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Expert Review

Does Age Matter in Psoriatic Arthritis? A Narrative Review

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ABSTRACT. Psoriatic arthritis (PsA) affects approximately 0.8% of the general population. PsA, together with psoriasis (PsO), constitute psoriatic disease (PsD). Comorbidities play an important role in the clinical expression and treatment of PsD. Aging adds another level of complexity, partly because age directly accrues increasing risk of comorbidities, but also because of its complex interactions with several factors such as depression and social determinants. Aging seems to have a "paradoxical association" with cardiovascular comorbidities, for which the relative risk is more pronounced in younger patients with PsD. It also affects treatment decisions and treatment response in patients with PsD. Finally, there is convincing evidence that there are clinical, genetic, and histopathological differences between early- and late-onset PsA and PsO. Herein, we review the effect of age in patients with PsD, with a focus on PsA, highlighting the need to consider this factor in routine clinical practice as well as in research.

Key Indexing Terms: aging, comorbidities, psoriatic arthritis

Psoriatic arthritis (PsA) is an inflammatory condition affecting approximately 0.8% of the general population and approximately 10–30% of patients with psoriasis (PsO).[1] PsA is a highly heterogeneous condition with joint involvement, ranging from monoarthritis to severe destructive polyarthritis and arthritis mutilans. Joint involvement in PsA is often accompanied by characteristic clinical manifestations such as nail lesions, dactylitis, and enthesitis that help differentiate it from other forms of skin and joint disease.

Beyond direct musculoskeletal or dermatologic manifestations, other coexisting conditions (comorbidities) accumulate over the course of the disease. These may be linked to common mechanistic pathways, primarily inflammatory, or could occur independently of underlying inflammation. Therefore, this clinical syndrome may be better described as a composite, namely, *psoriatic disease* (PsD)[2]. The occurrence of comorbidities adds significantly to the burden of the disease, reducing quality of life (QOL),[3] increasing mortality (especially when cardiovascular [CV] comorbidities are present),[4] and affecting clinical response to treatment.[5]

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Aging adds another variable to this composite, partly because it is inherently a natural precondition for the accumulation of comorbidities. Age also interacts independently with various factors such as mental health, obesity, and work status,[6,7] all of which affect clinical expression and outcomes of PsA and PsO. Further, age influences therapeutic decisions, driven, for example, by concerns around polypharmacy and the increased potential for side effects and risks of drug interaction for concurrent conditions. Finally, there is evidence of clinical, genetic, and histopathological differences between early- and late-onset PsA and PsO.

In this narrative review, we explore the effect of age in PsD, with a focus on PsA, in 3 domains: (1) effect of aging on the type and frequency of comorbidities encountered; (2) treatment response and safety in older vs younger patients with PsD; and (3) differences between early- and late-onset PsA or PsO.

The effect of age on comorbidities in PsD

General aspects. In general, the presence of ≥ 2 long-term conditions, termed *multimorbidity*, increases with age in all people.[8] Further, studies have shown that patients with PsD suffer from multimorbidity at a younger age than expected.[9] Approximately half of the patients with PsO who are aged > 65 years may have ≥ 3 comorbid conditions.[10]

The majority of comorbidities in the context of PsD belong to the spectrum of cardiometabolic syndrome.[11] Thus, CV comorbidities are frequently present and in part driven by the higher prevalence of traditional CV risk factors such as hypertension, diabetes mellitus (DM), obesity, and hyperlipidemia.[12] Other clinical conditions, such as gastrointestinal manifestations, nonalcoholic fatty liver disease, osteoporosis, depression, and anxiety, have been described to occur more frequently than in the general population.[8,12,13] Superimposed on this are conditions

that constitute part of the spondyloarthritis spectrum, including inflammatory bowel disease and uveitis.

Husted et al analyzed clinical databases from a university hospital and observed that 42% of PsA patients with a mean disease duration of 13 years had ≥ 3 comorbidities.[3] These patients were more likely to be older and female.[3] In a population-based study from a Scandinavian registry for patients with PsA treated with biologics, patients with larger numbers of comorbidities were older, predominantly female, and had longer disease duration and increased BMI.[5] Further, in a prospective longitudinal PsA cohort,[14] it was found that the prevalence of almost all commonly described comorbidities (hypertension, coronary artery disease [CAD], DM, chronic obstructive pulmonary disease) increased with age; this is in contrast to what was observed for Crohn disease and depression, for which the prevalence was higher in younger patients.[14]

Metabolic and CV comorbidities in PsD. Data from many studies have shown that, compared to the general population, metabolic-related comorbidities are more common in patients with PsD; their prevalence is 21–62%, 28–47%, and 11–20% for hyperlipidemia, hypertension, and type 2 DM, respectively.[12,15,16,17] The increased prevalence and incidence of DM described in PsA is partially linked to the high prevalence of obesity and insulin resistance, although shared genetic links between PsA and DM have also been implicated.[18]

The aberrant metabolic profile of these patients with PsD could partially explain the increased risk of CV disease (CVD) and mortality.[4,8,19] Large cohort studies indicate that patients with PsA exhibit increased risk for major adverse CV events (MACEs), including myocardial infarction (MI)/acute coronary syndrome and stroke.[20,21,22] A previous systematic literature review (SLR) and metaanalysis confirmed the high risk of patients with PsA for MI.[23] In PsO, although subject to ongoing debate,[24] it appears that more severe inflammatory skin disease is associated with a significantly increased risk for MACE (including MI, stroke, and CV mortality), independent of other CVD risk factors.[25]

The effect of age on the risk of CVD-related comorbidities in patients with PsD is of particular interest. In a previous study, age > 55 years—along with male sex and longer disease duration—was an adverse prognostic factor for increased risk of coronary atherosclerosis in patients with PsA.[26] Another study[27] reported that PsA patients with more severe carotid atherosclerosis were of older age, and were more likely to be obese, smokers, and to have DM, hypertension, and dyslipidemia. After adjusting for age and sex, only white blood cell count and higher erythrocyte sedimentation rate and Disease Activity Index for PsA score were associated with more severe atherosclerosis. However, these associations were attenuated following adjustment for traditional risk factors for CVD. Interestingly, disease duration was not associated with more severe atherosclerosis in this study.[27]

Li et al used data from longitudinal population-based electronic medical records and observed an increase in the incidence of MACE and CVD events with age.[21] On the other hand, Ogdie et al demonstrated that the relative risk for MACE, MI, stroke, and CV mortality—in contrast to the absolute risk—was higher in younger people with PsA, compared to age- and sex-matched population controls without PsA.[22] An SLR and metaanalysis[23] also confirmed that the relative risk for MI in patients with inflammatory arthritis (IA) tended to be higher in younger patients.

In PsO, in which metabolic syndrome appears to start at an earlier age compared to the general population,[9,28] disease duration was recognized as an independent factor for MACEs.[24] However, as observed for PsA, the relative risks for MI and MACEs are higher in younger patients.[22,25]

The reasons for the increased relative risk of CVD-related comorbidities in younger patients with PsD are not clear. It has been argued that patients with earlier disease onset might have more severe disease (as discussed below) and also that there might be a "survivorship effect," as increased mortality at a younger age means some of these patients are not available for analysis at a later stage.[25] A plausible explanation could be also that younger patients' perception about the disease and its psychosocial impact (as discussed below) might contribute to the higher risk for CVD-related comorbidities.

Common mental health comorbidities in PsD. Depression and anxiety are noteworthy in PsD; they are common comorbidities, with prevalence ranging (in PsA and PsO, respectively) between 9–27% and 10–62% for depression[12,15,29,30,31,32] and 6–37% and 13–43% for anxiety.[15,30,31,32] Their occurrence is associated with demographic variables (eg, working status, sex); subjective and objective variables of higher disease activity, such as higher number of actively inflamed joints, disability, pain, and fatigue[32,33]; and features of decreased QOL, such as sleep disturbance.[34]

The effect of age on the presence of depression in PsD appears to have an inverse relationship compared to the other comorbidities. In a prospective PsA cohort, it was found that depression was more common in younger patients.[14] The same was also observed in PsO. In a large, multicenter study it was shown that the frequency of most comorbidities (including those related to metabolic risk) increased with age, but this was not the case with depression.[35] Additionally, in another large population-based cohort study,[36] it was found that the HR for depression was greater in younger patients with PsO. The distribution pattern of depression frequency relative to age appears to be diverse compared to that observed in the general population. Although there is some controversy around this topic,[37,38,39] in the general population it seems that depression might have a U-shaped distribution, reaching low levels in middle-aged individuals and then rising with increased age.[40]

The increased rates of depression in younger patients with PsO is replicated in reports focusing on QOL, which is significantly impaired in these patients.[35,41] Younger individuals with PsO report more depression and experience related problems (eg, sleep problems, discrimination) more often, further affecting their well-being and behavioral and psychosocial status.[9,35] In fact, older patients (> 60 yrs) exhibited lower scores in the Dermatology Life Quality Index (DLQI), indicating lower impact of PsO on their everyday lives.[35,41]

Older patients with PsD: Should treatment be different?

The effect of age on treatment response and safety in patients with PsD has not been extensively examined so far, with inferences drawn mainly from the rheumatoid arthritis (RA) literature. Surprisingly, data for conventional disease-modifying antirheumatic drugs (DMARDs) are very limited. Neither the efficacy nor safety profile of methotrexate seem to be affected by age,[42] although some authors report limited toxicity of this drug in older patients with RA, possibly reflecting more cautious patient selection (channeling bias), less aggressive dose escalation, or less exposure overall to the drug.[43] Similarly, the safety profile of leflunomide did not seem to be altered in elderly individuals in a long-term retrospective study.[44]

With regard to biologic DMARDs, data about the efficacy of anti–tumor necrosis factor (TNF) treatment in older individuals with RA are not in absolute agreement.[45,46,47,48] In general, it appears that treatment with these agents is not significantly less effective in older patients with RA compared to younger ones, and that the safety profile between the 2 groups is largely comparable.[46,48,49]

In patients with PsD, the limited data appear to be more consistent. Costa et al reported that treatment with anti-TNF agents had good efficacy, comparable—indirectly—with that seen in younger patients with PsA.[50] Similarly, in a long-term observational study, etanercept (ETN) and adalimumab (ADA) were safe and efficacious for the treatment of elderly patients (aged ≥ 65 yrs) with PsO and PsA[51]; and in a large retrospective study, Migliore et al[47] reported that infliximab, ADA, and ETN were safe options in people with IA (including patients with RA, ankylosing spondylitis, and PsA) who were aged ≥ 65 years. Additionally, data from phase III trials indicate that in older patients with PsO, ADA and ETN had comparable efficacy as in younger patients.[52,53] Of note, in these studies, no differences were noted in relation to sex across age groups.

Additionally, it seems that treatment with TNF inhibitors (TNFi) in patients with PsA has beneficial effects on age-related CV surrogate markers such as atherosclerosis, as assessed by the number of atherosclerotic plaques and measurement of intima-media thickness.[54,55,56] This is reflected in improved CV outcomes in patients treated with anti-TNF compared to those who were not.[57]

Data for biologic drugs targeting the interleukin (IL)-23/17 axis are limited. A posthoc analysis of 3 phase III studies in PsO indicated that secukinumab is both effective and safe in elderly patients (aged ≥ 65 yrs), regardless of sex.[58] Two small observational studies[59,60] indicated that the p40 IL-23 inhibitor ustekinumab (UST) also appears safe and effective for older patients with PsO. Data for the effect of anti–IL-17 drugs on CV outcomes are still lacking, although in a recent large study, risk of atrial fibrillation or major CV outcomes was similar between patients treated with TNFi or UST.[61]

Despite Janus kinase (JAK) inhibitors being relatively new drugs in the therapeutic armamentarium, there are several studies regarding their safety and efficacy in older individuals with RA. Data from 2 phase III RA studies indicated that baricitinib (JAK1/2 inhibitor) exhibits comparable efficacy between younger and older people, although a higher percentage of the latter group reported adverse events and serious infections.[62] For tofacitinib (JAK1/3 inhibitor), pooled data from phase III and open-label extension studies for RA showed that although responses were of similar magnitude, adverse effects were numerically higher in patients aged ≥ 65 years.[63] Herpes zoster infection, one of the main predicted side effects of this drug category, is reported more often in elderly individuals and those on concurrent treatment with corticosteroids.[64] Of note, corticosteroids are used less commonly in PsA compared to RA. Future studies will be helpful in demonstrating whether the observed increased age-related adverse effects of JAK inhibitors in the RA population are replicated in PsA.

Late- vs early-onset PsA and PsO: Different entities?

Evidence suggests that late-onset disease, defined as age over a given but as yet nonstandardized age, is not as rare as previously thought, representing up to 25% of incident PsA.[65] There are a number of studies investigating late-onset PsA and its differences with PsA diagnosed in younger individuals[66,67,68,69,70] (Table 1). Of note, there is no uniformly accepted age cut-off to distinguish early- vs late-onset PsA, so studies are not directly comparable. Punzi et al observed that individuals in whom PsA was diagnosed > 60 years old had more aggressive disease, as assessed by the number of joints involved, inflammation levels at baseline, and outcome after 2 years, compared to those with onset ≤ 60 years of age.[68] These results were confirmed in a previous study reporting higher pain and fatigue scores, more comorbidities (hypertension, DM, and CAD) and increased inflammatory markers in patients with late-onset PsA compared to those with early-onset disease (albeit defined here as age < 65 yrs).[66] This study also reported less dactylitis and nail involvement as well as decreased PsO Area Severity Index (PASI) scores in these patients. A different clinical picture consisting of extremity swelling and pitting edema, along with higher inflammatory markers, have also been reported in late-onset PsA.[71] Finally,

Table 1. Features that have been suggested to associate with late-onset psoriatic disease[a].

Late-onset PsA	Late-onset PsO
More common in females	Less frequent family history of PsO
Less common presence of HLA-C*06	Less common presence of HLA-Cw6
Longer PsO duration	More common presence of comorbidities
More aggressive disease	Less severe skin involvement
↑ levels of inflammation markers	
↑ mortality risk	
↑ baseline mSS	
↑ BMI	
↓ dactylitis	
↓ nail involvement	
↓ PASI scores	

[a] Cut-off for late-onset disease differs between studies. mSS: modified Steinbrocker score; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; PsO: psoriasis.

another recently published study with PsA patients followed longitudinally,[72] also showed that there were some differences between late-onset (cut-off was set to 50 yrs old) and patients with early-onset PsA. Patients with late-onset PsA were likely to be male and HLA-C*06–positive and had higher BMI, longer duration of PsO, and higher modified Steinbrocker score (mSS) at baseline[72]; after 5 years of follow-up, they had worse outcomes, exhibiting higher mean mSS and a trend for higher mean active joint count.[72] In patients with psoriatic spondylitis, it was observed that patients aged > 40 years had a different clinical picture compared to the younger ones, with unilateral sacroiliitis, concurrent polyarthritis, and silent axial disease being more commonly observed in the former, although outcome scores including Bath Ankylosing Spondylitis Disease Activity Index and Bath Ankylosing Spondylitis Functional Index were comparable.[70] Further, a study examining the mortality risk in PsA[73] reported that this risk was associated with increased age at disease diagnosis.

Overall, we conclude that late-onset PsA exhibits some distinct clinical characteristics compared to earlier PsA presentation. These characteristics, along with the worse disease outcomes reported, could be attributed to different genetic profiles,[69,72] increased comorbidities and polypharmacy, or possibly to a reluctance of commencing biologic treatments in this older PsA subpopulation.[66] Further, alterations in the immune system that come with aging, known as immunosenescence,[74] and accumulated epigenetic modifications[75] might also contribute to these observations. It remains an open question whether the age at PsO onset plays a role in the observed differences between early- and late-onset PsA.

Definitions of early- and late-onset PsO (EOP and LOP, respectively) are also rather unclear, with different cut-offs used. It has been suggested that EOP and LOP are 2 distinct subsets of the disease[76] (Table 1). Clinical, genetic, and histopathological differences have been observed between these 2 groups. It has also been suggested that family history of PsO, association with HLA-Cw6, and more severe skin involvement are more frequent in patients with EOP,[76,77,78] whereas higher epidermal CD4+/CD8+ ratio[78] and alterations in the genes of *IL-1β* and *IL-1R1* are linked with LOP.[79,80] Also, the presence of comorbidities such as DM and thyroiditis was more commonly seen in LOP.[78] People with LOP were less likely to be on treatment with biologics[78]; this was even more noticeable in those with very late–onset PsO (> 70 yrs old).[81] Further, posthoc analysis of data from 4 clinical trials of ETN for PsO reported that treatment was more effective in patients with EOP compared to those with LOP.[76,82] Finally, using a relatively low age cut-off (20 yrs old), a cross-sectional study reported that patients with EOP were significantly more anxious than those with LOP,[83] although the reverse has been reported by other studies.[76,78,82] Depression levels and their relationship to age of onset require further investigation as the results are conflicting,[78,82,83,84] possibly attributed to differences in the age cut-off levels and the use of different measures of depression.[76] Also, the subjective perception of individuals about their condition and its effect might be different between EOP and LOP.[85] Phan et al reported that for the same PsO severity, as assessed by PASI score, the effect on QOL, as measured by the DLQI, was less in older people.[81]

Discussion

It is could be hypothesized that PsD involves some kind of "premature" aging, manifesting comorbidities (many of which are CVD-related) more commonly and/or earlier than expected, leading to decreased QOL and increased mortality.[9] This could be attributed to the increased and chronic inflammatory burden[26,27] associated with these conditions, although it appears that there is also a complex interplay with other factors commonly observed in PsD, such as obesity and depression, which are themselves also related to inflammation.[86]

It is also important to highlight that the elderly population (commonly defined as age > 65 yrs) is usually underrepresented in randomized clinical trials (RCTs), at least due in part to increased concomitant comorbidities and related treatments, which serve as common exclusion criteria.[51] Thus, it is debatable whether RCT results are generalizable to this specific population group in wider clinical practice. Reassuringly, limited data from observational studies have largely confirmed the efficacy and safety of the major drugs used in rheumatology, including biologic treatments, for older individuals. These accumulating real-world data could be used by experts formulating treatment recommendations for IA to offer guidance for the treatment of specific population subgroups, such as the elderly.

We acknowledge that definite conclusions cannot be easily drawn from the currently available literature. There are several reasons for this. First, there is no universal agreement about the most appropriate age cut-off value that should be used to define this group. Even then, analysis of age as a dichotomous or continuous variable adds another level of complexity and variability.[87] Second, disease duration may confound the assessment of the effect of age on outcomes in PsA and PsO. Third, it is possible that late-onset PsA or PsO has distinct clinical and genetic characteristics. Therefore, especially in studies examining the effect of aging in these diseases, patients with late-onset disease should be analyzed as a separate group. Finally, although PsA and PsO share common pathogenetic mechanisms, it remains to be defined whether the effects of various characteristics such as age, obesity, and others, are the same in these 2 conditions.

In conclusion, it seems that accumulation of comorbidities in people with PsD is age-related but also multifactorial, as many interactions have been observed between their occurrence (eg, mental illness, CVD) and aging (Figure 1). Prospective, multicenter studies, stratifying patients with PsD according to specific clinical phenotypes and different demographic (eg, age, obesity), social (eg, alcohol, smoking, employment), and psychological (eg, depression, anxiety) variables, may allow for better understanding of the complex interplay between these factors. Current treatment strategies are not significantly affected by the age of the patient, although much of the data, especially regarding newer drugs, are derived from studies in RA and may not be equally applicable to PsA. Finally, age of onset of PsD seems to be an important covariate that might affect the clinical and laboratory manifestations of the disease and its outcomes. Aging and

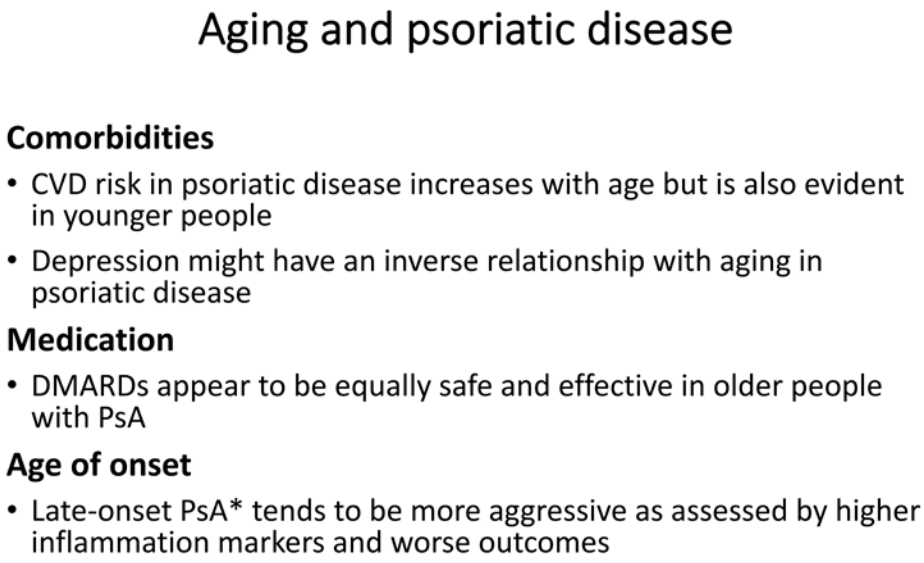

Figure 1. Association of aging with psoriatic disease. * Usually age > 60–65 years, but there is no clearly defined cut-off. CVD: cardiovascular disease; DMARD: disease-modifying antirheumatic drug; PsA: psoriatic arthritis.

age of disease onset should thus be considered in routine clinical practice, as well as in the research setting.

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