Gender-related differences in patients with psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory arthritis that affects up to 30% of patients with psoriasis. Gender-related differences have been extensively investigated in spondyloarthritis, particularly in ankylosing spondylitis, which shares several genetic and clinical characteristics with PsA. PsA affects men and women equally. Sex may play a role in the underlying genetic mechanisms of PsA. The inheritance of psoriasis and PsA may be implicated by genomic imprinting, which is a differential expression of a gene depending on the sex of the transmitting parent. Gender-related differences are observed in the clinical expression of PsA. Males are more likely to develop axial involvement, while women tend to present with peripheral polyarticular disease. Men also develop more severe radiographic damage in their spine, as well as in their peripheral joints. Women tend to discontinue treatment with anti-TNF-α agents earlier than men owing to inferior response and more side effects. Women with PsA also tend to suffer from worse quality of life and more severe fatigue and work disability compared to men. The causes for these differences may be related to the effect of sex hormones, different gene expression, occupational exposures or differences in perception of pain.

KEYWORDS: gender medicine ■ psoriatic arthritis ■ sex ■ spondyloarthritis ■ women's health

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Why investigate gender-related difference?

Up until recently, medical knowledge was gender neutral, and physicians applied that knowledge to their patients irrespective of their gender. However, over the past decade, numerous studies in various medical fields refuted that notion and revealed that medicine is actually gendered. The gendered nature of medicine has significant implications for patients as gender can affect clinical presentation, natural history and response to medications in numerous medical conditions [1–4]. Until the late 1990s, most medical knowledge was based on studies that were mostly limited to males. Women were thought to add variability to the results owing to their hormonal cycle. Furthermore, there was a reluctance to include women of childbearing age in drug trials owing to the potential for damage to their reproductive ability or future offspring [5]. In studies that did include women, in most occasions stratification by gender was not performed, thus, gender-related differences could not be determined [6]. During the 1990s, the number of women that were included in clinical drug trials and medical research increased significantly and attention was shifted towards women's health research.

Although the terms 'sex' and 'gender' are often used interchangeably, these are two distinct entities. WHO defines 'sex' as the biological and physiological characteristics that define men and women; therefore, 'sex differences' can originate from differences in chromosomes or hormones. Gender refers to the socially constructed roles, behaviors, activities and attributes that a given society considers appropriate for men and women, thus the term 'gender differences' takes into consideration the impact that social role and lifestyle issues have on men's and women's health [101]. It is often difficult to disentangle the effect of sex (biological differences between males and females) from gender (a result of social role difference between men and women). Therefore, the new approach has shifted from exclusively focusing on biologic sex to focus on gender. In this article, the authors therefore review gender differences in several aspects of psoriatic arthritis (PsA).

Gender differences in PsA

Psoriasis is a common skin disease affecting 1–3% of the population [7,8]. PsA is an inflammatory arthritis that affects approximately 7–42% of patients with psoriasis [9,10]. PsA belongs to spondyloarthritis (SpA), which is a group of diseases that share certain genetic, clinical and radiographic features. Spondylitis, the most distinguishing feature of the group, is an inflammation of axial joints manifested by inflammatory

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back pain and progressive restriction in spine movements due to formation of bony bridges in the axial joints. Additional characteristic clinical features are asymmetric oligoarthritis, dactylitis and enthesitis. Although most patients with PsA have axial involvement, it is less severe than in ankylosing spondylitis (AS), the prototype of SpA [11]. Five patterns of arthritis have been described: the symmetric polyarticular pattern being the most common; distal arthritis that involves the distal interphalangeal joints; asymmetric oligoarthritis in which less than five joints are affected; arthritis mutilans, which is characterized by deforming and destructive arthritis; and spondyloarthritis, which includes sacroiliitis and spondylitis [9]. These patterns, however, do change over time and distal joint disease, spinal disease and arthritis mutilans may occur with other patterns. Currently, most investigators in PsA consider the presence of peripheral disease alone, peripheral plus axial or axial disease alone. *HLA-B*27* is the strongest genetic risk factor for SpA although the underlying mechanism for that association is unclear. *HLA-B*27* is associated with an increased risk of developing PsA among psoriasis patients; however, only approximately 20% of the PsA patients carry that risk allele [12].

Sex ratio

Although AS is a male predominant disease with a male to female ratio of 3–5:1 [13,14], both psoriasis and PsA affect men and women equally [15–17]. Gender distribution may change with relation to disease presentation as males tend to present with axial involvement, while females are more likely to suffer from peripheral arthritis [18,19]. A male predominance among PsA patients with a male-to-female ratio of 2.1–4.8:1 was reported by several population-based surveys [13,20,21]; however, these studies oversampled patients with axial involvement, which is more prevalent in males. A recent population-based survey from Sweden reported that the prevalence of SpA was similar in men and women [22]. However, the subtype PsA was more common in women, while AS was more common in men. Variation in reported sex ratios may also be secondary to local differences in genetic and environmental factors and due to differences in diagnostic criteria.

Difference in clinical expression of PsA across the genders

The predilection for axial involvement among males is common in both PsA and AS patients. This finding has been demonstrated in numerous surveys among patients from different ethnicities. A large body of evidence exists for AS patients, suggesting that women are more likely to develop peripheral arthritis compared to men [23–26]. Only a few studies specifically addressed the issue of gender-related differences in clinical expression among PsA patients. Queiro *et al.* assessed 100 patients with psoriatic spondyloarthritis and reported that men were more likely to develop isolated axial disease (male-to-female ratio of 3.6), while women had higher swollen joint count (17 vs 8; p = 0.002) [27]. Gladman *et al.* assessed 82 women and 112 men with psoriatic spondyloarthritis and found that men tended to have more severe axial involvement as evident by the restriction of back movements [28]. Surveys from Ireland and Spain have shown that the pattern of arthritis differed across the genders with a predominant polyarticular involvement in women (male-to-female ratio of ~2:1), compared with an oligoarticular pattern in males, which was the most common pattern in men. Spondylitis was also more common in males compared with females [29–31]. A recent analysis of data from a cohort of early SpA patients, which consisted mostly of PsA patients, and suggested that females were more likely to present with knee pain compared to men [32]. Unlike joint disease, there is no difference in severity or clinical expression of cutaneous psoriasis across the genders [33]; however, psoriatic nail lesions were more frequent in males, affecting approximately 60% compared with approximately 45% in females [30].

Analysis of radiographic data mirrors these clinical findings. Bilateral radiographic sacroiliitis was more frequent in males compared to females in a Spanish cohort of PsA patients (55 vs 35%), although not statistically significant [27]. The Toronto cohort analysis has shown that men suffered from more severe radiographic damage compared to women in both axial and peripheral joints [34]. In agreement with previous observations in PsA, axial involvement, defined by radiological evidence of either bilateral at least grade 2 sacroiliitis or unilateral grade 3 or 4 sacroiliitis, was more frequent in men (42.9 vs 31%; p = 0.003). After adjusting for duration of PsA, men were 1.8-times more likely to develop axial involvement. Furthermore, men were more likely to develop syndesmophytes in the cervical, thoracic and lumbar spine, and the average modified Stokes Ankylosing Spondylitis Spine Score (mSASSS), which scores radiographic spinal damage, was higher in men compared with women.

An interesting finding was the tendency of men to develop more severe radiographic damage in the peripheral joints, despite more pronounced active peripheral arthritis in women. Data from the Toronto cohort have shown that women were more likely to have nonerosive disease (FIGURE 1). Men were more likely to be in a higher peripheral radiographic damage category compared to women after adjusting for duration of PsA (odds ratio: 1.6; p = 0.005) [34]. The underlying mechanisms of this difference in radiographic damage are unknown. One potential mechanism can be related to physical trauma that has been suggested to be a risk factor for PsA [35–37]. Engagement in physically demanding occupational activities that involve recurrent micro-trauma is a risk factor for more severe radiographic damage in AS patients [38]. Thus it can be hypothesized that more frequent engagement of men in heavy labour may explain these differences. However, this link has not been specifically investigated in PsA patients.

Gender-related differences in response to medications

Methotrexate is often the first disease-modifying antirheumatic drug (DMARD) used to control active peripheral arthritis in PsA patients despite the lack of documented efficacy. No gender-related differences were observed in a study among PsA patients participating in a longitudinal observational cohort that assessed predictors for early discontinuation of methotrexate treatment [39]. Anti-TNF-α agents have dramatically changed the treatment of PsA over the past decade. These agents have been found to be effective for controlling the symptoms and signs of the disease and preventing radiographic damage. Several recent large studies have shown that women tended to discontinue anti-TNF-α agents earlier than males. Glintborg *et al.* analyzed information on 761 PsA patients treated with anti-TNF-α agents from the Danish biologics registry DANBIO. They have shown that female sex was associated with shorter drug survival with a hazard ratio of 1.4. This finding could be explained by inferior response to treatment, as male gender was associated with the European League Against Rheumatism good clinical response with an odds ratio of 1.5. However, female gender was also associated with shorter survival on the medication in a stratified model that only included adverse effects as the event causing drug termination, suggesting that women also suffered from more side effects that have led to discontinuation of the drug [40]. Similar results were found following analysis of data from the British Society for Rheumatology Biologics Register. Among 566 PsA patients that received anti-TNF-α agents, female gender was associated with higher drug discontinuation rates (hazard ratio: 1.3) [41]. A similar trend was observed in AS and RA patients [42–44]. Therefore, this phenomenon is probably not unique to PsA. The reason for these gender differences in drug survival and response to therapy remains unclear. It was suggested that sex hormones and musculoskeletal performance may explain the poor response of women to anti-TNF-α agents; however, such a linkage has not been established.

Functional limitation & work disability across the genders

Female gender is a risk factor for work disability in RA and AS [45–47]. Similar findings were demonstrated in PsA patients. Wallenius *et al.* reported that women had a twofold increased risk of work disability compared to men of the same age among patients with peripheral PsA starting immunosuppressive treatments [48]. These gender differences may be a consequence of the way men and women perceive their health, as females with PsA have worse scores in patient-reported outcomes than males. Women with a PsA score higher in the Health Assessment Questionnaire, the Fatigue Severity Scale and the Bath Ankylosing Spondylitis Functional Index and lower in the physical component score of the Medical Outcome Study Short Form 36 Health Survey (SF-36) compared with men (FIGURE 2) [34]. These differences were

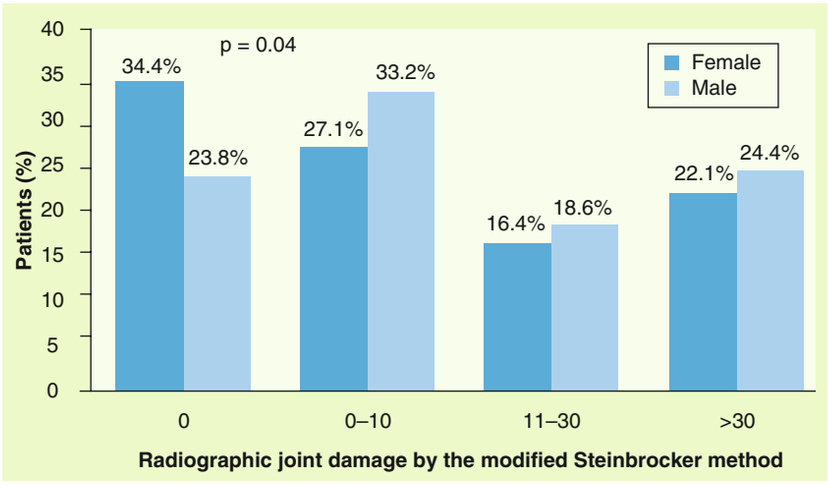

Figure 1. Distribution of radiographic peripheral joint damage across the genders among psoriatic arthritis patients as scored by the modified Steinbrocker method.
Data taken from [34].

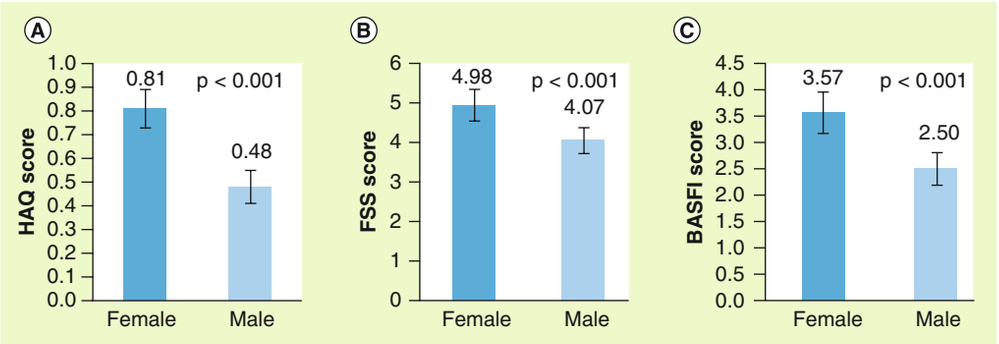

Figure 2. Patient-reported measures of function and fatigue stratified by gender among patients with psoriatic arthritis. (A) HAQ, **(B)** FSS and **(C)** BASFI. Values are means (95% CI).
BASFI: Bath Ankylosing Spondylitis Functional Index; FSS: Fatigue Severity Scale; HAQ: Health Assessment Questionnaire.
Data taken from [34].

independent of age and other disease-related variables, including joint damage, suggesting that women experience more limitations in daily physical function [49,50]. No differences were observed in the mental component score of the SF-36, which scores mental and social function, and the Dermatology Life Quality Index, which emphasizes the effect of skin disease on quality of life.

These differences were intriguing as although men develop more severe axial and peripheral joint damage, women suffer from more limitation in function and worse quality of life. These gender differences in quality of life have also been found among patients who suffered from RA and AS. A potential explanation for these observations is the more pronounced pain perception in women than in men [51], which can lead to limitation in function and poorer quality of life. Moreover, since muscle strength has been shown to affect Health Assessment Questionnaire score [52], pain may have a greater impact on women owing to their lower muscle mass, which can result in more difficulty in performing daily activities. Finally, men tend to underscore their disability, as they overestimate their functional activity by 0.21 Health Assessment Questionnaire units [53].

No significant difference across the genders was observed in a study that assessed the impact of severity of psoriasis on appearance and socialization; however, men reported greater work-related stresses [33].

Differences in mortality across the genders

Mortality rates have not been extensively investigated in PsA and it is unclear whether mortality rates are higher among PsA patients compared with the general population. A study from our center demonstrated a higher mortality rate in patients with PsA compared with the general population [54], but there was no significant difference among the genders, although the Standardized Mortality Ratio (SMR) was higher among men. Another study from Bath did not find an increased mortality risk among patients with PsA, but it too reflected more recently observed patients [55]. A recent large study form Hong Kong that used hospital registries to calculate SMR has shown that mortality was only increased among women (SMR 1.96; 95% CI: 1.14–2.77) compared with the general population, but not among men (1.4; 95% CI: 0.89–1.9) [56]. A similar trend was noted in the analysis of data from the Toronto PsA cohort where SMRs were slightly higher among women (1.47; 95% CI: 1.13–1.91) compared to men (1.25; 95% CI: 0.95–1.65), although a trend for decline in mortality rates was noted in both genders over time [57,58].

Pregnancy & postpartum period in PsA

The post-partum period is of particular interest since it is associated with significant hormonal changes and an increased risk of developing inflammatory arthritis such as RA. There are conflicting results regarding the risk of developing PsA during the post-partum period. McHugh *et al.* interviewed 33 PsA female patients retrospectively and found that 18% of patients and 30% of all mothers developed arthritis in the first 3 months of postpartum period [59]. All of the patients who had pregnancy-related onset had polyarticular pattern of arthritis. On the other hand, Thumboo *et al.* showed that pregnancies were decreased among PsA patients compared to psoriasis patients in the window of exposure period prior to the

onset of arthritis [60]. Two additional studies that investigated environmental risk factors for PsA among psoriasis patients did not find an association between pregnancy and other female hormonal exposures (i.e., menopause and use of exogenous estrogen) and PsA [35,37].

The etiopathogenesis of gender differences in PsA

The underlying pathogenic mechanisms of the differences between men and women are unknown. We will review the current literature on several potential mechanisms that may explain gender-differences in PsA.

Sex hormones

It is reasonable to hypothesize that sex hormones mediate gender differences in the presentation of any medical condition. However, there is limited information about changes in the levels of these hormones in patients with SpA in general and in particular among PsA patients. Several small studies have not found any differences in the levels of luteinizing hormone, follicle-stimulating hormone, testosterone and dehydroepiandrosterone among AS patients compared with healthy controls [61,62]. Other studies have reported slightly higher levels of testosterone in patients with AS compared to controls; however, the differences were small and testosterone levels were within the normal range, furthermore, many of the studies did not adjust for potential confounders such as age [63,64]. Jimenez-Balderas *et al.* did not find any differences in 17-α-etradiol and progesterone levels among female AS patients compared to controls, although 17-α-etradiol levels were lower among five women with active disease [65]. McHugh *et al.* did not find an association between disease activity and the use of oral contraceptives in a retrospective study that included 33 PsA patients [59]. In summary, there is limited data to suggest that sex hormones are directly responsible for gender differences in PsA.

The interaction between sex & genetic mechanisms

Several studies of SpA patients suggested that women may require a greater genetic load to develop the disease or that exposure to environmental risk factors is more frequent in males. This hypothesis stems from studies in AS patients that have shown that males tend to develop sporadic AS, while women are more likely to have a positive family history of the disease [13,66]. Additionally, a preferential transmission of AS from father to son as opposed to a more balanced transmission from mother to children of both genders was reported [67]. Our recent study has found similar results among PsA patients [34]. A positive family history of psoriasis was reported by 53.1% of the women versus 44.3% of the men ($p = 0.04$) and 10.2% of the women had a first-degree family member with PsA compared to only 5.5% of the men ($p = 0.03$). *HLA-B*27* and *HLA-C*06* are strong genetic risk factors for PsA and psoriasis, respectively [68]. The distribution of these autosomal genes across the genders was assessed among patients with PsA in two studies showing conflicting results. Queiro *et al.* reported that the frequency of *HLA-B*27* was higher in males compared to females among patients with psoriatic spondyloarthritis (48 vs 11%; $p = 0.002$) and no difference was found in the frequency of *HLA-C*06* across the genders (54% in males vs 58% in females) [27]. By contrast, a recent analysis of 590 PsA patients from our cohort found that the frequency of *HLA-B*27* was similar among men and women (16.8% in males vs 15.2% in females) while *HLA-C*06* allele was more frequent among females (33.2 vs 21.9%; $p = 0.005$) [34]. It is unclear whether these findings can explain the different familial aggregation of PsA across the genders or merely reflect different inclusion criteria that resulted in sampling different subphenotypes of PsA. Additional genetic mechanisms that are affected by gender and may explain the difference in inheritance of the disease include epigenetic mechanisms, such as genomic imprinting [69,70]. Genomic imprinting is a non-Mendelian mode of transmission that can lead to differential expression of a gene depending on the sex of the transmitting parent. The imprinting process allows gene expression from only the maternally or paternally derived chromosome [71]. Burden *et al.* observed a higher penetrance of psoriasis if the father was affected or a presumed gene carrier [72]. Rahman *et al.* reported a similar phenomenon among PsA patients from our cohort: the proportion of PsA patients with an affected father was significantly higher than the expected proportion (0.65 vs 0.5; $p = 0.001$) [69]. These findings were supported by a linkage study in PsA that noted a significant linkage on chromosome 16q only after conditioning for paternal transmission [73]. Thus, genetic imprinting may play a role in the inheritance pattern of psoriasis and PsA.

Environmental factors & social aspects

Recent literature suggests that environmental factors including physical trauma, smoking, obesity and occupational exposures can trigger or protect from the development of PsA among patients with psoriasis [37,74,75]. Although not specifically investigated, it is likely that several of these factors can also affect the clinical presentation of the disease and the development of joint damage and disability. As previously discussed, physical trauma that is considered to be a risk factor for both skin psoriasis and PsA [35–37] may explain the tendency of men to accumulate more severe joint damage through their more frequent engagement in physically demanding occupational activities [38]. However, this link has not been specifically investigated in PsA patients. The effect of the remaining factors such as obesity and smoking on clinical presentation and development of damage among PsA patients has not been investigated.

Other factors that may explain the difference in presentation of PsA across the genders may be related to social aspects such as the way men and women perceive their health, their different social role and pain perception. The tendency of women to have worse scores in patient-reported outcomes is not unique to PsA and is repeatedly found in other medical conditions.

Conclusion & future perspective

Similar to other type of arthritis, there are several gender-related differences in clinical expression, response to medications and function in patients with PsA. Males are more likely to develop axial involvement while women tend to present with peripheral polyarticular disease. Men also develop more severe radiographic damage in their spine as well as in their peripheral joints. Women tend to discontinue treatment with anti-TNF-α agents earlier than men owing to inferior response and more side effects. Women with PsA also tend to suffer from worse quality of life, more severe fatigue and work disability compared to men. Some of these differences are specific to PsA, while others were observed in other types of arthritis and probably represent general differences across the gender in perception of pain, social function or lifestyle. Furthermore, it is unclear whether these differences are related to 'biological' mechanisms, such as differences in hormone levels and gene expression or to 'social' mechanisms, such as exposure to different environmental risk factors or different behaviors. From the clinician's point of view, this body of information highlights the importance of considering gender differences in clinical practice. The tendency of men to accumulate more radiographic damage may necessitate earlier and more aggressive medical treatment. On the other hand, pain control has an important role in the management of women with PsA and may improve function and reduce disability. Future studies are required to assess the progression of these changes over the course of the disease and the underlying mechanisms that lead to these differences.

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Executive summary

Male-to-female ratio

- Psoriatic arthritis (PsA) affects men and women equally.

Difference in clinical expression of PsA across the genders

- Men with PsA develop more severe axial disease, while women with PsA tend to develop more frequent polyarticular involvement.

Gender-related differences in response to medications

- Women with PsA respond less favorably to TNF-α agents and develop more frequent side effects that result in earlier discontinuation of these drugs.

Functional limitation & work disability across the genders

- Women with PsA develop more severe limitation in daily function, which frequently results in work disability.

The etiopathogenesis of gender differences in PsA

- There is insufficient information to suggest that sex hormones are directly responsible for the observed gender differences in PsA patients.
- Genetic imprinting may play a role in the inheritance pattern of psoriasis and PsA.

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