

Gender medicine and psoriasis

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Core tip: The study of specific differences between women and men is arousing huge interests in various fields of medicine, including dermatology. The available data on gender medicine applied to common skin diseases are unfortunately still scanty. The objective of this brief review is to provide hints for the presence of sex differences in various aspects of psoriasis, from epidemiology to pathogenesis, from clinical aspects to therapeutic management, trying to examine the evidence available in the literature.

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Abstract

The study of specific differences between women and men is arousing huge interests in various fields of medicine, including dermatology. The available data on gender medicine applied to common skin diseases are unfortunately still scanty. Psoriasis is a chronic immune-mediated skin disease which affects 1%-3% of most populations worldwide and can involve also the joints and entheses. The pathogenesis of the disease is very complex, resulting from the interaction between genetic predisposition and several environmental triggers. The pathogenic role of sex hormones has also been hypothesized. The analysis of gender-specific differences in psoriasis seems to suggest some interesting findings, such as an earlier age of disease onset in females, a higher probability of severe disease in men, or different tendencies in care utilization, adherence to treatment, development of psychological distress, and coping strategies. Moreover, sex-related differences have been recently described in some epidemiological and clinical features among patients with psoriatic arthritis. The objective of this article is to review briefly the available evidence regarding gender differences in various aspects of psoriasis, such as epidemiology, genetics, risk factors, associated conditions, quality of life, clinical and therapeutic aspects.

INTRODUCTION

The ever-increasing interest in the study of gender medicine in the last years has led to gain awareness of the differences between men and women in the clinical presentation, pathophysiology, management and prognosis of a wide variety of human diseases, including skin diseases^[1].

Gender differences in disease characteristics can be influenced by complex interactive mechanisms involving the effect of sex hormones, ethnic background, anatomy, physiology, immunity, genetics, epigenetics, as well as geographical, sociocultural, and environmental factors. Differences in the skin structure and physiology between the sexes can also contribute to different expression of some skin disorders^[1,2].

Psoriasis is a common chronic inflammatory skin dis-

ease that affects 1%-3% of most populations in developed countries, with a predilection for Caucasians^[3]. Histopathologically, the disease is characterized by signs of increased proliferation and abnormal differentiation of keratinocytes (hyperkeratosis with parakeratosis, loss of granular layer, acanthosis and elongation of rete ridges), dilatation and tortuosity of the capillary loops, and inflammatory infiltration of the papillary dermis and the epidermis, with a preponderance of lymphocytes and neutrophils.

Psoriasis is considered an immune-mediated disease characterized by a predominant Th1-type and Th17-type cytokine profile, although a complex interplay between various cells of the innate and adaptive immune system contributes to the induction of inflammatory processes, epidermal hyperplasia, and ultimately to the development of clinical manifestations. Pathogenesis is only partially known and particularly complex, involving an interaction between genetic factors and several environmental triggers^[4,5].

The objective of this brief review is to provide hints for the presence of sex differences in various aspects of psoriasis, from epidemiology and pathogenesis to clinical aspects and therapeutic management, trying to examine the evidence available in the literature.

EPIDEMIOLOGY

Psoriasis can present at any age and most studies have identified a bimodal age of onset, with a first peak between the ages of 15 and 20 years and a second one occurring at 55-60 years^[6]. In spite of minor deviances in some studies, psoriasis prevalence is estimated to be equal in males and females^[7]. An earlier age of psoriasis onset has been reported in females^[8], although other authors did not confirm this finding^[7]. Interesting results were extrapolated by a survey conducted in a historical cohort of Norwegian twins aged 19-31 years^[9]. There were no sex differences in the overall prevalence rates, but significantly higher point-prevalences emerged in females in the teenage-year intervals. The mean age at onset was also significantly lower in females than in males. The absolute risk of developing psoriasis appeared higher for females across the entire age range. However, by the age of 31 the cumulative risks were similar in females and males.

A population-based retrospective study carried out in the United States examined the incidence of adult-onset psoriasis over three decades and found that the overall age- and sex-adjusted incidence in males was more elevated than in females, except for the sixth decade of life, when there was a peak incidence in women^[10], thus suggesting the potential pathogenic relevance of sex hormones in psoriasis. Previous observations indicated the role of menopause not only in the onset but also in the exacerbation of psoriasis^[11].

PATHOGENESIS AND RISK FACTORS

Psoriasis pathogenesis is multifactorial and recognizes a

strong genetic background, as suggested by the frequent presence of a positive family history and the identification of putative susceptibility loci on several chromosomes^[4]. One of the most important loci is the MHC region on chromosome 6p21 named PSORS1, harboring the human leukocyte antigen-C (*HLA-C*) gene. HLA-Cw6 (HLA-Cw*0602) was found to be the most relevant risk allele and has been associated with a lower age at onset. It was reported that Cw6-positive women might have an earlier disease onset than Cw6-positive men, but such a difference was not observed for the Cw6-negative patients^[12].

There is interesting evidence concerning the impact of sex of the transmitting parent (genomic imprinting). The sex of the psoriatic parent was found to influence the birth weight of offspring, with children from psoriatic fathers being heavier than offspring of female psoriatic patients, and also the disease manifestation, which was more likely to occur when the father was affected^[13]. In the opinion of some authors^[14], the genes underlying this imprinting might contribute to a higher disease activity in males although there is a paucity of information on this aspect.

As above mentioned, the development of psoriasis is a complex phenomenon resulting from the action of environmental triggers in predisposed individuals. These triggers include trauma, psychogenic stresses, infectious agents (*i.e.*, streptococcus, HIV and other viruses), drugs (*e.g.*, lithium, antimalarials, interferon, beta-blockers, nonsteroidal anti-inflammatory drugs, or rapid tapers of high-dose steroids)^[5]. The possible role of hepatitis C virus infection is discussed in the paragraph regarding comorbidities and clinical associations.

The influence of stressful life events on psoriasis has also been suspected for long time. The association with stressful events occurring in the year preceding the diagnosis of psoriasis was documented in one study^[15], which showed that this risk was more evident for women.

Alcohol has long been suspected to be a triggering and precipitating factor of psoriasis. Alcohol misuse is common in patients with moderate-to-severe psoriasis and appears to interfere with the course of the disease and treatment outcome^[16]. An increased alcohol consumption was shown in both male and female psoriatics as compared to controls, with a statistically significant difference reached only for men^[17], whereas other data suggested a tendency to drink more after psoriasis diagnosis especially in women^[18].

Smoking has also been implicated in the development of psoriasis. The cumulative association between smoking and psoriasis seems stronger in women^[15,19], although one study identified smoking as a risk factor only in males^[18]. A recent report highlighted the role of smoking as an independent risk factor for psoriasis, without however disclosing differences in the association among younger vs older women or between women and men^[20]. Other results supported a positive association with both adulthood exposure to passive smoking^[20], and the ex-

smoker status only for men^[17].

CLINICAL ASPECTS

Psoriasis is a papulo-squamous disease with variable morphology, distribution, and severity of skin lesions. It has a variable course, that is usually lifelong, chronic and recurrent^[3,21]. The most common clinical presentation is chronic plaque psoriasis, which can affect any body site with preferential involvement of the scalp, the extensor aspects of limbs, and the lumbosacral area. The presence of lesions in body folds depicts the so called flexural or inverse psoriasis. Psoriasis may also develop at the site of trauma, known as Koebner's phenomenon. The progressive diffusion of lesions can lead to psoriatic erythroderma, which is a rare severe form characterized by generalized erythema and scaling in more than 90% of the body surface area. Other variants include guttate psoriasis, consisting of eruptive small papules usually distributed on the trunk and the proximal aspects of limbs, and pustular psoriasis, that can be distinguished into localized palmoplantar forms and the more severe generalized forms.

Nail changes may be present, especially in patients with concomitant arthritis. Morphological differences in psoriasis between males and females have not been documented so far^[7]. Some observations seem to suggest that moderate to severe extent of involvement is more frequent in men than in women^[22]. With respect to the distribution of clinical variants, a remarkable gender-related feature regards palmoplantar pustulosis that more commonly affects women, with a female/male ratio of 9:1^[6]. Palmoplantar pustulosis has a special predilection for female smokers^[23]. A retrospective evaluation of 102 patients with adult-onset generalized pustular psoriasis reported a female to male ratio of 2:1^[24].

PSORIATIC ARTHRITIS

Psoriasis may also affect the joints and the entheses. The estimated prevalence of psoriatic arthritis (PsA) among patients with psoriasis has varied widely from 6% to 42% according to different case series^[25]. In the vast majority of psoriasis patients with PsA, the skin manifestations precede arthritis^[5].

Uncertain data exist on the prevalence of PsA in men and women. PsA is generally thought to occur equally in both sexes^[25]; indeed, recent findings indicate that the incidence of PsA is less in women than in men until the sixth decade of life^[26], thus providing indirect evidence of the potential role of sex hormones in PsA pathogenesis. PsA in Iceland seems to be more common in women, with the female to male ratio close to 2:1^[27]. A female predominance was also registered in Kuwait while other studies noted a male predominance^[28,29].

Very limited information is available about gender differences in PsA patients. A positive family history of psoriasis and PsA was reported more frequently by women with PsA in some instances^[30]. Females appear

to progress more than males^[25]. The results of a recent cross-sectional analysis have shown that there was a clear-cut trend towards a polyarticular involvement in women, whereas oligoarthritis was the most common pattern in men. Moreover, men with PsA were more likely to have psoriatic nail lesions, to develop axial involvement and also more severe radiographic damage in the peripheral joints, while women had more fatigue and severe limitations in function, as well as a worse quality of life^[30]. It is unknown whether these findings can be secondary to differences in occupational physical activity, hormonal changes, or genetic factors. A differential overexpression of certain *MHC* genes between the two genders has been hypothesized^[31]. A close correlation between male sex, HLA-B27 positivity, and the risk of psoriatic spondyloarthritis was also described^[32,33]. On the contrary, in accordance to other authors^[30], no difference in the frequency of HLA-B27 was detectable across the genders among PsA patients. The analysis of a cohort of PsA patients revealed an increased frequency of the HLA-Cw6 allele in women as compared to men^[30]. Another recent study confirmed that women were affected more frequently by polyarthritis as the main joint pattern during follow-up, and had significantly greater functional impairment and higher number of swollen joints^[31]. Among the PsA patients with psoriasis developing before 40 years of age, a significantly shorter psoriasis-PsA latency period was noted in men^[31].

Work disability in PsA patients below 45 years of age was shown to be independently related to educational level, disability score, erosive disease, disease duration, and female gender^[34].

COMORBIDITIES AND CLINICAL ASSOCIATIONS

Psoriasis is associated with a number of systemic disorders including Crohn's disease, obesity, type 2 diabetes mellitus, essential hypertension, dyslipidemia, metabolic syndrome, nonalcoholic fatty liver, and depression^[5]. The persistent systemic inflammation and endothelial activation may predispose to the increased risk for cardiovascular disease existing in patients with psoriatic disease^[35]. Few studies systematically examined gender-specific differences in comorbidities associated with psoriasis. On recent occasions^[36,37], higher prevalence rates of diabetes and metabolic syndrome were detected in psoriatic women than in psoriatic men, although other authors demonstrated that the increased association of psoriasis with diabetes consisted of similar proportions in men and women^[38]. Another study investigated the prevalence of masked hypertension, defined as normal office blood pressure with elevated ambulatory blood pressure, which represents a risk factor for full-blown hypertension, cardiovascular morbidity and mortality^[39]. For this purpose, normotensive and non-obese subjects with psoriasis and controls were evaluated. Male sex was detected as an in-

dependent predictor of masked hypertension, together with waist circumference and psoriasis severity.

Regardless of obesity and psoriasis, there are pronounced differences in body fat distribution between men and women, and these differences become more evident in puberty due to changes in sex hormone levels. Women have more body fat, and more peripheral or subcutaneous adipose tissue, while men have a relatively more central distribution of fat, with more visceral and hepatic adipose tissue^[40,41]. These differences, in combination with differences in sex hormones and adipokines, can at least in part explain a greater propensity of men to develop insulin resistance, dyslipidemia, and nonalcoholic fatty liver disease^[40]. It is not known if these distinct gender-related features in body composition may have direct effects on the development of metabolic and cardiovascular comorbidities, as well as on the proinflammatory state of psoriasis patients, taking into account that adipose tissue should be regarded as a source of endocrine and proinflammatory mediators. Compared with men, premenopausal women were shown to have increased concentrations of C-reactive protein, a well-established marker of inflammation and an independent predictor of cardiovascular events, and this result was correlated to subcutaneous adiposity^[42].

In a population-based case-control study, psoriasis was found to be associated with osteoporosis among males, but not among females^[43], although a recent report documented the association of osteoporosis with prior psoriasis diagnosis in both men and women^[44].

Significantly, more male patients appear to have migratory glossitis compared to female patients^[45]. Even though thyroid autoimmune disorders have shown no differences between psoriasis patients and the general population^[46], other findings suggested a significantly elevated prevalence of thyroid autoimmunity in men and women with PsA and of subclinical hypothyroidism in women with PsA than in the general population^[47].

An increased prevalence of concomitant extragenital psoriasis and anogenital lichen sclerosus was revealed in adult women^[48]. Currently, there are no published reports of this clinical association in men.

Retrospective population-based cohort studies in Taiwan disclosed that psoriasis may carry a high risk of malignancies, particularly in male and younger patients^[49]. The most common cancer was nonmelanoma skin cancer (NMSC) which was more frequent in women^[49,50]. Moreover, a Danish follow-up study showed that the significantly increased risk of cancer in psoriasis patients was mainly related to NMSC and lung cancers in both sexes, and cancer of the pharynx and larynx in men^[51]. Women had the highest risk of basal cell carcinoma in the age range 20-40 years, while men in the age range 30-60 years run an elevated risk of cutaneous squamous cell carcinoma. In a Swedish PUVA cohort study^[52], the relative risk of skin squamous cell carcinoma was 5.6 for men and 3.6 for women, and significant increases were also found in the incidence of respiratory cancer in men and women

and of kidney cancer in women.

An epidemiological association between psoriasis and hepatitis C virus infection has been recently reported, suggesting a potential role of the infection as an induction factor for psoriasis, especially in late-onset forms, and showing a consistent male predominance^[53,54].

QUALITY OF LIFE

Although psoriasis generally does not affect survival, it has pronounced negative effects on physical and psychosocial well-being, demonstrable by a significant detriment to quality of life. Quality of life is significantly worse in patients with psoriasis than in healthy subjects and similar to patients with major illnesses, such as diabetes and heart disease^[6,55].

The effect of gender on quality of life is less clear, as controversial results have been obtained so far. Based on earlier observations^[56], the male gender has been associated with lower psychosocial morbidity. In another work, no gender differences were observed in items linked to socialization, although men reported greater work-related stresses as a result of their psoriasis^[57]. A recent Japanese experience demonstrated the presence of a more severe deterioration of quality of life in female patients with psoriasis^[58], whereas German authors observed a moderate but significant relevance of feeling of stigmatization over time only in psoriatic men^[59].

In an Italian cross-sectional study in 936 patients hospitalized with a diagnosis of psoriasis, women had consistently worse quality of life than men and older women suffering from anxiety or depression had the greatest impairment in quality of life^[60]. The same authors more recently analyzed the prevalence of some psychosocial features^[61]. The problems most frequently experienced were shame, anger, worry, difficulties in daily activities and social life. Shame, worry and annoyance were more common in women than in men.

In the Italian multicenter study named PSYCHAE, the presence of minor and major psychological distresses was investigated in more than 1580 patients with psoriasis^[62]. Overall, minor psychological distress was present in 46% of patients and major psychopathological distress in 11%. Female gender was the most important predictive factor for the onset of psychological distress, while no association between severity of psoriasis and psychological distress was disclosed. Among the strategies most commonly employed by patients to cope with psoriasis, women tended to have lower (worse) scores compared with men in different areas, such as diverting attention, religion, use of emotional support, and negation. Women had a higher score only in the area related to humor.

Social support may be an important strategy capable of controlling the negative effects of psoriasis-associated psychosocial stress and improving the quality of life and adaptation to the disease. The strengths of these effects were found to be different in women and men suffering from psoriasis. In fact, higher social support was slightly

Table 1 Main gender-specific features among patients with psoriatic disease

Disease onset	Earlier in females
Prevalence	Reported as similar in men and women Some studies however showed an overall higher incidence in males and a peak incidence in women during the sixth decade of life
Genetic aspects	Earlier disease onset in Cw6-positive women than in Cw6-positive men Higher risk of disease manifestation and higher birth weight in offspring of psoriatic fathers
Triggering and risk factors	Association with stressful events more frequent in women Alcohol: increased consumption in both sexes, with statistical difference reached only for men (in one study); increased consumption after diagnosis more evident for women Smoking: association more consistent in women (one study identified smoking as a risk factor only in males); association with adulthood exposure to passive smoking and the ex-smoker status among men
Clinical features	Moderate to severe extent of involvement more frequent in men Palmoplantar pustulosis particularly frequent in females
Psoriatic arthritis	Controversial data on the prevalence in men and women (different results collected in case series from different countries) Most common clinical forms: polyarthritis in females and oligoarthritis in men Females with higher risk of disease progression, greater functional impairment, fatigue and work disability, and worse quality of life; men with higher risk of nail psoriasis lesions, axial involvement and more severe radiographic damage in the peripheral joints
Clinical associations	In a few studies (not always confirmed by others), different prevalence rates of some comorbid conditions among men and women (<i>i.e.</i> , increase of diabetes, metabolic syndrome, anogenital lichen sclerosis, and subclinical hypothyroidism in women, and increase of masked hypertension, osteoporosis, migratory glossitis, and hepatitis C virus infection in men) High risk of malignancies particularly in male patients
Quality of life	More severe impact on quality of life, more psychological and sexual distress in females Greater work-related stresses in men Moderate but significant relevance of feeling of stigmatization over time in men Gender differences in coping strategies and effects of social support
Treatment	Men more likely to receive intensive systemic treatments for severe psoriasis Gender differences in psoriasis care utilization Overall higher medication adherence in women (however, survival of anti-tumor necrosis factor therapies longer in male patients) Sporadic reports of gender differences in a few aspects of the efficacy and safety profiles of some treatment modalities

more strictly associated with better acceptance of life with the disease in men than in women. However, higher social support was more closely associated to lower depression and better quality of life in women than in men^[63]. Other data seemed to support that women with psoriasis, similarly to those suffering from other serious diseases, were more inclined to use social support resources for coping purposes than men^[64]. As for the satisfaction with specific life domains, no gender differences were noted, but the only psoriasis-specific effect in this context was the satisfaction with sexual life, which was better in men. While confirming the psychosocial morbidity in psoriatic subjects, with more anxiety, depression symptoms and phobic fears compared to general population, the presence of gender differences in such issues was denied, as the distribution in frequency and severity among males and females closely resembled that documented in the general population^[64].

Psoriasis can have a significant impact upon sexual function and health. Sexual distress was found to be particularly present when the genital area was affected^[65]. Sexual distress and dysfunction were also more prominent in women^[65,66].

The relationship between psoriasis and sexual behavior was assessed in two distinct studies in United States women and men, respectively, analyzing data from the

National Health and Nutrition Examination Survey^[67,68]. Psoriasis was not associated with differences in sexual orientation in both men and women. Psoriasis has been associated with a significantly reduced number of sexual partners in nonheterosexual women, and of female oral sexual partners in heterosexual men^[67,68].

THERAPEUTIC MANAGEMENT

There are many treatment options which can control the clinical manifestations of psoriasis without being curative. These options vary from simple topical medications to phototherapy, from traditional systemic drugs (*i.e.*, cyclosporine, acitretin, and methotrexate) to biologic drugs, such as those targeting tumor necrosis factor (TNF) or interleukin-12 and -23. The choice of therapy is strictly dependent on the severity of the disease, but also on several other variables, such as patients' characteristics, the response to previous therapies, and the impact on quality of life. Some drugs, particularly methotrexate and retinoids, have a known teratogenic risk which limits their use in women of child-bearing age.

Some studies performed in the "pre-biologics era" have found that men were more likely than women to receive intensive systemic treatments for severe psoriasis, partly because of the teratogenic potential of some of

these treatments^[69-72]. The majority of patients registered in European registries for psoriasis systemic therapies were men^[14,73], and more male patients have been treated with biologic drugs^[14]. This discrepancy was recently attributed to the higher probability of severe psoriasis in men, rather than to a mere discrimination against women for the access to systemic therapy including biological therapy^[14]. Data taken from the Swedish registries of patients treated with biologics showed no significant differences between men and women in the choice of biologics. At treatment start, psoriatic women had worse scores than men in the subjective disease measurements while men with psoriasis had worse scores for objective disease activity measures^[74].

Psoriasis care consumption seems to be strongly conditioned by several factors, including the gender. In a cross-sectional survey, female patients with psoriasis were 1.47 times more likely to seek care compared with males^[75]. A questionnaire-based study carried out in Sweden demonstrated gender differences in psoriasis care utilization, showing that men visited a dermatologist more often, while women visited a general practitioner, treated themselves topically and wanted information about the disease more frequently^[76]. These differences between genders were explained on the basis of diversities in income and gender roles. Other authors confirmed that women prescribed self-care more often than men^[70].

As for other chronic disorders, compliance and adherence to treatment are fundamental requisites to ensure treatment effectiveness but are difficult to be preserved in the long-term also because patients can be dissatisfied with the management of their disease. Adherence can be affected by a range of disease-related and social factors, including the gender. In fact, women with psoriasis were found to have a significantly higher mean medication adherence rate than men^[77]. A German study evaluated treatment preferences according to some specific attributes (such as probability and duration of benefit, tolerability profile, frequency and methods of delivery), and the subgroup analysis did not disclose any gender differences^[78]. Male sex was included among the conditions associated with longer drug survival in patients with either PsA or psoriasis treated with anti-TNF biologics^[79-82].

To the best of our knowledge, there are very limited data concerning gender differences in the safety and efficacy profiles of treatments available for psoriatic disease. To cite a few examples, in some studies, phototherapy with narrowband ultraviolet B radiations was reported to be more efficacious in females^[83], while females with PsA were less likely to achieve a response, defined using the European League against Rheumatism improvement criteria, to anti-TNF therapies^[84].

As concerns the tolerability of treatments, a retrospective cohort review among patients with either rheumatoid arthritis or psoriasis treated with at least one dose of methotrexate revealed that the pre-disposing factors predictive of liver damage were female gender and a higher cumulative dose of methotrexate without any ap-

parent effect of the disease itself^[85]. Moreover, infliximab-related hepatitis is thought to have an immune-mediated nature resembling autoimmune hepatitis type I, with a clear-cut preference for female sex^[86]. The paradoxical induction and exacerbation of psoriasis in patients treated with TNF inhibitors was described more frequently in females according to some case series or literature reviews^[87-90] but not to others^[91]. A significant weight gain has been described in patients with psoriasis treated with anti-tumour necrosis factor-alpha agents. Male gender and psoriasis severity were identified as risk factors for weight gain (defined as an increase of more than 2% of baseline weight) in psoriatic patients on infliximab^[92].

CONCLUSION

There is paucity of information derived from systematic assessment of differences between men and women with psoriatic disease. However, the literature review seems to suggest the existence of some interesting gender-specific differences among patients with psoriasis and PsA. The main aspects are summarized in Table 1.

There are very limited data concerning the safety and efficacy profiles of treatments for psoriatic disease in the two genders, especially with respect to the “real-life” setting. In this context, one paradigmatic example of a gender-specific study in psoriasis is represented by a multicenter Italian study, recently completed, that is named “GENDER ATTENTION”^[93]. This study was aimed at assessing the influence of gender and hormones on the incidence of adverse events and adverse reactions in patients with plaque psoriasis treated with cyclosporine.

We think that this topic should deserve more extensive and adequate attention in future evaluations, with special focus on the practical implications that gender-specific characteristics may have on the prognosis and therapeutic management.

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