of enthesitis, vertebral ankylosis and other extra-articular features of disease emphasise a common pathological process in a unique immune microenvironment. Moving forward, studies focusing on the impact of movement and physical forces in SpA particularly with respect to progression of disease might play an important role in our understanding of the pathophysiology and outcomes, and potential prevention, associated with the axial SpA.

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