The pink side of spondyloarthritis: a narrative review across pathogenesis and clinical manifestations in women

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SUMMARY

Objective. The aim of the present review was to highlight gender and sex differences in spondyloarthritis (SpA) to achieve a better awareness of the unmet needs of women with SpA.
Methods. A literature search of PubMed was performed, including manuscripts in English published in the last twenty years, to select and analyze articles related to SpA and sex and gender differences in epidemiology, genetics, immunology, clinical features, and response to treatment.
Results. Women and men with SpA have different disease phenotypes, and this heterogeneity mirrors anatomical, physiological, and hormonal differences, as well as peculiar variability in response to treatment. These underestimated differences, which include several biological factors and intertwined social factors, contribute to diagnostic delay and increased disease burden in women with SpA.
Conclusions. This review elucidates gender differences in SpA and raises awareness about the need for gender-related stratification of SpA patients with the concomitant implementation of SpA gender differences in future research and upcoming clinical trials. A deeper knowledge of SpA in women is indispensable to pave the way for real personalized medicine for SpA patients to reduce misdiagnosis and delay in intercepting the disease.

Key words: *Spondyloarthritis, sexual dimorphism, gender medicine, precision medicine, immunology, clinical phenotype.*

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INTRODUCTION

Spondyloarthritis (SpA) encompasses a broad spectrum of diseases, including predominantly peripheral or axial forms. Axial SpA (axSpA) is further divided into non-radiographic (nr-axSpA) and radiographic axSpA (r-axSpA), also known as ankylosing spondylitis (AS).
AxSpA has long been considered to be more common in men than women. However, recent data suggested a more homogenous sex prevalence, reaching a range of 2:1 to 1.2:1 ratio in favor of men in AS (1), while the differences in prevalence between males and females are negligible in patients with nr-axSpA (2, 3).
Interestingly, axSpA female patients show longer diagnostic delays compared to axSpA male patients, who are younger at the time of diagnosis (4). The reasons for this reside mainly in the lack of awareness of gender-related differences in disease occurrence and in the misdiagnosis of fibromyalgia (5). Furthermore, few studies stratifying disease features by gender in patients with axSpA have been published, highlighting a poor treatment response and an impaired health-related quality of life in women compared to men (6).
Sex differences also have important implications for clinical research on psoriatic arthritis (PsA) in terms of epidemiology, clinical, radiological and laboratory characteristics, and response to treatment.
They may reflect the complex interactions

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between biological and social factors that influence disease history from the female perspective. Women are often underrepresented in randomized clinical trials, and analyses are often not stratified for gender distribution (6). This review aims to highlight gender and sex peculiarities in SpA to direct research towards the evaluation of gender differences in terms of pathogenesis, clinical manifestation, treatment and outcome, and achieve a better awareness of the unmet needs of women with SpA.

The major differences between men and women with SpA will be discussed in the following paragraphs and are summarized in Table I.

METHODS

A literature search was performed to achieve a comprehensive and structured analysis of the studies. The PubMed search was performed using key words related to the diseases of interest (SpA and PsA) and the main topics (sex and gender differences in epidemiology, genetics, immunology, and clinical features). We searched the PubMed database for English-language articles pub-

Table I - Sex and gender differences in spondyloarthritis.

Spondyloarthritis		
		
Genetics		
	HLA-B27, *ANKH*	X-linked genes, *TLR9*
Hormones		
	↑ Testosterone	↓ Estrogens (?)
Immunology		
	↑ TNFα, IL-17, IL-18	↑ IL-6
Predictors of progression		
	Smoking; elevated CRP levels	BASMI scores; bisphosphonates
Clinical manifestation		
Back pain	+ +	+
Enthesitis	+	+ +
Dactylitis	+	+ +
Peripheral arthritis	+; oligoarthritis (PsA)	+ +; polyarthritis (PsA)
Spinal radiographic progression	Lumbar spine	Cervical spine
Extra articular manifestation		
Psoriasis	+	+ +
IBD	+	+ +
Acute anterior uveitis	+ +	+
Fibromyalgia	+	+ + +
Anxiety, depression, fatigue, psychosomatic disorders	+	+ + +
Comorbidities		
Cardiovascular diseases	+ +	+
Osteoporosis	+ +	+

TNF, tumor necrosis factor; IL, interleukin; CRP, C-reactive protein; BASMI, Bath Ankylosing Spondylitis Metrology Index; PsA, psoriatic arthritis; IBD, inflammatory bowel disease.

lished over the last twenty years with relevance to disease pathogenesis, clinical manifestations, and their impact on disease management.

RESULTS

Epidemiology

From an epidemiological point of view, axSpA has historically been considered a predominantly male disease, with early studies showing a male-to-female ratio of 10:1 (7). Recent findings have shown a gradual and progressive change towards a gender-equal prevalence of AS, with a male-to-female ratio up to 1.2:1 in the Swiss cohort in 2016 (1). In contrast, a higher prevalence of nr-axSpA in women compared to men was found (8); this confirms how differences in the presentation of axSpA, as well as in the severity of structural damage, between male and female patients may have led to a lower prevalence reported in women for many years and consequent longer diagnostic delays. As a matter of fact, it is known that axSpA has a longer diagnostic delay, which is approximatively 7 years, than other forms of inflammatory artrhtis (9). However, although the age of onset of AS does not differ between males and females, women present a longer delay in diagnosis (8.2 years *versus* 6.1 years) (4, 10).

Real-world data from patients with axSpA enrolled in the Corrona PsA/SpA registry revealed a higher prevalence of peripheral symptoms (arthritis and enthesitis), worse Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, pain, fatigue, and quality of life in women compared to men (8), consistent with other studies in real-world (11, 12).

The epidemiology of PsA does not generally differ between males and females. Some studies have reported slight variations in the male/female ratio, which depend on the specific population studied, ethnicity, methodology, and study design. Despite the equal prevalence of PsA between men and women, the latter experience a greater burden of disease in terms of pain, disability, and fatigue (13, 14). In the Dutch Southwest Early Psoriatic Arthritis Cohort, women reported a significantly longer duration of symptoms before diagnosis, significantly higher disease activity, and functional impairment compared to men at baseline but also at one year of standard-of-care treatment (15). This further suggests the existence of sex bias in SpA and may support the need for sex-specific adjustment of disease assessment.

Genetics

Accumulating evidence accounts for an important role of genetics and epigenetics in driving the sex bias in the pathogenesis of SpA. Most literature has focused on AS genetics since the discovery, in 1973, of the HLA-B27, a class I MHC allele strongly associated with the development of the disease. 90% of patients express HLA-B27, which was shown to be highly prevalent in males *versus* females (16, 17). Notably, HLA-B27 expression was linked to higher concentrations of testosterone, emphasizing the differential contribution of hormones to disease manifestations between men and women (18). The observation of a lower prevalence of HLA-B27 has been further confirmed in women with nr-axSpA. In this specific group, even the overall polygenic risk score shows lower mean values (19), stressing the relevance of other genes in contributing to AS development.

To date, no studies have described the differential expression of all non-HLA genes involved in SpA pathogenesis, such as *ERAP1* and *ERAP2* or *RUNX3* (20-22), among men and women. However, the complexity of genetic susceptibility was clearly depicted in a very elegant paper by Gracey *et al*., in which 291 genes were found to be selectively expressed in AS females. In functional network analysis, male AS patients, but not female patients, displayed a strong upregulation of pathways related to adhesion, autophagy, osteoclast differentiation, myeloid cell, and mitogen-activated protein kinase signaling. On the other hand, females with AS presented an upregulation of gene pathways involved in translation and ribosome functions (23). Such differences may justify the typical structural damage occurring in men. In this regard, a sex-specific

locus of the *ANKH* gene, encoding for a progressive ankylosing protein, was associated with male disease, especially in the presence of distinct haplotypes in the 3' region (24). Additionally, a single nucleotide polymorphism in the *TNAP* gene, encoding for a tissue-nonspecific alkaline phosphatase, is a marker of AS only for men, and, from a functional point of view, there is intimate cooperation of *ANKH* and *TNAP* in driving new bone formation (25).

An important role in the differential genetic background between men and women with AS is undoubtedly played by sex chromosomes. Women carry two X chromosomes that, during embryogenesis, undergo the so-called lyonization, consisting of the random and permanent inactivation of one of the two X chromosomes to balance the X-linked gene expression level. X-inactivation ensures the presence of a single functional copy of the X chromosome in each body cell (26). However, several genes may naturally escape inactivation and consequently be overexpressed in women. The X chromosome encodes for many immune-related genes, such as *TLR* or *FOXP3* genes, that partly explain the different immunologic backgrounds of women. As an example, the presence of the rs5743836*C allele of the *TLR9* genes was linked to an increased risk of developing SpA in women (27). X-inactivation could be considered one major epigenetic mechanism controlling gene expression. Very interestingly, several miRNAs involved in the immune response are encoded in such chromosomes, further enhancing the role of sex chromosomes in shaping the proinflammatory microenvironment in SpA and other diseases (28).

In PsA, scant data exists regarding any sex difference in genetic predisposition. Even though the majority of the study did not stratify patients by sex, a potential role of genomic imprinting in PsA susceptibility was reported. Briefly, genomic imprinting is an epigenetic phenomenon that affects gene expression in a parent-of-origin-specific manner, meaning that it intimately depends on the sex of the transmitting parent. In PsA, it was demonstrated that patients had significantly more affected fathers than mothers, underlining a paternal mode of transmission (29). Moreover, a subsequent study confirmed that sons were more frequently affected by PsA with respect to daughters when the father suffered from the same disease (30). Finally, a study conducted in Iceland using an imprinting-based scoring system, revealed a PsA predisposing gene in chromosome 16q when considering conditioning for paternal transmission (31). Epigenetics may then play a crucial role in determining the sexual dimorphism inheritance patterns of PsA, as well as in explaining the overall different gender distribution of SpA, in which variants of DNA methyltransferase 3A and 3B, known to participate in genomic imprinting and X-inactivation, were well described (32).

Despite the progression of genetics studies, the genetic differences that distinguish the disease course between men and women have not been fully characterized yet and more research is mandatory in this fascinating field.

Immunology

The immune system response in females is characterized by more vigorous activity compared to what is observed in men, thus justifying the increased rate of autoimmune diseases in women. This phenomenon has been strongly related to the different hormone milieu according to sex (33). In particular, the protective role of estrogens has been outlined in previous studies. Estrogens may exert an immunosuppressive function through the downregulation of tumor necrosis factor (TNF) α and interleukin (IL)-17 production, which results in a decrease in females with axSpA compared to men (23, 34). In addition, in experimental models of SpA treated with 17β-estradiol, a marked reduction of TNFα was demonstrated in joint tissues (35), with female mice with high estrogen levels displaying less severe SpA manifestations, such as arthritis, enthesitis, and bowel inflammation (36). Parallelly, estrogen-deficient rats presented an altered balance between pro- and anti-inflammatory cytokines with an impaired production of immunosuppressive molecules, namely IL-4, IL-10, and transforming

growth factor β, with a concomitant increase in IL-17, Interferon γ, and IL-6 (37). To strengthen such observations, low estrogen levels were correlated with a more severe SpA phenotype in women, and estrogen treatment seemed to ameliorate arthritis in AS women in a small cohort of patients (38). Unfortunately, contradictory results emerged from a larger study, including 448 female patients who used estrogen therapy and 123 who did not, that demonstrated no differences in AS onset or disease activity between the two groups (39). Thus, the eventual benefit of treatment with hormone replacement therapy is still a matter of debate.

The paramount importance of the IL-23/IL-17 axis as a major driver of disease in SpA has been demonstrated (40), and interestingly, T cell differentiation towards a Th17 immunophenotype can be inhibited by estrogens. The consequence is a lower level of IL-17 in AS women, in whom different cytokine signatures may perturb immune system homeostasis. Specifically, an increase in IL-6 levels was pointed out, and it seems reasonable to suppose that this can partly explain the predominant peripheral manifestations commonly observed in women. On the other hand, men displayed higher levels of IL-18 that were correlated with syndesmophyte formation, explaining the stronger burden of axial disease (41).

The microenvironment in SpA pathogenesis has a pivotal role, especially when considering important immunological niches, such as the gut, that are believed to function as a base camp for the activation of dysreactive immune cells. The crosstalk between immune cells and the microbiota at this level has been extensively studied in the last decades, leading to the definition of the so-called gut-joint axis as a major pathogenic driver in SpA development (42). Subclinical gut inflammation is found in almost 60% of patients with SpA at the ileal level, and 10% of patients develop overt inflammatory bowel disease, stressing the intimate link between gut inflammation and SpA (42). The alteration of the local microbiota, known as dysbiosis, together with the disruption of the mucosal barrier due to tight junction impairment, leads to the translocation of bacteria and their metabolites in the lamina propria where immune cells are primed and, once aberrantly activated, reach the vascular system and recirculate to target sites of disease (43-46).

Sex hormones may influence the gut microbiota, as suggested by the different flora identified in women, with a direct effect on immune system activation. No studies have addressed the role of estrogens in shaping the intestinal flora so far. However, a profound biological difference between men and women resides in the genital and reproductive organs. In particular, the female genital tract, including the vagina and the uterus, is considered a potent immune organ characterized by the presence of a specific microbiota. The mucosal barrier at this level acts as an interface between the immune system and the microbiota, and, to date, several studies have described the mucosal immunology of the female reproductive tract (47, 48). Coming to SpA, a very elegant paper published in 2021 demonstrated that female mice infected intravaginally with *Chlamydia muridarum* presented an important infiltration of neutrophils and macrophages, which were responsible for the subsequent systemic dissemination of the pathogen and the concomitant onset of arthritis (49). Whether a shared pathway linking the uterus and joints exists is an actual hot topic of research as it can possibly explain the differential pathogenesis and burden of disease between men and women suffering from SpA.

Clinical manifestations

During the last few years, some sex-specific differences in SpA have been highlighted, manifesting as high variability in clinical presentation, patient-reported outcomes (PROs), and response to treatment.

Compared to males, axSpA female patients have a more active disease, higher disease activity, and a lower quality of life; however, male sex is associated with a higher prevalence of radiological damage and disease progression. Indeed, it is generally known that AS is more common in males than in females, with a ratio of 3:1, whereas nr-axS-

pA is equally prevalent between the two sexes (50). Additionally, although males with axSpA were more likely to be HLA-B27 positive than females, this allele is a predictor of progression from nr-axSpA to r-axSpA in both sexes (51). Moreover, in men but not in women, smoking and elevated C-reactive protein (CRP) levels were significant predictors of progression, while in women, progression was predicted by high Bath Ankylosing Spondylitis Metrology Index scores and exposure to bisphosphonates (52).

Recent data have reported that in axSpA pain presentation differs between females and males, as females report more widespread pain, as well as pelvic and heel pain, and fewer axial symptoms (53).

Several studies reported a different prevalence of articular and extra-articular manifestations in males and females. Females with axSpA had enthesitis and peripheral arthritis as their initial presentations more often than low back pain. Moreover, females have been found to have more prevalent or severe enthesitis and dactylitis than males, as well as a higher prevalence of inflammatory bowel disease and psoriasis. Patients with radiographic damage and long disease duration have an increased risk for uveitis in both male and female SpA, even though acute anterior uveitis has been observed more in males than females with axSpA (8, 54, 55). The concomitant presence of extra-articular manifestations and chronic back pain could speed up the diagnosis of axSpA in both sexes. Despite that, females are usually older and display a longer diagnostic delay compared to males, possibly due to an underdiagnosis or misdiagnosis of axial involvement in women (56). Gradual and insidious disease progression, as well as the concomitant presence of fibromyalgia, mechanical back pain, or widespread pain, may interfere with the timely and accurate diagnosis of axSpA in females (53). Literature data reported that widespread pain and fibromyalgia are more common in females than in males and occur in about 4-25% of female axSpA patients. Moreover, several peripheral symptoms of axSpA are experienced disproportionately by women, and they may overlap with fibromyalgia symptoms (57, 58).

Interestingly, men typically exhibit higher rates of progression in the lumbar spine, while women typically display higher rates of radiographic progression in the cervical spine, which is not commonly examined in axSpA. This rarer or slower involvement of the lumbar spine may also contribute to the misdiagnosis in females (59). Regarding comorbidities, such as cardiovascular diseases and osteoporosis, contrasting data are available on sex differences. In SpA, osteoporosis seems to be more likely to affect males than females, in contrast with what happens in the general population (26). Evidence on cardiovascular diseases is scarce, but levels of CRP that were suggested as predictive markers of cardiovascular events in axSpA are higher in male patients compared with females, eliciting the assumption of a lower cardiovascular risk in females (60).

In PsA, females tend to have less axial involvement than males, who present a more severe axial involvement depicted by a restriction of spine movements (61). However, since there is no definition of axial PsA, it is currently not possible to discern between patients with radiographic and non-radiographic changes. Furthermore, there is no evidence linking sex differences in axial PsA disease to prognosis or disease severity (62). A female predominance among PsA patients was reported in peripheral arthritis, where females displayed a higher number of tender and swollen joints (62). Moreover, pain in the metatarsophalangeal joints appears to be associated with female sex (63). As a clinical PsA phenotype, females are more likely to present oligoarthritis and polyarthritis than male patients, who more frequently present with oligoarthritis. These gender-specific variations may be linked to the age at which males and females experience the highest prevalence of disease; in fact, since the later peak of prevalence in females and the increase in joint involvement over time, a polyarticular presentation appears to be more expected in females (64). Intriguingly, when considering

peripheral involvement, men show a tendency to experience more severe radiographic damage, in contrast with women, who usually have more active peripheral arthritis in the absence of erosive disease (13).

Data on sex-related differences in enthesitis and dactylitis is conflicting, as some studies report a female predominance and others report no differences between males and females (64). Sex-related differences have been observed in the most common extra-articular manifestations. Psoriasis and palmoplantar pustulosis seem to be more prevalent and severe in males but with less impact on disease burden and health-related quality of life (65). Uveitis in PsA has a more insidious onset than in axSpA and tends to have a slight predominance in females, although the prevalence of uveitis seems to be linked to the disease phenotype. It was observed that PsA patients with axial involvement and uveitis tend to be male, while those with peripheral disease and uveitis tend to be female (66).

In both nr-axSpA and AS, females present higher disease activity, more pain, and a worse quality of life, as measured by several patient-reported outcomes, such as BASDAI, Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Patient Global Score, Ankylosing Spondylitis Quality of Life questionnaire, Health Assessment Questionnaire_AS, and 36-Item Short Form Survey (SF-36). In addition, in females, a lower Bath Ankylosing Spondylitis Radiology Index score was observed (11, 67). No sex differences have been reported in AS disease activity scores (68).

AxSpA negatively affects mental health, leading to anxiety and depression. Mental health is equally affected in males and females and appears to be correlated with disease activity (69, 70). Anxiety, depression, and psychosomatic disorders are more frequently diagnosed in females compared to males, also before the onset of axSpA. Moreover, females are more likely than men to experience neuropathic pain, which was found to be associated with increased BASDAI and Assessment of Spondyloarthritis International Society (ASAS)-CRP scores, increased fatigue, and more depression and anxiety (71, 72). Both r-axSpA and nr-axSpA patients appear to have similarly reduced work productivity, require a less physically demanding job and early retirement (73). Similar outcomes were found in patients with PsA and axial PsA. Females appear to be more disabled in daily activities and have higher disability scores than males, as well as worse patient-reported outcomes and overall quality of life. In particular, the female sex is characterized by higher Health Assessment Questionnaire and BASFI scores, higher fatigue scores, more disability, poorer functional performance, and quality of life with respect to the male sex (74). A Dutch study found that females with early PsA exhibit higher SF-36 mental component and physical component summaries compared to a reference population (75). Additionally, females with PsA showed a higher impact of disease in multiple domains, including pain, skin, fatigue, work, function, discomfort, sleep, anxiety, coping, embarrassment, participation, and depression (76).

Therapy

Sex differences may influence the response to treatment. In the light of a modern treat-to-target approach with the aim of reaching remission or, alternatively, minimal or low disease activity, as endorsed by both the European Alliance of Associations for Rheumatology and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis guidelines for the management of PsA and axSpA, such variations should be carefully considered.

Several studies on r-axSpA and nr-axSpA have demonstrated that females treated with TNF inhibitors (TNFi) experience a lower response rate and lower disease remission compared to males. Additionally, females tend to switch TNFi more often than males, primarily due to inefficacy (5). Females with nr-axSpA treated with TNFi are less likely to achieve ASAS40 when compared to AS female patients, a difference not observed in males (77). Female sex and high BMI are associated with a

lower response in axSpA patients treated with TNFi, suggesting that in these patients, body weight may be a modifiable factor in achieving a better outcome (78). Although most studies found a significantly lower retention rate of TNFi in females compared to males, these data were not confirmed for IL-17Ai drugs, such as secukinumab. A *post-hoc* analysis of the MEASURE 1-4 trials suggested that the response to secukinumab did not differ between male and female patients with r-axSpA. These findings might be explained by the role of IL-17A in the pathogenesis of enthesitis and by the higher levels of IL-17 in females, which could determine a higher prevalence of enthesitis in female patients than in males (79). Real-life evidence supports that sex is not a relevant factor for treatment response with secukinumab and ixekizumab (80-82).

Similar differences in treatment response between the two sexes were found in PsA. In the TICOPA trial, which evaluated tight disease control in early PsA patients treated with disease-modifying antirheumatic drugs, fewer females achieved minimal disease activity (MDA) compared to males, who outperformed women in all seven MDA domains (83). Other studies confirmed a lower rate of MDA and remission in females compared to males. In particular, tender joint counts and CRP levels were higher in females than in males at baseline and after a 5-year follow-up (84, 85). Recent analyses have confirmed previous data and have shown that the presence of fibromyalgia in females was a negative prognostic factor for the achievement of MDA or low-disease activity (86, 87).

Several recent large studies have shown shorter TNFi survival in females with PsA, who tend to stop TNFi earlier than males. This finding could be partly explained by the more frequent adverse events experienced in female sex, causing drug discontinuation (13). The reason for these sex differences in drug response and survival remains unclear and might be due to biological differences or/and an interaction between pharmacogenomics and environmental factors.

CONCLUSIONS

Current data support the hypothesis that sex differences should be considered when treating patients with SpA. The genetic and cytokine signature, the hormone microenvironment, as well as the presence of female-specific immunological niches, such as the uterus, are peculiar in women and may drive different clinical presentations and responses to treatment.

Still, an important lack of knowledge about the etiology and disease manifestations in women is outlined in the present review. Moreover, in clinical trials, women are underrepresented despite significant differences in drug metabolism, and post-marketing studies do not stratify results according to sex to effectively detect gender and sex differences.

However, upcoming novelties from basic and clinical science will change the perspective on SpA assessment, revolutionizing our approach to study design, diagnosis, and management. The final goal of all efforts aimed at deeply understanding SpA immunopathogenesis in women is the definition of a real personalized medicine for SpA patients to reduce misdiagnosis and delay in intercepting the disease.

Contributions
All the authors made a substantial intellectual contribution, read and approved the final version of the manuscript, and agreed to be accountable for all aspects of the work.

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The authors declare no potential conflict of interest.

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