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## REVIEW

# Sex-associated and gender-associated differences in the diagnosis and management of axial spondyloarthritis: addressing the unmet needs of female patients

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## ABSTRACT

Emerging evidence suggests that axial spondyloarthritis (axSpA) should not be seen as a predominantly male disease, as the non-radiographic form occurs with roughly equal frequency in women and men. However, men and women experience this disease differently. The purpose of this review is to highlight sex-associated and gender-associated differences in the patient's journey through the diagnosis and management of axSpA, in order to increase the awareness about the unmet needs of female axSpA patients.

Female patients experience a longer diagnostic delay compared with men, possibly due to the different pattern of clinical presentations across genders. Therefore, it is crucial to sensitise physicians to pay attention and identify the red flags of axSpA in women and promote early referral to a rheumatologist. Women with a diagnosis of axSpA experience greater limitations in physical function, although they have less structural spinal damage compared with men. Women tend to have less adherence and a lower response to treatment, so more gender-oriented data are needed about drugs used for axSpA, especially biological disease-modifying antirheumatic drugs.

Lifestyle factors have a strong impact on the disease course. Interventions regarding physical activity, smoking cessation and diet should be communicated to the patients, with particular attention to the gender-related cultural background.

Patients of childbearing age living with axSpA should be engaged in a discussion about reproductive health, in terms of preservation of fertility, management of pregnancy and delivery and use of biologic drugs during pregnancy and breastfeeding.

## INTRODUCTION

Axial spondyloarthritis (axSpA) is a chronic inflammatory rheumatic disorder that

## Key messages

- ▶ Female patients experience a longer diagnostic delay compared with male patients; therefore, better and earlier identification of signs and symptoms of axSpA according to sex is needed.
- ▶ The response to treatment with biologic agents (especially tumour necrosis factor inhibitors) may be lower in females with axSpA as compared with male patients.
- ▶ Women with axSpA should be educated about the relevance of lifestyle factors and be informed about the benefits of regular physical exercise, maintenance of a normal body weight and smoking cessation.
- ▶ Women of childbearing age living with axSpA should be educated about the impact of active disease on fertility and pregnancy outcomes and receive counselling about the use of biological agents during pregnancy and breastfeeding.

primarily affects the sacroiliac joints and spine; peripheral and extra-articular manifestations also exist and may affect the burden of disease.<sup>1</sup> AxSpA was long seen as a predominantly male disease, with estimates as high as 10:1, but more recent reports have indicated little difference in the sex prevalence.<sup>2,3</sup> Differences in the presentation of axSpA between male and female patients may have led to the lower reported prevalence in women for many years. Male patients with axSpA have greater structural damage compared with women, whereas female patients have a higher disease burden, probably due to more peripheral manifestations, longer diagnostic delays (DDs), higher disease activity and lower

efficacy of treatments.<sup>4,5</sup> Moreover, evidence suggests a higher prevalence of non-radiographic axial SpA (nr-axSpA) in women than in men, which makes diagnosis difficult to achieve.<sup>4,6</sup> In addition, female patients are also under-represented in clinical trials in axSpA, which has led to a male bias in disease classification and management and treatment response. Access to treatments and patient-centred healthcare for female patients and lifestyle factors (e.g., smoking, exercise) may vary in different parts of the world. Higher disease burden and disease activity and lower efficacy of treatment reported for female patients represent some of the areas that need improved awareness for non-rheumatologist healthcare professionals (HCPs) and further research on the sex-associated differences in axSpA.<sup>6</sup> In this review, we highlight some key areas of unmet needs that may help to improve the clinical and therapeutic management of female patients with axSpA.

### Diagnosis and early referral

Women are more likely than men to present with peripheral manifestations of axSpA (arthritis and enthesitis), while the perception of pain in women is more widespread than that reported by men, and women report more stiffness, fatigue and loss of mobility.<sup>5,7</sup> Widespread pain can be misdiagnosed as fibromyalgia, which is prevalent in patients with axSpA, and can mimic enthesal pain.<sup>8</sup> The results from the Corrona Psoriatic Arthritis (PsA)/SpA registry including 498 patients with axSpA (307 (61.6%) men and 191 (38.4%) women) underline the need of improving the awareness of sex differences in the presentation of axSpA.<sup>5</sup> Authors revealed that the patient journey to diagnosis of axSpA is much longer and more arduous in women, as measured by clinical assessment and in patient-reported outcomes (PROs): women had higher disease activity as measured by Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index and physician global assessment and had higher tender/swollen joint counts and enthesitis scores. Women also had worse patient-reported symptoms (pain, fatigue, Health Assessment Questionnaire for the spondyloarthropathies and EuroQol-visual analogue scales; all  $p$  values  $<0.05$ ), greater work and activity impairment, and were less likely to work full time than men.<sup>5</sup> Prior conventional synthetic disease-modifying antirheumatic drugs (DMARDs) and prednisone use was more common in women than in men. Additionally, women were more likely to have concomitant diagnoses of depression and fibromyalgia<sup>5</sup> and to report higher disease activity, greater functional impairment and worse quality of life.<sup>7</sup> These data were also confirmed in the European map of axial spondyloarthritis (EMAS) in a larger sample size: 1100 (38.7%) men and 1746 (61.3%) women. In addition, women reported a higher degree of disease activity, greater psychological distress through general health questionnaire-12 items ( $4.4 \pm 4.2$  vs  $5.3 \pm 4.1$ ;  $p < 0.001$ ) as well as a greater use of alternative therapies.<sup>9</sup>

Although underdiagnosis of female patients with axSpA is common, the imaging workout can actually lead to overdiagnosis. Due to the moderate diagnostic utility of magnetic resonance imaging (MRI) lesions, the discrimination between bone marrow oedema due to early axSpA and non-SpA lesions can be challenging.<sup>10</sup> Analysis of 423 MRI scans of the sacroiliac joint in nulliparous, early postpartum and late postpartum women with no personal or family history of inflammatory disease showed that bone marrow oedema was more frequent in early postpartum women (33%) than in nulliparous women (14%,  $p=0.001$ ).<sup>11</sup> Moreover, 21% of late postpartum women still had spinal cord injury lesions, 80% of which met the Assessment of SpondyloArthritis international Society (ASAS) criteria.<sup>11</sup> New MRI studies have demonstrated adapted cut-offs of what is thought to be a positive MRI with regards to bone marrow oedema in the context of axSpA.<sup>12</sup> Together with the issue of postpartum bone marrow oedema, this might imply a much higher number of misdiagnosis in women than in men, especially in nr-axSpA. Making the right diagnosis as early as possible in the disease course of female patients with inflammatory back pain remains a challenge.

A meta-analysis of 42 papers, including 23883 patients (32.3% women) with SpA, found a delay in diagnosis of 8.8 years (7.4–10.1) for women and 6.5 years (5.6–7.4) for men ( $p=0.01$ ).<sup>13</sup> Furthermore, a recent survey of 2846 patients (61.4% female) across 13 countries confirmed a significantly greater DD in female patients [mean (SD), 8.2 (8.9) years] compared with men [6.1 (7.4) years;  $p < 0.0001$ ].<sup>14</sup> Women also tend to have a slower radiographic progression compared with men, as well as lower objective markers of inflammation, that is, less frequently abnormal C reactive protein (CRP) levels or lower levels of CRP and less MRI inflammation of the axial skeleton, particularly in relation to the depth and intensity of bone marrow oedema.<sup>14</sup> These differences in inflammatory markers between men and women may underpin the differences in their response to biologics, particularly in nr-axSpA.

Data from 2652 patients included in the EMAS demonstrated an average DD of  $7.4 \pm 8.4$  years and the variables associated with longer DD were younger age at symptom onset, female gender and higher number of HCPs seen before diagnosis. Interestingly, there was a significant interaction between the female gender and the number of HCPs seen before diagnosis.<sup>15</sup> These results indicate a need for continuing efforts dedicated to recognition of patients with a high probability of axSpA, such as young patients and women, by non-rheumatology specialists in order to facilitate earlier referral to a rheumatologist. New referral strategies might decrease the DD in female patients, with referral recommendations leading to a probability of axSpA diagnosis of about 40%.<sup>16</sup> Some difficulties for a delayed referral are linked to the variability of symptoms for clinical diagnosis. In the USA, to try to improve the time to diagnosis, non-rheumatologist HCPs are advised to refer patients with

**Box 1 Suggestions for earlier diagnosis and referral**

- ▶ Increase education of non-rheumatologist healthcare professionals on the clinical manifestations of axial spondyloarthritis to aid earlier referral.
- ▶ Question patients regarding back pain and extra-articular manifestations, as this may improve overall diagnosis rates.
- ▶ Question patients regarding stiffness and fatigue — these are two important symptoms that are not well reported in the literature.
- ▶ Determine whether composite measures used in clinical practice require modification for female patients since many were developed in populations with higher proportions of men.

back pain plus  $\geq 1$  of 3 SpA features [human leucocyte antigen (HLA)-B27 positivity, current inflammatory back pain or radiographic/MRI evidence of sacroiliitis] to a rheumatologist.<sup>15 16</sup> In this context, educational efforts in axSpA should focus on providing front-line clinicians with a better understanding of inflammatory back pain, the non-radiographic form of axSpA and accepted principles in axSpA management.<sup>16</sup> Author suggestions for earlier diagnosis and referral are summarised in [box 1](#).

**Assessment of treatment response**

The management of axSpA needs to be improved in order to identify preventive and therapeutic interventions. The clinical effect of biological DMARDs may be affected by gender as well as the clinical, genetic and psychosocial lifestyle context. This difference in efficacy between women and men might be due to biological differences or/and an interaction between genetics and environment. Sex-specific gene expression likely triggered by gene-specific epigenetic modifications may contribute to the differences in response pattern in PRO.<sup>17</sup> Disease characteristics of 264 women and 231 men with nr-axSpA were included the prospective Swiss Clinical Quality Management Cohort. Response to a first tumour necrosis factor inhibitor (TNFi) was assessed in 85 women and 78 men without fibromyalgia. Again, compared with men, women had a longer DD, a higher level of perceived disease activity, more enthesitis and a lower prevalence of HLA-B27. Concerning disease activity, response rates to TNFi are significantly lower in women than in men: ASAS 40 response was achieved by 17% of women and 38% of men [odds ratio (OR): 0.34; 95% confidence intervals (CIs) 0.12 to 0.93;  $p=0.02$ ].<sup>18</sup> Gender effect was also evaluated in axial PsA, assessed by clinical and radiological data according to modified New York City or ASAS criteria in a Turkish study. Of the 373 patients with axial involvement, 150 were men (40.2%) and 223 (59.8%) were women. Spondylitis was detected in 14.7% of men and 21.9% of women in all patients. Pain score, PROs, disease activity scores as well as Functional Assessment of Chronic Illness Therapy (FACIT)—Fatigue and the presence of anxiety and depression were statistically worse in women than men with axial PsA. However, quality of life was better and Psoriasis Area Severity Index score was statistically worse in male than

in female patients with axial involvement.<sup>19</sup> Although TNFi agents have shown considerable efficacy in patients with SpA, up to 40% discontinue therapy; with the main reasons for discontinuation being lack of efficacy, followed by adverse events.<sup>20 21</sup> Some data suggest that female patients with axSpA experience lower response rates to treatment and lower disease remission when treated with TNFi.<sup>20–22</sup> Published data also indicate that women tend to switch TNFi more often than men.<sup>20–22</sup> A study of 223 consecutive patients with r-axSpA, which examined long-term drug survival of TNFi treatment over a 10-year period, revealed that female patients had significantly lower treatment survival rates than men (33.4 vs 44.9 months;  $p=0.031$ ).<sup>23</sup> Differences in immunological markers between male and female patients with axSpA have been reported in the literature and may be responsible for different treatment responses to TNFi. One study showed that male patients with axSpA have significantly higher levels of TNF and IL-17A than female patients.<sup>24</sup> It was also reported that differences in the levels of TNF, IL-6 and IL-18 were found between sexes and this could be associated with different treatment responses.<sup>24</sup> Furthermore, when women are exposed to inflammatory stimuli, they produce more IL-17A and Th17, whereas men produce more TNF. Recent data support that IL-17 is implicated in the pathogenesis of enthesitis and, if female patients produce higher levels of IL-17, this could account for the higher perception of enthesitis in female patients. In light of these findings, a post-hoc analysis of the MEASURE 1–4 trials suggests that the response to an anti-IL-17 agent, secukinumab, does not differ between male and female patients with r-axSpA.<sup>25</sup>

Real-life evidence supports the efficacy of secukinumab and ixekizumab in several clinical scenarios.<sup>26–28</sup> Data from 1-year follow-up of 169 patients affected by r-axSpA and PsA starting secukinumab were collected in a real-life prospective observational study on 169 consecutive outpatients (r-axSpA: 39 (23%); PsA: 130 (77%)). Results confirmed that women have higher Disease Activity in Psoriatic Arthritis (DAPSA) scores and erythrocyte sedimentation rate (ESR) levels at baseline, and Ankylosing Spondylitis Disease Activity Score-CRP (ASDAS-CRP) was positively correlated with ESR level and female sex ( $R^2=0.34$ ;  $p=0.004$  and  $p=0.06$ , respectively). However, no gender difference was found in the efficacy of secukinumab, since gender was not a relevant factor in patient outcomes.<sup>26 27</sup> Larger cohort studies on axSpA patients are expected in order to confirm these results.

Newly published subanalyses for secukinumab in nr-axSpA show that, while clinically meaningful efficacy was seen in both male and female patients, higher responses were consistently observed in men across all outcome measures.<sup>29</sup> Sufficiently powered studies are needed to further investigate these findings. Comorbidities may have an impact on disease activity, disease assessment and treatment response. Data from national and international registries support the evidence that baseline disease severity is higher in patients with comorbidities

and treatment discontinuation is increased in those with  $\geq 2$  comorbidities.<sup>30</sup> The effect of female sex is particularly significant if associated with a high body mass index (BMI). Disease activity scores (ASDAS and BASDAI) are significantly associated with a higher percentage of body fat (BF) or fat mass index (FMI) in women, although the opposite is observed in men.<sup>31</sup> Gremese and colleagues aimed to determine whether BMI and gender could lead to a different response rate to TNFi in patients affected by axSpA. Overall, 170 patients with active axSpA treated with a TNFi (adalimumab, etanercept, infliximab) were retrospectively evaluated. After 12 months of TNFi treatment, 67.8% of men and 46.2% of women reached the BASDAI50 ( $p=0.01$ ). According to BMI categories, the rate of BASDAI50 achievement decreased from 72.8% in normal weight subjects to 54.5% in overweight and 30.4% in obese subjects ( $p<0.001$ ). In the logistic regression analysis, the best independent predictors of failure to obtain a BASDAI50 response at 12 months in axSpA patients were female gender (OR 3.23; 95% CI 1.52 to 7.14) and a BMI  $\geq 30$  (OR 3.57; 95% CI 1.15 to 11.11). Being female, overweight and mostly obese were associated with a lower response in axSpA patients treated with TNFi, suggesting as body weight could represent a modifiable factor to reach the best outcome in axSpA patients treated with TNF blockers.<sup>32</sup>

Typically associated to female sex, fibromyalgia may have an impact on disease activity (BASDAI-based) in axSpA. Son and colleagues recently analysed in a meta-analysis the role of fibromyalgia in patients affected by axSpA. Evidence supports that patients with axSpA and fibromyalgia had considerably higher pain severity, disease activity and worse quality of life than patients without fibromyalgia. In patients with and without fibromyalgia, the sex ratios (female to male) are approximately 3:2 and 1:3, and rates for HLA-B27-positive patients were 45.1% and 65.6%, respectively.<sup>33</sup>

Insights for the research agenda for improving the assessment of treatment response are reported in [box 2](#).

## Lifestyle factors and interventions

### Smoking habit

Cigarette smoking has been shown to be independently associated with spinal radiographic progression in patients with early axSpA in different SpA cohort.<sup>34</sup> The

DESIR cohort study, which examined 647 patients with early inflammatory back pain fulfilling at least one of the internationally accepted SpA criteria and with available smoking data, found that smoking was independently associated with earlier onset of inflammatory back pain, higher disease activity, increased axial inflammation on MRI scans, increased axial structural damage on MRI scans and radiographs, poorer functional status and lower quality of life.<sup>34</sup> A Norwegian population-based study also reported that incident r-axSpA was associated with current smoking and hypertension.<sup>35</sup> In the cohort described by Haroon *et al*, the higher the pack-years of smoking, the greater the rate of modified stoke ankylosing spondylitis spinal score progression, with the highest rate seen in smokers with more than a 10 pack-year history.<sup>36</sup> Zhao *et al* also reported that baseline smoking status was independently associated with worse disease in AS, including worse fatigue, sleep, anxiety and depression.<sup>37</sup> Differences between current and ex-smokers were more consistently observed in men, and women were more likely to have never smoked. The associations between smoking and disease severity are likely explained, at least in part, by the inflammatory effects of smoke inhalation, with current smokers having higher CRP levels. This systemic inflammatory burden may exacerbate the localised disease process in axSpA, as supported by more current smokers having active inflammation on MRI. Another study by Zhao *et al* reported that ex-smokers and current smokers had worse disease at baseline than patients who never smoked.<sup>38</sup>

Smoking has long been considered a male problem; however, in recent years, there has been a sharp decline in smoking men with an increase in women. According to the WHO, 40% of men and less than 9% of women worldwide were smokers in 2010; however, the numbers of women who use tobacco and who are exposed to secondhand smoke, especially in poor communities, are expected to increase in the coming decades.<sup>39</sup>

### Physical activity

Although there is limited evidence with few studies published to date, exercise intervention is recommended in patients with axSpA as it can improve pain and fatigue, both of which significantly affect patients' quality of life.<sup>40</sup> A recent study examining the effects of high-intensity exercise for 3 months in patients with axSpA found a significant treatment effect of the intervention on ASDAS and BASDAI as well as on inflammation, physical function and cardiovascular health.<sup>41</sup>

In many countries, female patients are less involved in sports than male patients,<sup>14</sup> so they can require more convincing to undertake exercise therapy. Female patients may find it more difficult to distinguish between pain caused by axSpA, and that caused by exercise due to the delay in diagnosis compared with men.<sup>14</sup> As such, female patients may be more reluctant to undertake exercise interventions, but they should be encouraged to do so. Furthermore, a significant relationship has

## Box 2 Improving the assessment of treatment response

- ▶ Establishing whether differences between women and men exist in tumour necrosis factor inhibitor (TNFi) efficacy and switching between women and men could be beneficial for informing better treatment decisions.
- ▶ Establishing whether earlier switching to an anti-IL17 following treatment failure with a TNFi in female patients with axial spondyloarthritis might be beneficial for better disease control.
- ▶ Determining whether anti-IL17 treatment is affected by body mass index, similarly to TNFi, would be beneficial for dose optimisation.

**Box 3 Relevance of lifestyle factors and interventions**

- ▶ Educate patients on the benefits of a healthy lifestyle, and the impact that this may have on their symptoms/disease activity.
- ▶ Educate patients on the benefits of physical activity, indicating that it is complementary to their drug treatment and that they will need to remain on medication.
- ▶ Question patients about their physical activity levels at each visit to improve adherence to their exercise programmes.
- ▶ Question patients about their smoking habits at each visit and inform them that quitting smoking will improve their symptoms.

been found in axSpA between female patients with high disease activity scores and a high BF percentage or FMI, which differs from male patients who have high disease activity scores and low BF percentage and FMI. Exercise interventions to reduce BF percentage and FMI may help reduce disease activity in combination with patients' current medication.<sup>40</sup>

Adherence to physical activity interventions is an issue among patients with axSpA, with some patients performing the exercises initially for a few months, but stopping thereafter. Patients may benefit from regular appointments with a trainer, who can reaffirm that they are doing well with their programme, which may motivate the patient to better adhere to the intervention. Supervised group exercise has proven effective in patients with axSpA in the Netherlands, and more patients may benefit from the wider introduction of these programmes across Europe.<sup>42</sup>

Box 3 summarises relevant points to consider about lifestyle factors and interventions.

**Counselling of women regarding pregnancy**

Many questions arise in women of childbearing age with axSpA and physician-patient communication should address them (box 4). Factors that may have a negative influence on fertility of patients with axSpA are older age, nulliparity and longer disease duration, although the time-to-pregnancy was found to be similar to that of patients with rheumatoid arthritis and was less than 12 months in nearly 80% of patients.<sup>43</sup> Biologics have

**Box 4 Counselling of women with axial spondyloarthritis (axSpA) regarding pregnancy**

- ▶ Inform patients of childbearing age with axSpA about the possible negative influence on fertility by increasing age, longstanding disease and chronic use of nonsteroidal anti-inflammatory drugs.
- ▶ Educate patients who are planning a pregnancy on the use of biologics during gestation, as uncontrolled disease activity can be detrimental for pregnancy outcome.
- ▶ Discuss the mode of child delivery with women who are looking to conceive, as vaginal delivery may be too difficult in some patients with axSpA.
- ▶ Educate patients on the use of biologics during breastfeeding, allowing them to make an informed decision.

not been shown to affect fertility, unlike nonsteroidal anti-inflammatory drugs, which may impair fertility by inducing luteinised unruptured follicle syndrome; this should be communicated to patients.<sup>44</sup> Patients who are already pregnant or wishing to conceive need to discuss the risks for fetal and maternal health and whether they should continue or discontinue treatment. In most cases of pregnancy, female patients with axSpA are likely to show aggravated symptoms of back pain and impaired function, especially during the second trimester.<sup>43</sup> The withdrawal of TNFi at the beginning of pregnancy is associated with increased risk of flares during pregnancy.<sup>45</sup> The management of flares with corticosteroids is actually associated with preterm delivery; therefore, it is convenient to consider the use of TNFi during pregnancy, which are currently thought to be compatible with pregnancy with no increased risk for adverse fetal and maternal outcomes.<sup>45–47</sup> The general cultural belief that no drugs are compatible with pregnancy can cause fear in women with chronic disorders who wish to get pregnant and the use of drugs during pregnancy should be thoroughly addressed during counselling.

Regarding pregnancy complications and outcomes, a systematic literature review highlighted that axSpA women have an increased prevalence of caesarean sections compared with the general population and there is a trend towards increased prevalence of pre-eclampsia, intrauterine growth restriction and small-for-gestational-age babies.<sup>48</sup> Consideration must also be taken when choosing the mode of delivery for pregnant women with axSpA, as there may be difficulties with vaginal delivery owing to hip stiffness and pain.<sup>48</sup>

Another consideration regarding the counselling female patients with axSpA who are pregnant is the use of biologics while breastfeeding, and it should be explained according to two main principles<sup>49</sup>:

- ▶ Biologics are large molecules with minimal transfer rates in breast milk.
- ▶ Even if present in breast milk, biologics would be digested in the newborn's intestinal tract with no chance for absorption.

Based on this information, the patient can make a choice whether to breastfeed or not while taking biologics. Breastfeeding is a personal choice and the degree of motivation highly varies across women, so the patient should be informed of the information available and that which is unknown, to allow them to make their own decision. For instance, milk-specific studies are important for the counselling of patients, such as the CRADLE study showing the minimal to no transfer of certolizumab pegol into breast milk and the lack of adverse events in babies who were breastfed during maternal intake of the TNFi.<sup>50</sup>

**CONCLUSION**

Female patients with axSpA experience significant disease burden owing to delayed diagnosis and differences in clinical manifestations compared with male patients.

Differential treatment responses and adherence to life-style interventions between sexes require further investigation to improve the application and efficacy of these interventions. Greater awareness and understanding of biologic treatment during pregnancy are needed for improved quality of life in female patients with axSpA.

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