Does age matter in Psoriatic arthritis? A narrative review

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Keywords: Psoriatic arthritis, Ageing, comorbidities

Competing interest: none declared

Funding: no specific funding has been received for this study

Running head: Ageing and psoriatic arthritis

Ethical approval: Not required

Abstract

Psoriatic arthritis (PsA) affects about 0.8% of the general population. Together with psoriasis is termed psoriatic disease. Comorbidities play an important role in the clinical expression and treatment of psoriatic disease. Ageing adds another level of complexity, partly because age directly accrues increasing risk of comorbidities, but also due to its complex interactions with several factors such as depression and social determinants. Ageing seems to have a "paradoxical association" with cardiovascular comorbidities for which the relative risk is more pronounced in younger patients with psoriatic disease and also to affect treatment decisions and response in patients with psoriatic disease. Finally, there is convincing evidence that there are clinical, genetic and histopathological differences between young- and late- onset PsA and psoriasis.

Herein, we review the effect of age in patients with psoriatic disease, with a focus on PsA, highlighting the need to consider this feature in routine clinical practice as well as in the research domain.

Introduction

Psoriatic arthritis (PsA) is an inflammatory condition, affecting about 0.8% of the general population and approximately 10-30% of the patients with psoriasis (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 co-existing conditions (comorbidities) accumulate over the course of the disease. These may be linked to common mechanistic pathways, primarily inflammatory, or could occur independent of underlying inflammation. This clinical syndrome may be better described therefore as a composite namely, 'psoriatic disease' (2). The occurrence of comorbidities adds significantly to the burden of the disease; it reduces quality of life (3), increases mortality, especially when cardiovascular comorbidities are present (4) and impacts on clinical response to treatment (5).

Ageing adds another variable to this composite, partly as it is inherently a natural precondition for the accumulation of comorbidities. Age also interacts independently with various other factors such as mental health, obesity and work status (6, 7), that affect clinical expression and outcomes of PsA and psoriasis. Furthermore, age influences therapeutic decisions, driven for example by concerns around polypharmacy, increased potential for side effects and risks of interactions with medications for concurrent conditions. Finally, there is evidence that there are clinical, genetic and histopathological differences between young- and late- onset PsA and psoriasis.

Through this narrative review, we explore the impact of age in psoriatic disease, with a focus in PsA, in three domains: i. effect of ageing on the type and frequency of comorbidities encountered, ii. treatment response and safety in older versus younger patients with psoriatic disease and iii. differences between early- and late- onset PsA or psoriasis.

i. The effect of age on Comorbidities in Psoriatic disease

General aspects

In general, the presence of two or more long term conditions, termed multimorbidity, increases with age in all people (8). Furthermore, studies have shown that patients with psoriatic disease suffer from multimorbidity at a younger age than expected (9). About half of patients with psoriasis who are above 65 years old may have 3 or more comorbid conditions (10).

The majority of comorbidities in the context of psoriatic disease belong to the spectrum of cardiometabolic syndrome (11). Thus, cardiovascular comorbidities are frequently present and in part driven by the higher prevalence of 'traditional' cardiovascular risk factors like hypertension, diabetes, obesity, and hyperlipidaemia (12). Other clinical conditions, like gastrointestinal manifestations, non-alcoholic 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 comprise part of the spondyloarthritis spectrum, including inflammatory bowel disease and uveitis.

Husted et al. analysed clinical databases from a university hospital and observed that 42% of PsA patients with a mean disease duration of 13 years had 3 or more comorbidities. These patients were more likely to be older and female (3). In a population-based study from a Scandinavian registry for PsA patients treated with biologics, patients with larger numbers of comorbidities were older, predominantly female, and had longer disease duration and increased body mass index (BMI) (5). Furthermore, in a prospective longitudinal PsA cohort (14) it was found that the prevalence of almost all commonly described co-morbidities (hypertension, coronary artery disease, diabetes, chronic obstructive pulmonary disease) increased with age, in contrast to what was observed for Crohn's disease and depression for which the prevalence was higher in younger patients (14).

Metabolic and cardiovascular comorbidities in psoriatic disease

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

The aberrant metabolic profile of these patients could partially explain the increased risk of cardiovascular disorders (CVD) and mortality (4, 8, 19). Large cohort studies indicate that PsA patients exhibit increased risk for major adverse cardiovascular events (MACE) including myocardial infarction (MI)/acute coronary syndrome and stroke (20-22). A recent systemic literature review (SLR) and meta-analysis confirmed the high risk of PsA patients for MI (23). In psoriasis, although subject to ongoing debate (24) it appears that more severe inflammatory skin disease is associated with a significant increased risk for MACE (including MI, stroke and cardiovascular mortality), independent of other CVD risk factors (25).

The effect of age on the risk of CVD-related comorbidities in patients with psoriatic disease is of particular interest. In a recent study, age greater than 55 years old, along with male gender and longer disease duration, were adverse prognostic factors 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, more likely to be obese, smokers, and to have diabetes, hypertension and dyslipidaemia. After adjusting for age and gender, only white blood cell count, higher ESR and Disease Activity for PsA (DAPSA) 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.

Li et al interrogated 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 cardiovascular mortality – in contrast to the absolute risk- is higher in younger people with PsA, compared to age- and sex-matched population controls without PsA (22). An SLR and meta-analysis (23) also confirmed that the relative risk for MI in patients with inflammatory arthritis tended to be higher in younger patients.

In psoriasis, in which metabolic syndrome appears to start at an earlier age compared to the general population (9, 28), duration of disease 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 people 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 in 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 Psoriatic Disease

Depression and anxiety are noteworthy in psoriatic disease; they are common comorbidities, with prevalence ranging, in PsA and psoriasis, respectively, between 9-27% and 10-62% for depression (12, 15, 29-32) and 6-37% and 13-43% for anxiety (15, 30-32). Their occurrence is associated with demographic variables (e.g working status, gender), subjective and objective parameters of higher disease activity such as higher number of actively inflamed joints, disability, pain and fatigue (32, 33) and features of decreased quality of life, such as sleep disturbance (34).

The effect of age on the presence of depression in psoriatic disease appears to have an inverse relationship compared to the other comorbidities. Based in a prospective PsA cohort it was found that depression was more common in younger patients (14). The same was also observed in

psoriasis. In a large, multicentre 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 hazard ratio for depression was greater in younger patients with psoriasis. 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 (37-39), 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 psoriasis is replicated in reports focusing on quality of life, which is significantly impaired in these patients (35, 41). Younger individuals with psoriasis report more depression and experience related problems (e.g sleep problems or discrimination) more often, which further impacts on well-being and behavioural and psychosocial status (9, 35). In fact, older (>60 years old) patients exhibited lower scores in Dermatology Life Quality Index (DLQI), indicating lower impact of psoriasis on their everyday lives (35, 41).

ii. Older patients with psoriatic disease. Should treatment be different?

The effect of age on treatment response and safety in patients with psoriatic disease 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), while some authors report limited toxicity of this drug in older patients with RA, possibly reflecting more cautious patient selection (channelling 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 aged individuals in a long-term retrospective study (44).

As regards biologic DMARDs, data about the efficacy of anti-TNF treatment in older individuals with RA are not in absolute agreement (45-48). In general it appears that treatment with these

agents is not significantly less effective in older RA patients, compared to younger ones and that the safety profile between the two groups is largely comparable (46, 48, 49).

In patients with psoriatic disease, 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 and adalimumab were safe and efficacious for the treatment of elderly patients (aged≥65 years) with psoriasis and PsA (51) and in a large retrospective study, Migliore et al. (47) reported that infliximab, adalimumab and etanercept were safe options in people with inflammatory arthritis (including patients with RA, ankylosing spondylitis and PsA) who were aged 65 years or more. Similarly, data from phase 3 trials indicate that in older patients with psoriasis, adalimumab and etanercept had comparable efficacy as in younger patients (52, 53). Of note, in these studies, no differences were noted in relation to gender, across age groups.

Additionally, it seems that treatment with TNF-inhibitors in PsA patients has beneficial effects on age-related cardiovascular surrogate markers like atherosclerosis, as assessed by number of atherosclerotic plaques and measurement of intimal medial thickness (54-56). This is reflected in improved cardiovascular outcomes in patients treated with anti-TNF, compared to those who did not (57).

Data for biologic drugs targeting the IL-23/-17 axis are limited. A post-hoc analysis of three phase 3 studies in psoriasis indicated that secukinumab is both effective and safe in elderly (≥ 65 years-old) patients, irrespective of gender (58). Two small observational studies (59, 60) indicated that ustekinumab also appears safe and effective for older patients with psoriasis. Data for the effect of anti-IL-17 drugs on cardiovascular outcomes are still lacking, while in a recent large study, risk of atrial fibrillation or major cardiovascular outcomes was similar between patients treated with TNF-inhibitors or the p40 IL-23 inhibitor ustekinumab (61).

Despite 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 two phase 3 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 3 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-old (63). Herpes zoster infection, one of the main predicted side-effects of this drug category, is reported more often in aged people and those on concurrent treatment with corticosteroids (64). Of note, the latter 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.

iii. Late- versus early- onset Psoriatic arthritis and Psoriasis. Different entities?

Evidence suggests that late-onset disease, defined as age over a given but as yet non standardised 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 (66-70) (Table-1). Of note, there is no uniformly accepted age cut-off to distinguish younger- *versus* late-onset PsA, so studies are not directly comparable. Punzi et al observed that individuals in whom PsA was diagnosed after 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 before 60 years age (68). These results were confirmed in a recent study reporting higher pain and fatigue scores, more comorbidities (hypertension, diabetes mellitus and coronary artery disease) and increased inflammatory markers in patients with late-onset PsA compared to those with young-onset (albeit defined here as less than 65 years old) (66). This study also reported less dactylitis, nail involvement and decreased Psoriasis 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, another recently published study, followed-up longitudinally PsA patients, also showed that there were some differences between late-onset (cut-off was set to 50 years old) and young-onset PsA patients. The former were less

likely to be male and HLA-C*06 positive and they had higher BMI, longer duration of psoriasis and higher modified Steinbrocker score (mSS) at baseline (72). After 5 years of follow-up, late-onset PsA patients 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 older than 40 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 (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were comparable (70). Furthermore, a study examining the mortality risk in PsA (73) reported that this risk was associated with increased age at disease diagnosis.

Collectively, we conclude that late-onset PsA exhibits some distinct clinical characteristics compared to younger PsA presentation. This, along with the worse disease outcomes reported by some authors in this group of patients, could be attributed to different genetic profiles (69, 72), increased co-morbidities and polypharmacy or possibly a related reluctance to commence biologic treatments in this older PsA subpopulation (66). Furthermore, alterations that come with ageing in the immune system, also known as immunosenescence (74), and accumulated epigenetic modifications (75) might also contribute to these observations. It remains an open question whether the age at the onset of psoriasis plays a role in the observed differences between early- and late-onset PsA.

Definitions of early- and -late- onset psoriasis (EOP and LOP, respectively) are also rather unclear, with different cut-offs used. It has been suggested that EOP and LOP are two distinct subsets of the disease (76) (Table-1). Clinical, genetic and histopathological differences have been observed between these two groups. It has been suggested that family history of psoriasis, association with HLA-Cw6 and more severe skin involvement are more frequent in patients with EOP (76-78), while 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 like diabetes mellitus and thyroiditis was more commonly seen in LOP (78). People with LOP were less likely to be on treatment with biologics (78), which was even more noticeable in those with very late onset psoriasis (>70 years old) (81). Furthermore, post hoc analysis of data from four clinical trials of etanercept for

psoriasis 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 years 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, 82-84), which could be 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 impact might be different between EOP and LOP (85). Phan et al reported that for the same psoriasis severity, as assessed by PASI score, the effect on quality of life, measured by the DLQI was less in older people (81).

Discussion

It is could be hypothesized that psoriatic disease comprises some kind of "premature" ageing, manifesting co-morbidities, many of which are CVD-related, more commonly and/or earlier than expected leading to decreased quality of life 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 psoriatic disease, such obesity and depression, which are themselves also related to inflammation (86).

It is also important to highlight that the elderly population (commonly defined as > 65 years-old) is usually under-represented in randomized clinical trials (RCT), at least partly due 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 inflammatory arthritis to offer guidance for the treatment of specific population subgroups like the elderly.

We acknowledge that definite conclusions cannot be easily drawn from the currently available literature. There are several reasons for this: firstly, 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). Secondly, disease duration may confound the assessment of the effect of age on outcomes in PsA and psoriasis. Thirdly, it is possible that late-onset PsA or psoriasis have distinct clinical and genetic characteristics. Therefore, especially in studies examining the effect of ageing in these diseases, late-onset patients should be analysed as a separate group. Finally, although PsA and psoriasis share common pathogenetic mechanisms, it remains to be defined whether the effect of various characteristics, like age, obesity and others, have the same impact in these two conditions.

In conclusion (Figure-1), it seems that accumulation of comorbidities in people with psoriatic disease is age-related but also multifactorial, as many interactions have been observed between their occurrence (e.g mental illness, cardiovascular disease) and ageing. Prospective, multicentre studies, stratifying patients with psoriatic disease according to specific clinical phenotypes and different demographic (e.g age, obesity), social (e.g alcohol, smoke, employment) and psychological (e.g depression, anxiety) parameters, may allow for better understanding of the complex interplay between these factors. Current treatment strategies are not significantly affected by the age of the patients, 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 psoriatic disease seems to be an important covariate that might affect the clinical and laboratory manifestations of the disease and its outcomes. Ageing and age of disease-onset should thus be considered in routine clinical practice, as well as in the research setting.

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Figure legends

Figure-1: Association of ageing with psoriatic disease. CVD: cardiovascular, DMARDs: disease modifying anti-rheumatic drugs, PsA: psoriatic arthritis. * no clearly-defined cut-off. Usually > than 60-65 years-old.

Features of late onset psoriatic disease*	
Late onset psoriatic arthritis	**Late onset psoriasis**
More common in females	Less frequent family history of psoriasis
Less common presence of HLA-C*06	Less common presence of HLA-Cw6
Longer duration of psoriasis	More common presence of comorbidities
More aggressive disease	Less severe skin involvement
↑ levels of inflammation markers	
↑ mortality risk	
↑ baseline modified Steinbrocker score	
↑ BMI	
↓ dactylitis	
↓ nail involvement	
↓ PASI scores	

Table 1: Features that have been suggested to associate with late onset psoriatic disease. * cut-off for "late-onset" differ between studies.

Ageing and psoriatic disease

Comorbidities

- CVD risk in psoriatic disease increases with age but is also evident in younger people
- Depression might have an inverse relationship with ageing in psoriatic disease

Medication

- DMARDs appear to be equally safe and effective in older people with PsA

Age of onset

- Late-onset PsA* tends to be more aggressive as assessed by higher inflammation markers and worse outcomes