Sex and gender differences in comorbidities in spondyloarthritis: a focus on psoriatic arthritis

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SUMMARY

Objective. Spondyloarthritis is a family of inflammatory diseases subdivided into those affecting the spine, called axial spondyloarthritis, and those involving peripheral joints, such as psoriatic arthritis (PsA). Several studies have reported differences in clinical manifestations, outcomes, and treatment responses between male and female PsA patients. The aim of our review was to evaluate if differences may also be identified in the context of cardiovascular (CV) risk factors and diseases.

Methods. Patients with PsA have a higher CV risk than the general population. The increased CV risk associated with PsA is likely caused by the complex interplay of traditional CV risk factors, chronic systemic inflammation, and side effects related to the use of certain anti-rheumatic drugs.

Results. Sex differences in CV risk factors in PsA patients, according to several studies, are controversial. However, the few studies that reported sex-stratified estimates did not find differences in the risk of stroke and myocardial infarction between sexes. The same also holds true for CV mortality. These mixed results may be related to the different study designs and case definitions, as well as genetic and geographical variability across the investigated populations.

Conclusions. In conclusion, our review suggests that the evaluation of sex-gender aspects of CV comorbidities in PsA should be a central step in the context of personalized medicine in order to prevent and treat properly associated comorbidities.

Key words: *Psoriatic arthritis, cardiovascular involvement, cardiovascular risk factors, diabetes, hypertension, dyslipidemia, mortality.*

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INTRODUCTION

Psoriatic arthritis (PsA) is a chronic systemic inflammatory disease that affects approximately one-third of patients with psoriasis (PsO) (1). PsA is part of the spectrum of spondyloarthritides (SpA) (1), which presents with various clinical manifestations such as peripheral arthritis, axial disease, dactylitis, and enthesitis in patients who have either visible or hidden PsO, typically within 10 years of PsO onset (2). The prevalence of PsA among patients with PsO is 23.8% in studies in which the Classification Criteria for Psoriatic Arthritis were applied (3), while in the general population, PsA is much rarer (0.13%) (4). The musculoskeletal features of PsA can be classified into two main types: peripheral (polyarticular, oligoarticular, distal arthritis, and arthritis mutilans) and axial manifestations (1, 5). The axial condition, known as axial PsA or psoriatic (pelvi)-spondylitis, primarily affects the spine and sacroiliac joints and is observed in 25-70% of patients with PsA, with exclusive axial involvement in 5% of patients (6).

Although PsA affects men and women equally (3), a growing body of research has demonstrated sex- and gender-related disparities in clinical characteristics, disease activity, patient-reported outcomes (PROs), and response to treatment. The term sex refers to the biological attributes that encom-

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pass physical and physiological features, while the term gender is related to socially constructed norms that determine roles and relationships in any society.

Peripheral arthritis has generally been observed to be more prevalent in women than in men (7). Polyarticular presentation is more common in the female population, whereas oligoarticular presentation predominates in the male population (8, 9), as previously shown by Eder *et al.* (10). Enthesitis is significantly more prevalent in women (8, 9), while psoriatic nail dystrophy and radiological axial involvement are more often encountered in men (8). However, a systematic review by Coates *et al.* (7) did not reveal sex differences in severity measures of enthesitis.

Globally, earlier literature and a recent review supported the finding that axial disease is more prevalent in men (7, 10, 11). However, this conclusion did not agree with the analysis of the United States (US) Corrona PsA/Spondyloarthritis Registry, which found no significant differences in the axial involvement percentages between men and women (12).

PROs, which are patients' reports of their health, quality of life, or functional status in relation to treatment, mainly recording pain and functioning, score worse in women than in men (13). Differences in pain perception between males and females arise from a complex interaction of biological, psychological, and socio-cultural factors. Experimental data indicate that sex hormones play a central role in influencing sex differences in pain sensitivity. In fact, estradiol and progesterone have composite effects on pain sensitivity, with studies describing both pro-nociceptive and anti-nociceptive properties (14). Of note, estrogen level fluctuations increase pain perception in women, while stable hormone levels have protective effects against nociception. On the contrary, testosterone protects males against pain probably through the reduced production of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) (15).

Moreover, women score significantly worse on the Health Assessment Questionnaire, indicating more pronounced difficulty than men with daily living activities (7). In patients with similar PsA disease activity and treatment, women experience greater disease impact with a worse quality of life score ($p=0.02$), greater disability ($p<0.01$), and work activity impairment ($p<0.01$) than men (16).

Several observational studies have reported differences in outcomes between male and female patients with PsA, similar to what has been observed in axial spondyloarthritis (axSpA) (17). Gender differences in response to and retention of biologic disease-modifying antirheumatic drugs (DMARDs), such as TNF inhibitors (TNFi), have been observed. The Danish DANBIO registry (18) and the British BSRBR registry (19) have shown that women with PsA receiving TNFi develop more side effects than men, possibly leading to an earlier discontinuation of these drugs. A systematic review by Generali *et al.* concluded that women have lower retention rates compared to men for TNFi but not for methotrexate (20). Moreover, women with PsA-initiating TNFi are less likely to achieve remission or minimal disease activity/very low disease activity than men (21, 22). A recent real-world study showed that while females with PsA manifested higher baseline disease activity and functional impairment, they experienced a less pronounced improvement than males with biological DMARDs (9). In fact, males had better 12-month responses and persistence with ustekinumab and TNFi than females. The same study highlighted gender differences in non-DMARD medications since females took non-steroidal anti-inflammatory drugs (NSAIDs) slightly less frequently than males but were more likely to be taking antidepressants (9). It is still unclear if the sex/gender differences observed in clinical manifestations, outcomes, and treatment responses of patients with PsA are also present in associated comorbidities. The aim of our review was to evaluate if differences may also be identified in the context of cardiovascular (CV) risk factors and CV diseases (CVD), which are recognized as the most frequent PsA comorbidities.

COMORBIDITIES

Cardiovascular risk factors

The analysis of the German BARMER health insurance database (23), comparing 11,984 people with PsA and DMARD therapy in 2021 with 119,840 sex- and age-matched controls, revealed that CV risk factors were more frequent in PsA than in controls. This applied to hypertension (57% *versus* 42% in controls), dyslipidemia (32% *versus* 27%), obesity (22% *versus* 11%), and diabetes (21% *versus* 13%). Men more often than women had dyslipidemia (36% *versus* 31%), CVD (21% *versus* 14%) and gout (8% *versus* 2.7%). Conversely, women more often had lung disease (22% *versus* 16%), depression (32% *versus* 21%), hypothyroidism (26% *versus* 9%), osteoporosis (18% *versus* 7%) and osteoarthritis (OA) (39% *versus* 28%). Of note, polypharmacy, consisting of PsA-specific, pain- and comorbidity-related medications, was significantly more frequent in PsA (49%) than in controls (17%) and higher in women (52%) than men (45%) (23).

PsA patients of Asian ethnicity share with Caucasians a significant burden of CV risk factors and CVD. An epidemiological survey of patients with PsA by the Japanese Society for Psoriasis Research from 2017 to 2020 revealed that 56.3% of the patients had a history of comorbidities including hypertension (35.9%; men 39.6%, women 29.2%), dyslipidemia (20.7%; men 22.9%, women 16.8%), diabetes mellitus (DM) (19.2%; men 21.5%, women 14.9%), hyperuricemia (13.5%; men 19.8%, women 2.2%), CVD (4.1%; men 5.0%, women 2.5%), and cerebrovascular disease (3.9%; men 4.1%, women 3.4%) (24). Globally, more men than women had comorbidities, especially hyperuricemia. Patients with PsO were less likely than patients with PsA to be affected by CVD. The cross-sectional study of Haque *et al.* compared comorbidities associated with PsA to those occurring in non-PsA forms of SpA (25). CV and metabolic comorbidities were increased in patients with PsA, with hypertension, coronary artery disease (CAD), and hyperlipidemia showing a significantly higher prevalence ($p<0.001$, $p=0.02$, and $p<0.001$, respectively) among patients with PsA compared to non-PsA SpA. Moreover, significantly ($p=0.03$) more patients with PsA (9.92%) met the criteria for metabolic syndrome (MetS) compared with those in the non-PsA SpA (4.68%). A higher prevalence of type II DM, gout, hyperuricemia, stroke, and CAD was found in men, while malignancy, depression, and hypertension were detected more commonly in women ($p<0.001$) in both the PsA and non-PsA SpA patients. Conversely, a population-based, cross-sectional study in Israel showed a higher prevalence of type II DM in female patients with PsA compared to age- and sex-matched patients without PsA (26).

These inconsistent results in the prevalence of type II DM in males and females with PsA may be related to the variable impact of several sex and gender-related factors involved in the development of diabetes in the two studies. In particular, steroid hormones largely contribute to sex-related diabetes susceptibility. In premenopausal women, estrogen protects them from type 2 DM by increasing insulin sensitivity and glucose-stimulated insulin secretion, thus producing lower fasting glucose levels compared to men (27). In addition, women are less insulin sensitive during the luteal phase of the menstrual cycle, while they are more prone, at menopause, to develop DM due to estrogen deficiency (27).

Waist circumference describes visceral adipose tissue (VAT) more accurately than body mass index (BMI) in women, thus representing a more reliable predictor of cardiometabolic diseases. This may be due to the more pronounced loss of muscle and bone mass with age and the greater increase in VAT after menopause in women compared with men of similar age (28). A genome-wide association study supported the role of VAT as a potential independent risk factor for type 2 diabetes in Caucasian females (29). Additionally, psychosocial risk factors such as level of education, socioeconomic and occupational status, and income have a stronger impact on the risk of developing type 2 DM in women compared with men (30). Hypertension is also a well-rec-

ognized comorbidity of PsA. A study that compared 611 patients with PsA and 449 with PsO revealed that hypertension was the most frequent comorbidity of PsA (37.1%) and was more prevalent than in patients with PsO alone (20%) (31). Similarly, dyslipidemia is more frequent in patients with PsA compared to patients with PsO [28% *versus* 13.5%; odds ratio (OR) 2.5; 95% confidence interval (CI) (1.7- 3.3)] and those with rheumatoid arthritis (RA) (32). An abnormal lipid profile with an unfavorable atherogenic ratio [reduction in high-density lipoprotein (HDL) cholesterol and elevated circulating triglyceride levels] has been reported in PsA (33, 34). An epidemiological, observational, single-center, and retrospective study did not find differences between males and females with regard to the frequency of dyslipidemia (39.4% and 39.4%, respectively), nor in the concentrations of total HDL, low-density lipoprotein cholesterol, and triglycerides (8). A study on 940 consecutive patients who attended an outpatient arthritis clinic (35) revealed a significantly higher BMI in those with PsA compared to RA ($p<0.001$) or ankylosing spondylitis (AS) ($p<0.001$). Accordingly, patients with PsA have a higher mean BMI than those with PsO, RA, and the general population (29.6, 27.9, 27.3, and 26.1, respectively).

Increasing age and female gender were risk factors for obesity in PsO and PsA patients (36). There was a tendency (0.06) for women with PsA to be obese (39.4%) compared to men (24.2%) (8). On the contrary, a systematic review by Coates *et al.* on sex-specific differences in PsA disclosed that among the ten studies reporting BMI values, only two found significantly higher BMI values in females than in males (7). Overweight and obesity have been reported to be associated with a reduced likelihood of achieving sustained minimal disease activity in PsA, regardless of treatment (34). Moreover, a prospective study identified obesity as an independent risk factor for failure to achieve minimal disease activity [hazard ratio (HR) 4.9 (3.04-7.87)] as well as for relapse over 24 months (37). Of note, in 41 patients with PsA and BMI ≥33kg/m^2, a median weight loss of 18.6% from baseline weight through a very low-energy diet

Table I - Cardiovascular risk factors in psoriatic arthritis.

Authors	Study design	Study population	Main results	Sex/gender differences in CV risk factors
Albrecht *et al*., 2023	Cross-sectional	11,984 patients with PsA and DMARD therapy and 119,840 sex- and age-matched controls	Hypertension, dyslipidemia, obesity, and diabetes were more frequent in PsA than in controls	Dyslipidemia, cardiovascular disease, and gout were more frequent in men than women. Females had lung diseases, depression, hypothyroidism, osteoporosis, and osteoarthritis more often than men
Kamiya and Ohtsuki, 2023	Annual epidemiological surveys	1641 (1032 men and 609 women) enrolled from 131 medical institutions	56.3% of PsA patients had a history of CV and comorbidities	Globally, more men than women had comorbidities, especially hyperuricemia
Haque *et al*., 2016	Cross-sectional	262 patients with PsA and 256 patients with non-PsA SpA	CV and metabolic comorbidities were increased in patients with PsA, compared to non-PsA SpA	Males showed a higher prevalence of diabetes, gout, hyperuricemia, stroke, and CAD, while malignancy, depression, and hypertension were detected more commonly in females in both the PsA and non-PsA SpA patients
Menis *et al*., 2023	Observational, single-center, retrospective	132 with a confirmed diagnosis of PsA according to the CASPAR criteria	Polyarticular form, enthesitis, were more frequent in females. Oligoarthritis, nail dystrophy, radiological axial involvement, and hyperuricemia were more frequent in males	No differences between males and females in the frequency of dyslipidemia and in the levels of total, HDL, LDL cholesterol and triglycerides. There was a tendency (0.06) for females with PsA to be obese compared to males

CV, cardiovascular; PsA, psoriatic arthritis; non-PsA SpA, non-PsA forms of spondyloarthritis; DMARD, disease-modifying antirheumatic drug; CAD, coronary artery disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein; CASPAR, classification criteria for psoriatic arthritis.

led to a significant improvement in disease activity scores at 6 months (38). Weight loss was associated with decreased levels of leptin and cytokines, in particular interleukin-23, partly explaining the anti-inflammatory effect of weight reduction in PsA (39). Whether such intervention is equally effective for males and females is a matter of speculation. MetS is a pathologic condition characterized by abdominal obesity, insulin resistance, hypertension, and hyperlipidemia that significantly increase the risk of CVD. The overall prevalence of MetS is significantly ($p<0.001$) higher in PsA (38%), compared to the general population (10-12%), RA (20%), and AS (11%), with no relationship with disease duration (40). All data are summarized in Table I.

Cardiovascular diseases

A meta-analysis including 11 observational studies showed a 43% increased risk of CVD in patients with PsA compared with the general population [pooled OR 1.43; 95% CI (1.24-1.66)] (41). The risk for myocardial infarction (MI), cerebrovascular diseases, and heart failure was increased by 68%, 22%, and 31%, respectively. All the studies included were adjusted for age and gender, and no separate analysis for males and females was performed. A study that investigated risk factors and the incidence of CVD in a cohort of patients with PsA over more than 35 years revealed that a significant proportion of patients developed CVD during the course of their disease (42). An estimated 19.8% of patients fulfilled the composite CV event (with components including MI, ischaemic stroke, revascularization, or CV death) by age 70, and 30.1% of patients by age 80. In each of the investigated decades (50, 60, 70, and 80), men had a higher estimated cumulative probability of developing primary CVD than women. Similarly to what has been observed in the general population (43), in patients with PsA, the increase in CVD generally occurs in women a decade later than in men (7th decade in women and 6th in men). A population-based cohort study showed that the incidence of ischaemic heart disease, peripheral vascular disease [adjusted relative risk (RR_{adj}) 1.27 (95 CI 1.05, 1.54) and RR_{adj} 1.40 (95 CI 1.02, 1.92), respectively], but not of cerebrovascular disease, as well as the three CV conditions combined, was significantly higher in a PsA cohort than in the general population, with no significant difference between PsA and PsO for any CV outcome (44). No separate analysis for males and females was performed. A meta-analysis of cohort studies that aimed to quantify and compare the risk of stroke for the major types of arthritis revealed that stroke risk was significantly increased in RA [relative risk (RR) 1.38, 95% CI 1.29-1.48], AS (RR 1.49, 95% CI 1.25-1.77), PsA (RR 1.33, 95% CI 1.22-1.45), and gout (RR 1.40, 95% CI 1.13-1.73), but not in OA (RR 1.03, 95% CI 0.91-1.16) (45). Age and sex subgroup analyses indicated that stroke risk in arthritis was similar for both sexes (men: RR 1.44, 95% CI 1.28-1.61; women: RR 1.47, 95% CI 1.31-1.66). The finding that OA confers no additional risk of stroke suggests that systemic inflammation (a key feature of arthritis but not OA) may be the direct cause of the increased risk of stroke. A systematic review and meta-analysis compared the risk for incident MI across five major types of arthritis (RA, PsA, AS, gout, and OA) in population-based and case-control studies (46). In studies adjusted for age and sex only, the risk of incident MI was significantly increased in RA (pooled RR 1.69, 95% CI 1.50-1.90), gout (pooled RR 1.47, 95% CI 1.24-1.73), PsA (pooled RR 1.41, 95% CI 1.17-1.69), OA (pooled RR 1.31, 95% CI 1.01-1.71). Associations with MI were attenuated for all types of arthritis in studies that adjusted for traditional risk factors but remained significant for RA, gout, and PsA. Among studies that provided sex-stratified estimates, the pooled RR for MI was significantly increased in both women and men (46). In conclusion, although the estimation of CVD risk in PsA is controversial and data are limited, recent studies have suggested that patients with PsA may have an increased risk of CVD in comparison with healthy controls. Sex and gender differences in CVD burden in patients with PsA are poorly investigated, but the few studies that reported sex-stratified

Table II - Cardiovascular diseases in psoriatic arthritis.

Authors	Study design	Study population	Main results	Sex/gender differences in CVD
Polachek *et al*., 2017	Meta-analysis of observational studies	11 studies, comprising 32,973 patients with PsA	There was a 43% increased risk of cardiovascular diseases in patients with PsA compared with the general population	No separate analysis for males and females was performed
Eder *et al*., 2016	Cohort analysis	1091 patients with PsA followed from 1978 to 2013 at the University of Toronto PsA clinic	19.8% of patients had composite CV event (MI, ischaemic stroke, revascularization or cardiovascular death) by age 70, and 30.1% of patients by the age of 80	Similarly to the general population, in patients with PsA the increase in CVD occurred in women a decade later than in men (7th and 6th decade, respectively)
Charlton *et al*., 2019	Population-based cohort study	6783 incident PsA patients identified in the UK Clinical Practice Research Datalink between 1998 and 2014	The incidence of ischaemic heart disease and peripheral vascular disease in the PsA cohort was significantly higher than in the general population	No separate analysis for males and females was performed
Liu *et al*., 2021	Meta-analysis of cohort studies quantifying and comparing the risk of stroke in RA, PsA, AS, gout, and OA	Studies included in the meta-analysis n=32	The stroke risk was significantly increased in RA, AS, PsA, and gout, but not OA	The stroke risk in arthritis was similar for both sexes
Schieir *et al*., 2017	Systematic review and meta-analysis of studies comparing the risk for incident MI in RA, PsA, AS, gout, and OA	Population-based and case-control studies included in the qualitative systematic review n=27; in the quantitative analysis n= 25	82% of studies reported higher risks for MI in arthritis groups than in the general population. After adjusting for traditional risk factors, the risk of IMA remained significantly increased in RA, PsA and gout	Among studies that provided sex-stratified estimates, the pooled relative risk for MI was significantly increased in both males and females

CV, cardiovascular; CVD, CV, cardiovascular disease; PsA, psoriatic arthritis; RA, rheumatoid arthritis; AS, ankylosing spondylitis; OA, osteoarthritis; MI, myocardial infarction.

estimates did not find differences in the risk of stroke and MI between the sexes. All data are summarized in Table II.

MORTALITY RISK RELATED TO COMORBIDITIES

The population-based study of Karmacharya *et al.* showed that the overall mortality in PsA was similar to that of the US general population, with no significant changes over 5 decades (47). Likewise, another large population-based study (48), which examined the association between PsA and all-cause mortality from a medical record database, detected no clinically relevant increase in mortality. Malignancy was the leading cause of death (26%), followed by ischemic heart disease (15.8%), DM (6.2%), and cerebrovascular disease (5.5%), consistent with the leading causes of death in the general population. Older age, male sex, lower socioeconomic status, increased BMI, increased Charlson comorbidity index scores, and history of PsO or hospitalization over 1 year before entry were positive predictors for mortality. These results are consistent with data from previous population-based studies (49, 50). On the contrary, a population-based, retrospective cohort study showed that patients with PsA had standardized excess mortality rates of 2.43 per 1000 population (51). Similarly, Wong *et al*., Ali *et al*., and Mok *et al*. found in PsA patients a 1.62-fold, 1.36-fold, and 1.59-fold increased mortality risk, respectively (52-54). An increased mortality risk has been observed in some clinic- and hospital-based studies, which probably captured a more active or severe form of PsA. A British study analyzing a cohort of 709 patients with severe PsA started on a TNFi reported that all-cause

mortality was significantly increased, mainly due to an excess of CVD deaths (55). Standardized mortality rates (SMR) for CVD (SMR 1.89; 95% CI 1.01-3.24), and especially for coronary heart disease (SMR 2.42; 95% CI 1.11-4.59), were significantly higher than in the general population but reached statistical significance only for men (SMR 2.80; 95% CI 1.13, 5.78). The incidence of malignancy was similar to that of the general population except for non-melanoma skin cancer, which was significantly increased overall and in women. A recent systematic review and meta-analysis (56), which included both population-based studies and hospital or specialist clinic registries, did not find a significant overall increase in the risk of all-cause mortality in patients with PsA. However, women but not men with PsA were found to have an increased risk of all-cause mortality. Of note, patients with PsA had a significantly higher risk of death from CV, respiratory, and infectious causes than the general population, but no increased risk of death due to malignancy. A nationwide registry-based cohort study explored mortality and causes of death among Norwegian patients with RA, PsA, and axSpA compared with the general population (57). While RA and axSpA were associated with increased all-cause mortality, in the PsA cohort as a whole, all-cause mortality was not higher than in the general population. Women, but not men, with PsA, had a slightly increased mortality rate (HR 1.10; 95% CI 1.00-1.21 among women and HR 1.02; 95% CI 0.93-1.11 among men).

Results from mortality studies among PsA cohorts have been inconsistent, mainly supporting either no or a slightly increased mortality risk. Overall, conflicting evidence exists about the effect of sex on all-cause

Table III - Mortality risk related to comorbidities.

Authors	Study design	Study population	Main results	Sex/gender differences in mortality risk
Karmacharya *et al*., 2021	Retrospective, population-based study from January 1, 2000 to December 31, 2017	From 484 residents with a potential diagnosis of PsA, 164 patients fulfilled the CASPAR criteria	Overall survival in PsA did not differ from the general population	No separate analysis for males and females was performed
Haddad *et al*., 2022	Analysis of a population-based database	5275 patients with PsA and 21,011 controls included and followed for 7.2±4.4 years	8.9% of patients died in the PsA group compared to 7.9% in the control group. Malignancy was the leading cause of death (26%), followed by ischemic heart disease (15.8%), as in the general population	Male sex in addition to older age, lower socioeconomic status, increased BMI, increased Charlson comorbidity index scores, and history of psoriasis or hospitalization in the year prior to entry were positive predictors for mortality
Fagerli *et al*., 2019	Observational study from the British Society of Rheumatology Biologics Register	709 patients with severe PsA starting a TNF inhibitor	The incidence of malignancy in PsA patients was similar to that of the general population	The incidence of NMSC was significantly increased overall and in females. All-cause mortality was increased as well as mortality from circulatory disease, particularly coronary heart disease in males.
Chaudhary *et al*., 2023	Systematic review and meta-analysis	Studies included n=19 (11 of PsA, 7 of AS, 1 of both).	PsA studies did not show an increased mortality compared to the general population	Females, but not males, with PsA had an increased risk of all-cause mortality
Kerola *et al*., 2022	Nationwide registry study	36,095 RA, 18,700 PsA and 16,524 axSpA patients	Compared with the general population, RA and axSpA patients, but not PsA patients, had decreased survival	Females but not males with PsA had a slightly increased all-cause and cardiovascular mortality rates

PsA, psoriatic arthritis; AS, ankylosing spondylitis; RA, rheumatoid arthritis; axSpA, axial spondyloarthritis; NMSC, non-melanoma skin cancer; CASPAR, classification criteria for psoriatic arthritis; BMI, body mass index.

and CV mortality risks in patients with PsA. These mixed results may be related to the different study designs, case definitions, and genetic and geographical variability across the investigated populations. All the data are summarized in Table III.

DISCUSSION AND CONCLUSIONS

Recent research has identified a higher CV burden in patients with PsA compared to the general population. Meanwhile, focusing on gender and sex differences has emerged as a priority in several areas of medicine, including CV risk factors and diseases (58). The literature supports the presence of differences between the sexes in PsA patients, mainly in clinical characteristics, disease impact, and response to pharmacological treatments. However, while the role of CV comorbidities in patients with PsA has recently been increasingly studied and recognized, the impact of sex and gender differences in CV risk factors and diseases has yet to be elucidated. Our review showed conflicting results in the prevalence of CV risk factors and mortality in males and females with PsA.

The only metabolic parameter that several studies found increased exclusively in males with PsA is uricemia. Accordingly, gout, an inflammatory arthropathy caused by hyperuricemia and the deposition of monosodium urate crystals in and around joints, is more common in male patients with PsA than in females (8, 23-25). Of note, gout augments the risk of CVD in PsO, as suggested by a population-based study from Taiwan, which demonstrated that patients with PsO and gout had a significantly higher risk for CVD compared to those with PsO alone (59). Hyperuricemia is involved in the pathogenesis of CV disease by inducing endothelial dysfunction, which is a central mechanism in prompting the atherosclerotic process (60). Kymball *et al.* reported that CV comorbidity may be in part driven by smoking and alcohol habits as well as obesity in males with PsA (61, 62). The treatment of PsA should be aimed at the management of symptoms and comorbidities. This approach deserves more attention in light of two recent studies showing that the risk of developing CVD and being hospitalized for CV comorbidities in patients with PsA remains high, despite advances in the therapeutic armamentarium (63, 64). The pathogenesis of CVD in PsA depends on several interrelated variables. These include traditional CV risk factors, both modifiable (*e.g.*, hypertension, dyslipidemia, DM, and obesity) and non-modifiable (*e.g.*, gender, age, and genetic predisposition). Chronic underlying inflammation is thought to play a role in the pathogenesis of atherosclerosis in PsA, acting independently and/or synergistically with traditional risk factors. For this reason, control of disease activity, as is routinely recommended, is expected to lower CVD in patients with PsA. Conventional and biologic DMARDs have been shown to reduce CVD risk in RA and SpA, with a positive effect on lipid profile, carotid intima-media thickness and insulin resistance (65) in PsA patients. Moreover, mental health disorders (*e.g.*, depression and anxiety) also have a substantial prevalence, with a high risk of incident depression in the PsA population (66). A vast body of literature demonstrated that depression and CVD, including CAD, MI, stroke, and atrial fibrillation (AF), were associated with each other, with the relationship being bidirectional (67). In fact, the occurrence of depression can worsen CV morbidity and mortality, while pharmacological treatment of depression positively impacts CVD outcomes (68). Several biological (inflammation, endothelial and platelet dysfunction, genetic predisposition, homeostatic imbalance between the sympathetic and parasympathetic systems, hypothalamic-pituitary-adrenal axis activation), behavioral (physical exercise, and smoking), and psychosocial factors share mechanisms involved in the bi-directional link between depression and CVD. Moreover, studies suggest the existence of gender-specific differences in biological responses to mental stress due to a peculiar neuroendocrine setup. The European Alliance of Associations for Rheumatology (EULAR) group has published recommendations for

managing the CV risk in inflammatory arthritis, including PsA (69). In general, CVD risk management involves the determination of the patients' CV risk profile using different variables, including gender, age, smoking status, blood pressure, lipid values, and DM status, incorporated in risk prediction algorithms such as the Framingham risk score (FRS), which calculates the 10-year risk of CVD events. When the FRS exceeds the value of 10% for fatal or non-fatal CVD events, preventive interventions such as lifestyle changes and management of risk factors, such as the use of lipid-lowering drugs, are recommended. However, the existing risk prediction models that can identify those subjects from the general population that can benefit from primary prevention of CVD have been shown to inaccurately estimate the CVD risk in RA (69).

Consistently, a population-based cohort study (70), which compared the observed incidence of CVD events with that predicted by the FRS in newly diagnosed PsA patients, found that the FRS underestimated the true CV risk. In particular, a 10-year cumulative incidence rate for CVD of 17% was observed, which was about twice as high as that predicted by FRS. This underscores the need for further research on CVD risk assessment tools specific to PsA patients (71). Notably, the INTERHEART study has shown that FRS underestimates the female risk of CAD (72). EULAR recommends that all patients with PsA undergo a CVD risk assessment at least once every 5 years to identify risk factors for CVD and that preventive treatment be implemented as needed. Moreover, the choice of pharmacological intervention is crucial for the management of CV comorbidities. Several treatment options are available to treat PsA, including DMARDs and symptomatic drugs such as glucocorticosteroids (GCs) and NSAIDs. EULAR recommends a cautious prescription of NSAIDs in PsA patients with documented CV risk factors or CVD based on a meta-analysis that showed that both non-selective NSAIDs and COXIBs have adverse effects on CVD outcomes in patients with RA and PsA (69, 73). Similarly, the GC dosage should be kept to a minimum and tapered in case of remission or low disease activity. It is widely recognized that high-dose GCs may increase the risk of CVD, but it is still unclear whether this increase also applies to lower GC doses. A population-based cohort analyzed medical records from 87,794 adults with immune-mediated inflammatory diseases and no prior CVD registered at family practices in the United Kingdom Clinical Practice Research Datalink between January 1998 and March 2017 (74). After a year, the overall absolute risk of CVD doubled for individuals using a daily dose of less than 5 mg of prednisolone and was 6 times higher for users of 25 mg or greater. The study highlighted strong dose-dependent increases in the risk of all-cause CVD, atherosclerotic diseases, heart failure, AF, and abdominal aortic aneurysm, regardless of the underlying immune-mediated disease, its activity, and duration. Higher dose-response estimates in men than in women and for AF and heart failure compared to other types of CVD were detected. This review suggests that the evaluation of sex- and gender-specific aspects of CV comorbidities in PsA is in an early phase of development. Future perspectives should include, as a central step, the implementation of a disease- (focused on PsA) and sex-specific CVD risk prediction model.

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.

Conflict of interest

The authors declare no potential conflict of interest.

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