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Sex and gender differences in axial spondyloarthritis: myths and truths

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Abstract

Mounting evidence reveals evident sex differences in physiology, disease presentation and response to medication in axial SpA (axSpA). Unfortunately these data are often neglected in clinical practice and research. In this review, myths that still exist on diagnosis, disease manifestation and drug effectiveness were argued against data of the most recent literature. The aim is to increase awareness of sex differences in the clinical aspects of axSpA.

Key words: spondyloarthritis, biological therapies, epidemiology, inflammation, sex differences, patient reported outcomes

Rheumatology key messages

- Women with axSpA have a longer diagnostic delay compared with males.
- Women with axSpA show significantly lower TNF inhibitor efficacy and drug survival compared with males.
- Men have a higher radiological progression, but the disease burden is similar for both sexes.

SUPPLEMENT

Introduction

Many rheumatic diseases show a clear sex difference in prevalence, often with female predominating, as in RA and SLE. In contrast, AS or radiological axial SpA (axSpA) is more frequently diagnosed in men compared with women (3:1), whereas non-radiographic axSpA has an equal sex distribution. This sex distribution might be explained by differences in disease course between the two sexes. Men with axSpA show a higher radiological progression (45 *vs* 33%) [1], whereas women show higher disease activity scores (mean BASDAI 3.2–5.9 *vs* 3.9–6.3) [1–6] and extra-articular manifestations (73 *vs* 82%) [1, 7, 8].

Before we start with the myths, a clarification is needed for the terms sex and gender. In essence, the term sex differences can be described as biological processes that differ between men and women [9]. Gender refers to a person's self-perception as a man or woman and the behaviour they show during their life or the disease (coping style and disease perception) [7], but in some literature the word gender is also used to refer to physiological differences between sexes. This article aims to create awareness of the impact of sex differences in physiological, pharmacokinetics, disease presentation and treatment efficacy of biologics in axSpA.

Myth 1: Men and women with axSpA are physiologically the same

Sex differences in genes and immune modulation

Sex differences are observed not only in sex chromosomes, X and Y, but also in gene expression, immune modulation and physiological processes between men and women with axSpA. The most important genetic predisposition in axSpA is the association with the HLA-B27 allele. There are indications that women with axSpA are found to be less often positive for the HLA-B27 allele compared with males [1], which might explain the different presentation of axSpA in men and women, such as radiological progression [10–15]. The presence

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of the HLA-B27 allele is associated with a greater chance for a positive MRI of the SI joints [16]. In addition, HLA-B27 was also found to be a predictor for having a positive treatment response and better drug survival on biologics [17–20].

In addition, there are sex differences in other less familiar gene expressions. An interesting study on genetic expression in AS revealed that 1522 unique genes were expressed in men and 291 genes in women compared with healthy controls [21].

A study considering the *ANKH* gene, which encodes a protein that is involved in osteogenesis and plays a role in ankylosis in AS, showed that different loci of the *ANKH* gene were expressed in men and women with AS [22]. Furthermore, in multiplex AS families, a specific tissue-non-specific alkaline phosphatase (TNAP) haplotype, which interplays with the *ANKH* gene in ossification, was associated with AS in men but not in women [23]. These genetic predispositions in men might explain the higher radiographic progression and higher prevalence of AS in men compared with women.

Immune processes are also influenced by sex hormones. Testosterone decreases TNF-α production but increases the production of anti-inflammatory IL-10 [24]. Oestrogens increase the cell-mediated and humoral immune response and production of IL-1, IL-6 and TNF-α [25], which contributes to increased inflammatory values. Interestingly, syndesmophyte development in men was associated with significantly higher IL-18 levels, whereas in women IL-6 was significantly elevated [26].

In AS, IL-17A and Th17 cells were elevated in male patients but not in female patients [15]. However, the same study did not reveal sex differences in the components of the Th1 axis.

Pain mechanisms

Sex hormones also influence other physiological processes, such as pain transmission. Testosterone increases the pain threshold, whereas conflicting results were found for oestrogen and progesterone [27]. Accumulating data reveal that pain sensation fluctuates with hormonal changes, especially in women during the menstrual cycle, in contrast to men who have more stable hormone levels over time [28, 29]. Besides the influence of hormones, women have a greater number of pain receptors and a different expression of these receptors, for instance, in the opioid receptors [29]. This could explain the overall higher pain sensitivity in women compared with men, which might contribute to higher pain scores reported for patient questionnaires by women with rheumatic diseases.

Body composition

In addition, sex differences in body composition influence the immune modulation indirectly, especially due to fat disposition. Women have greater deposits of subcutaneous fat (SAT), whereas men have more visceral fat (VAT), which is located intra-abdominally [30]. Interestingly, adipose tissue acts as an endocrine organ, secreting not only adipokines, which can act as pro-(leptin) or anti-(adiponectin) inflammatory, but also cytokines, such as the pro-inflammatory cytokine TNF-α [31]. One study reported that female patients with higher disease activity scores [Ankylosing Spondylitis Disease Activity Score (ASDAS) and BASDAI] had a significantly higher percentage of body fat (BF) or fat mass index (FMI) [32]. In contrast, men in this study had significantly higher disease activity scores (ASDAS and BASDAI) when they had low BF or FMI [32]. In addition, several studies have reported an association between a high BMI and a lower TNF inhibitor (TNFi) treatment response [33, 34]. In one study a significant correlation was observed between BMI and the inflammatory marker CRP in female AS patients only [4].

Truth: Besides many sex differences in physiological processes, studies in axSpA have also revealed sex differences in gene expression and body composition. In addition, women with axSpA have different pain mechanisms and hormonal influences that might contribute to higher DASs compared with men.

Myth 2: axSpA is a predominately male disease

Sex differences in axSpA

axSpA encompasses non-radiographic axSpA (nr-axSpA) without radiographic changes and AS with radiological signs of sacroiliitis as classified according to the modified New York criteria [35–37]. For many years AS was considered a predominantly male disease. The initial studies showed a male:female ratio of 10:1 [38], but subsequently this ratio has decreased to ∼3:1 [39]. Recent studies report an even further decline in the male:female ratio among patients with axSpA in Switzerland, from 2.57:1 in 1980 to 1.03:1 by the end of 2016 [40]. In contrast with AS, no sex differences have been encountered in the prevalence of nr-axSpA [41].

Delay in diagnosis

Currently, the average delay to diagnosis in AS is ∼6–8 years [42–44]. Although the age of onset of AS is similar for men and women [2, 22, 23], women have a significantly longer delay in diagnosis compared with men (median 9–14 *vs* 5–7 years) [45, 46]. These data were confirmed by a recent meta-analysis covering 42 studies and 23 889 patients (32.3% women), revealing a significantly longer diagnostic delay in female patients compared with males (8.8 *vs* 6.5 years) [47]. So far, only one study has revealed a longer diagnostic delay in men compared with women (9.9 *vs* 6.3 years) [48]. A longer diagnostic delay was found to be a negative predictor for a positive biologic treatment response [49, 50].

Several explanations were put forward for the longer diagnostic delay among females, such as the differences in presenting symptoms, including more enthesitis-related

complaints instead of inflammatory back pain, more prominent widespread pain and a lower prevalence of radiographic changes [43, 45]. Importantly, patients with widespread pain, which occurs in at least 25% of female axSpA patients, are sometimes misdiagnosed as fibromyalgia, as it has some overlapping symptoms with axSpA [33]. In fact, one study reported that widespread pain doubled the delay in diagnosis in women [43]. An additional explanation for the difference in diagnostic delay might be the physician's bias, because axSpA is considered to be a 'male disease' [43]. Consequently, women who show more predisposing factors of axSpA [most importantly a positive family history and acute anterior uveitis (AAU)] might have an increased chance of being diagnosed.

AAU is one of the most important extra-articular manifestations of axSpA [51] and axSpA is the most common associated systemic disease in AAU; they also share the same genetic predisposition, the HLA-B27 antigen. AAU can be the first manifestation of axSpA. Approximately half of axSpA patients experience AAU before the onset of axSpA symptoms and, in addition, in patients presenting with AAU, ~40% appear to suffer from undiagnosed axSpA [52–54]. Male and female axSpA patients have about the same lifetime risk of developing AAU (~30%) [34, 51, 55]. However, males are more often diagnosed with SpA many years before AAU occurs, whereas the diagnosis in females is significantly more often made after the first attack of AAU [56]. Therefore screening of AAU patients by a rheumatologist, especially in the case of back pain, could reduce the diagnostic delay, especially in women.

Pitfalls in diagnosis

In AS, radiographic changes of the SI joints, graded according the modified New York criteria, are mandatory for the diagnosis. However, some radiological changes of the pelvis are important for the differential diagnoses, especially in women [35]. For example, iliitis condensans, with bilateral sclerotic lesions around the SI joints, is often accompanied by lower back pain and SI joint tenderness and occurs mainly in women after pregnancy [57, 58].

In addition. imaging of the SI joints by MRI, which can substantiate the diagnosis of non-radiographic axSpA by showing active bone marrow lesions, has some pitfalls as well [59]. Recent studies revealed that other factors, such as intensive sporting activities and pregnancy, can induce SI bone marrow oedema as well. Some studies show that up to 1 year after delivery, bone marrow oedema of the SI joints still can be detected [60].

Truth: AxSpA is not a predominately male disease. Diagnoses of axSpA are often missed or misdiagnosed in female patients, resulting in long diagnostic delays. New referral strategies, such as the occurrence of AAU, might decrease the diagnostic delay in female patients. On the other hand, it is important to be aware of diagnostic pitfalls, especially with MRI of the SI joints, since bone marrow oedema up to 1 year after pregnancy could lead to overdiagnosis.

Myth 3: Men with axSpA have a worse disease outcome compared with women

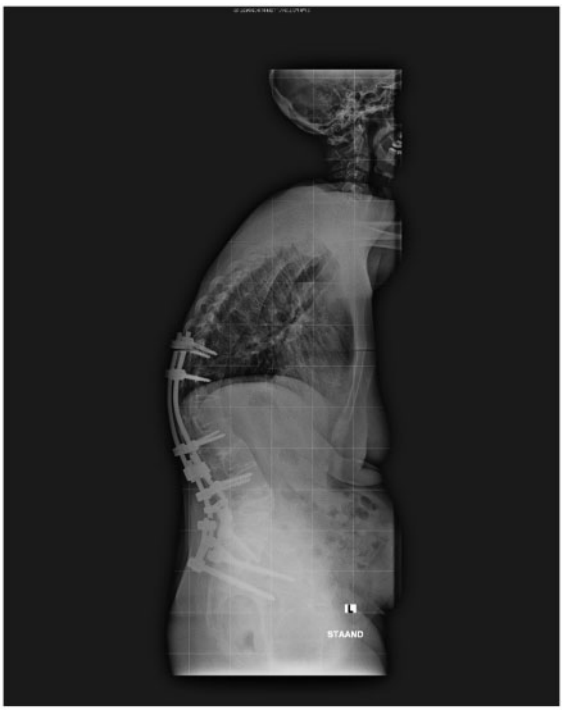
Radiological progression

Probably the main reason why men are often considered to have worse disease is the association of male sex with a higher radiological outcome. Most studies have revealed that men are more likely to show worse hip involvement and higher BASRI spine and modified Stoke Ankylosing Spondylitis Spine Score (mSASSS) compared with women [10–15, 61, 62]. However, it is important to note that severe radiographic deformities, including ankylosing, occur in both men and women (Fig. 1). A few studies observed greater radiological progression of the lumbar spine in male AS patients, whereas in female patients this progression was observed mainly in the cervical spine. The fact that most female AS patients seem to have slower radiological progression might be an explanation for the relatively greater number of women diagnosed with nr-axSpA and the longer delay in diagnosis [63]. Comparison studies between nr-axSpA and AS reveal an equal disease burden, independent of sex [64].

Extra-articular manifestations and disease manifestations

One of the reasons an equal disease burden is observed and a higher percentage of women are diagnosed with nr-axSpA could be the presence of extra-articular and other disease manifestations, such as enthesitis. Enthesitis was reported to occur more frequently, and

Fig. 1 Woman, 47 years old, with long-standing AS



be more pronounced, in female patients [1–3, 65–67] (Table 1). In addition, the absence of enthesitis was found to be a predictor for better biologic treatment efficacy [68], which might explain the lower efficacy in female patients.

Extra-articular manifestations seem to have a higher prevalence in women [1, 7, 8] (Table 1), although some studies show conflicting results [43, 61, 66]. Some studies showed a higher prevalence of AAU in men [6, 56, 69], whereas a systemic literature review suggested a somewhat higher prevalence in females (33.3%, *vs* 28.5% in males) [34]. However, the last study also included other types of uveitis, which could have compromised the results. Three studies, including a meta-analysis, suggested female patients are more likely to develop IBD compared with male patients [1, 8, 51]. In addition, some studies reported a higher risk of psoriasis in female axSpA patients [8, 69].

Comorbidity

Beside extra-articular manifestations, axSpA is also associated with an increased risk of comorbidities, such as cardiovascular diseases and osteoporosis [70]. Unfortunately, cardiovascular diseases in axSpA has not been systematically studied for sex differences (Table 1).

Osteoporosis shows a prevalence range of 19–50%, especially in AS patients with longstanding disease, and can lead to immobilization due to vertebral fractures [71, 72]. Osteoporosis is typically considered a woman's disease, due to the high prevalence and number of fractures in post-menopausal women compared with men of the same age. For example, at the age of 60 years, the risk in women is 44%, compared with 25% in men [73]. However, in a relatively young male axSpA population with a short disease duration, 51% had a low BMD and 13–16% had osteoporosis [74]. Another study revealed that male patients diagnosed with axSpA had a four times greater risk for low BMD compared with females [75]. A study on osteoporotic fractures in relatively young axSpA patients (mean age 37 years, mean disease duration 7 years) reported at least one osteoporotic fracture in 15% of all patients [76]. Most of these fractures were located at the thoracic spine, which is not included in the regular scoring method of the mSASSS. In relation to peripheral fractures, although women have a higher incidence of fractures, the risk of undertreatment of osteoporosis and mortality after a hip fracture in men is much higher [77, 78].

Inflammatory laboratory values

Studies on sex differences in CRP levels showed significantly higher baseline levels in male patients compared with females [1, 5, 6, 66, 67], but the ESR was inconclusive for sex differences. A possible explanation for finding no clear differences in ESR levels could be the already different cut-off levels for normal ESR levels by sex (15 mm/h for males *vs* 20 mm/h females).

Table 1 Extraspinal manifestations and comorbidities in axSpA

Manifestations and comorbidities	Gender differences
Extraspinal manifestations	
AAU	No differences
Enthesitis	↑ in women
IBD	↑ in women
Psoriasis	↑ in women
Peripheral arthritis	↑ in women
Comorbidities	
Cardiovascular diseases	↑ in men and post-menopausal women
Osteoporosis	Equal risk, but underdiagnosis in (young) males

Table 2 Sex differences in disease activity, function and physical measures in axSpA

Disease activity at baseline	Gender differences
BASDAI	↑ in women
ASDAS-CRP	No difference
CRP-levels	↑ in men
ESR-levels	No difference
Function	
BASFI	No difference
Quality of life	
ASQoL	↓ in women
ASASHI	↓ in women
EuroQoL	No difference
SF-36	No difference
Physical	
BASMI	↑ in men
MASES	↑ in women

↑: higher scores; ↓: lower scores; ASQoL: Ankylosing Spondylitis Quality of Life; ASASHI: Assessment of SpondyloArthritis international Society Health Index; MASES: Maastricht Ankylosing Spondylitis Enthesitis Score.

Disease activity and patient-reported outcomes

In both nr-axSpA and AS, women present themselves in general with higher disease activity, more pain and a worse quality of life (QoL) (Table 2). At baseline, before the start of biologics, BASDAI scores are significantly higher in female patients compared with males, especially the items total back pain, duration of morning stiffness and fatigue [1–3, 5, 6, 65, 66, 79–82]. Interestingly, the ASDAS showed no sex differences [5, 6], which might be due to the fact that men show higher CRP levels, whereas women show higher scores on the other components of the ASDAS-CRP. Sex differences in QoL and overall well-being were inconsistent, depending on the validated questionnaire used. Significantly worse

QoL scores were observed in female patients measured with the Ankylosing Spondylitis Quality of Life questionnaire, the Assessment of SpondyloArthritis international Society (ASAS) Health Index and the BAS-G [2, 3, 6, 66, 82]. Other QoL questionnaires, such as the EuroQoL and the 36-item Short Form Health Survey revealed no (large) gender differences [1, 2, 6, 79]. The BASFI showed no large sex differences, except one study that found a higher score in female patients [1] (Table 2).

Truth: Overall, men with axSpA show a higher rate of radiological progression compared with women, but severe ankylosis also occurs in female axSpA patients. Women with axSpA have, in general, higher disease activity scores and more peripheral manifestations compared with men. Comorbidities like cardiovascular events have not been studied for sex differences in axSpA, but osteoporosis, even with osteoporotic fractures, a manifestation mainly seen in post-menopausal women, has an unexpectedly high prevalence in young male axSpA patients.

Myth 4: No sex differences are present in efficacy and drug survival of biologics in axSpA

Sex differences in response and efficacy to biologic treatment

Two recent reviews [7, 83] described sex differences in treatment efficacy, but most clinical studies and safety trials are not powered to assess sex differences. For this reason, data from several randomized controlled trials (RCTs) on one biologic, etanercept, were pooled and analysed for sex differences, as the RCT studies separately included too few women to perform the analyses. This study revealed a significantly lower treatment response at 12 weeks according to the BASDAI score in female patients compared with males (−19.2 *vs* −23.4) [79] (Table 3). In addition, women also had a lower ASDAS-CRP response compared with men (68.4 *vs* 89.4%) at 12 weeks [5] (Table 3). Currently only two other studies have assessed disease activity for sex differences [83]. A prospective cohort study including the TNFis etanercept, adalimumab, infliximab and golimumab revealed, according to adjusted longitudinal regression analyses for repeated measurements, a significantly higher mean BASCAI score for women (0.9) over a 5 year follow-up period. However, no significant sex differences were observed in the longitudinal analyses for mean ASDAS-CRP. A possible explanation could be because of the high CRP level in men and the higher scores on BASDAI components in women [84]. However, assessment of the ASDAS-CRP clinical response revealed that men achieved the clinical response twice as often as women. The second study included the IL-17 blocker secukinumab and demonstrated no sex differences in treatment response at both 16 (46.9% for men *vs* 37.5% for women) and 52 weeks (61.7% for men *vs* 68.4% for women) [49]. Besides differences in response and efficacy, male sex was found to be a predictor for improvement of function (69.9% for men *vs* 50.0% for women) [50].

Table 3 Sex differences in efficacy and time on drug in axSpA

Disease activity (mean)	Differences (range 6–60 months)
BASDAI	Remains higher over time in females
ASDAS-CRP	No observed differences
CRP level	Remains higher over time in males
ESR level	No observed differences
Treatment response	Differences (range 6–60 months)
BASDAI 50%	↓ in females
ASDAS-CRP[a]	↓ in females
ASAS20/40	↓ in females
Drug survival	Differences (range 12 weeks–10 years)
Time on drug	↓ in female patients
Switch	↑ in female patients

[a]Clinically important improvement (ASDAS-CRP $\geq$ 1.1).
↑: higher scores; ↓: lower scores.

Sex and gender differences in time on drug

In addition to treatment efficacy and response, the reviews also described a clear sex difference in drug survival. Most studies that investigated sex differences in biologic found a significantly lower time on drug in women compared with men, except for the secukinumab study [5, 80, 85–89]. The studies revealed a doubled risk for treatment failure in female patients. A recent study found that 31.1% of males experienced a treatment failure compared with 50.0% of females [50].

Biologics and peripheral manifestations

Although few studies have investigated sex differences separately, a greater number of studies have assessed sex as a possible predictor in relation to treatment efficacy and drug survival [49, 50]. Studies including sex differences in their analyses also described several predictors for treatment efficacy and drug survival, such as presence of HLA-B27 antigen, being TNFi naive, short disease duration and absence of enthesitis [17, 18]. Remarkably, these factors are less prevalent among female patients, as women are less likely to be HLA-B27 positive, more often have enthesitis and a longer disease duration and are less often biologic naive compared with men [1–3, 5, 47, 62, 65–67, 83, 90, 91]. In addition, female patients have a greater fat mass, which is associated with a lower TNFi treatment response [92]. This might be an explanation for the fact that women were found to have a shorter drug survival on biologics compared with men.

Truth: There is substantial evidence found in different studies indicating women have a significantly lower efficacy, response rate and drug survival for TNFis

compared with men. Data on sex differences in other biologics, such as IL-17 inhibitors, are limited.

Conclusion

In axSpA, sex differences play a role in biologic processes such as immune responses, pain mechanisms and disease manifestations, such as involvement of the entheses, and disease course, such as radiological progression. Osteoporosis can be overlooked in men and pregnancies can hamper the diagnostic process with pelvis X-rays and MRI of the SI joints. Substantial sex differences were observed in lower TNFi efficacy and drug survival in women compared with men but remain to be determined in other biologics. In conclusion, it is of great importance to be aware of the sex differences in axSpA for diagnosis as well as treatment.

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