Psoriasis: Targets and Therapy

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REVIEW

Comorbidity in Adult Psoriasis: Considerations for the Clinician

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Abstract: Psoriasis is associated with several comorbidities ranging from cardiovascular comorbidity and mental disorders to other immune mediated inflammatory diseases. However, most of these co-morbidities are often overlooked or diagnosed late. Furthermore, evidence suggests that comorbidities are undertreated. Here, we provide an overview of comorbidities in psoriasis and present a simple rundown of considerations of relevance to the clinician. We hope that this review may raise clinicians' awareness of comorbidities in psoriasis and provide simple guidance regarding screening tools and treatment decisions in psoriasis with comorbidities.

Keywords: psoriasis, comorbidities, clinician guidelines

Introduction

Among dermatologists and other healthcare professionals (HCPs) involved in the treatment and care of psoriasis patients, awareness is growing that psoriasis is not solely a skin disease. A large body of research has been devoted to the study of psoriasis and its comorbidities. However, it remains to be demonstrated whether this translates into an increased awareness and effort to treat these comorbidities in routine clinical practice. The clinician has an impressive armamentarium for examining comorbidities associated with psoriasis, but how the information obtained when deploying this diagnostic arsenal is brought to best clinical use remains to be established; When should screening and examinations for comorbidities be initiated, and in which instances should a change of treatment be considered of skin and joint symptoms due to comorbidities?

We therefore attempted to provide an overview of considerations for the physician when treating patients with psoriasis in order to enhance patient-centric care in those who suffer from multiple concomitant conditions. See Table 1 and Figure 1 for comprised overview of comorbidities and relevant considerations.

Cardiovascular Comorbidity

Psoriasis, particularly severe psoriasis,[1] is associated with an increased risk of cardiovascular disease (CVD); acute myocardial infarction,[1,2,3] abdominal aortic aneurysm,[4] stroke,[5–7] aortic valve stenosis,[8] atrial fibrillation,[6] and coronary artery disease.[9,159] The increased incidence of traditional cardiovascular risk factors in psoriasis patients with psoriasis, e.g., hypercholesterolemia, metabolic syndrome and obesity, directly contributes to the overall increased risk of CVD in patients with psoriasis.[10,13–15,19] Metabolic syndrome represents a group of cardiovascular risk factors; including hypertension, dyslipidemia, obesity and insulin resistance.[13,16] The syndrome has been associated with an increased risk of CVD beyond the sum of the singular risk factors, and studies have shown an association between metabolic syndrome and psoriasis.[13]

The main cause of increased CVD risk in psoriasis patients is still being studied: Mechanistic studies indicate that chronic inflammatory processes drives premature atherosclerosis through shared immunopathogenic mechanisms in psoriasis patients.[17] Evidence of systemic inflammation in psoriasis[18,21] and an association of psoriasis with premature coronary artery disease has been reported.[9,159,160] However, other studies rebut these chronic inflammatory theories, and a final link between

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Table 1 Considerations for the Clinician Regarding Psoriasis Comorbidities

All Below	-Inform the Patient of the Increased Risk
Cardiovascular disease	- Screen patients with moderate-to-severe psoriasis, annually or biennially, for cardiovascular risk factors with a validated screening tool - Consider multiplying the score of the cardiovascular risk factor by up to 1.5 and treating them thereafter Cardiovascular risk factors: - In addition to pharmaceutical intervention and CVD prophylaxis, it is recommended to guide psoriasis patients to dietary intervention, physical training, weight loss to achieve a BMI <25, moderate alcohol intake, smoking cessation and weight loss programmes in accordance with local provisions - Attention toward obesity, diabetes type 2, hypertension and dyslipidemia
Psoriatic arthritis	- Be aware of joint symptoms including swelling, redness and soreness - Be aware of night - time axial pain, or pain in the Achilles tendon or plantar fascia - Screen with PEST (does not detect axial arthritis), ToPAS, PASE, EARP, PURE-4 or similar, or conduct annual individual assessments - Refer to a rheumatologist when PsA is suspected or positive scores on screening tools are obtained
Other immune - modulated diseases	Regarding IBD: - Awareness of postprandial stomach pain/cramps, weight loss, frequent diarrhea, blood or mucus in stool, rectal pain or bleeding, rectal tenesmus or bowel urgency ⇒ Referral to gastroenterologists if any of these symptoms are present - Awareness towards screening patients with psoriasis with severe skin disease since they bear the highest IBD risk
Mental disorders	- Be aware that longstanding undertreated psoriasis may increase the risk of depression, anxiety and other psychological challenges and illness - related stress - Screening tool Anxiety and Depression Scale ● Referral to psychiatrist if affirmative to ≥4 questions Goldberg A&D scale, or affirmative to ≥2 questions on Goldberg A&D subscale
Other comorbidities	- Be aware of fatigue - Be aware of the risk of impaired socioeconomic status in patients with psoriasis and assist the patient in obtaining guidance to avoid psoriasis-related decreased work productivity - Address reduced health-related quality of life and assist the patient in building knowledge and obtaining guidance as per local possibilities

Notes: We emphasize that this table lists considerations for the clinician regarding psoriasis comorbidities. For definite recommendations, we refer to guidelines regarding local and systemic treatment for psoriasis.[24–27,49,78,161]

psoriasis and CVD has yet to be established.[22] Thus, it remains elusive to which extent the increased risk of CVD may be due to an increased prevalence of CV risk factors or whether it is caused by psoriasis itself due to, for example, chronic low-grade inflammation.

Further to this, it has been shown that despite an increased risk of coronary calcification in patients with psoriasis, these patients do not have a poorer prognosis than similar patients without psoriasis. Thus, after adjusting for other predictors, no increased risk of CV events and death was demonstrated in patients with psoriasis.[9]

Nonetheless, despite a vast body of literature showing an overall increased risk of CVD in patients with psoriasis, it has been found, that patients with psoriasis and CVD risk factors receive less cardio-protective medical therapy than controls without psoriasis, or no such treatment at all.[23] Danish guidelines recommend that patients with psoriasis are treated according to the general guidelines for CVD risk factors, as a minimum.[24] It has been suggested that CVD risk factor scores should be multiplied by 1.5 for patients with severe psoriasis.[11]

The European Academy of Dermatology and Venerology's (EADV) guidelines recommend screening patients with psoriasis upon systemic treatment and local treatment for CVD risk factors every six and twelve months, respectively.[25]

The European Society of Cardiology recommends CVD screening as a minimum and that the severity of the skin disease is taken into account if it is uncertain whether treatment for CVD risk factors should be initiated.[26]

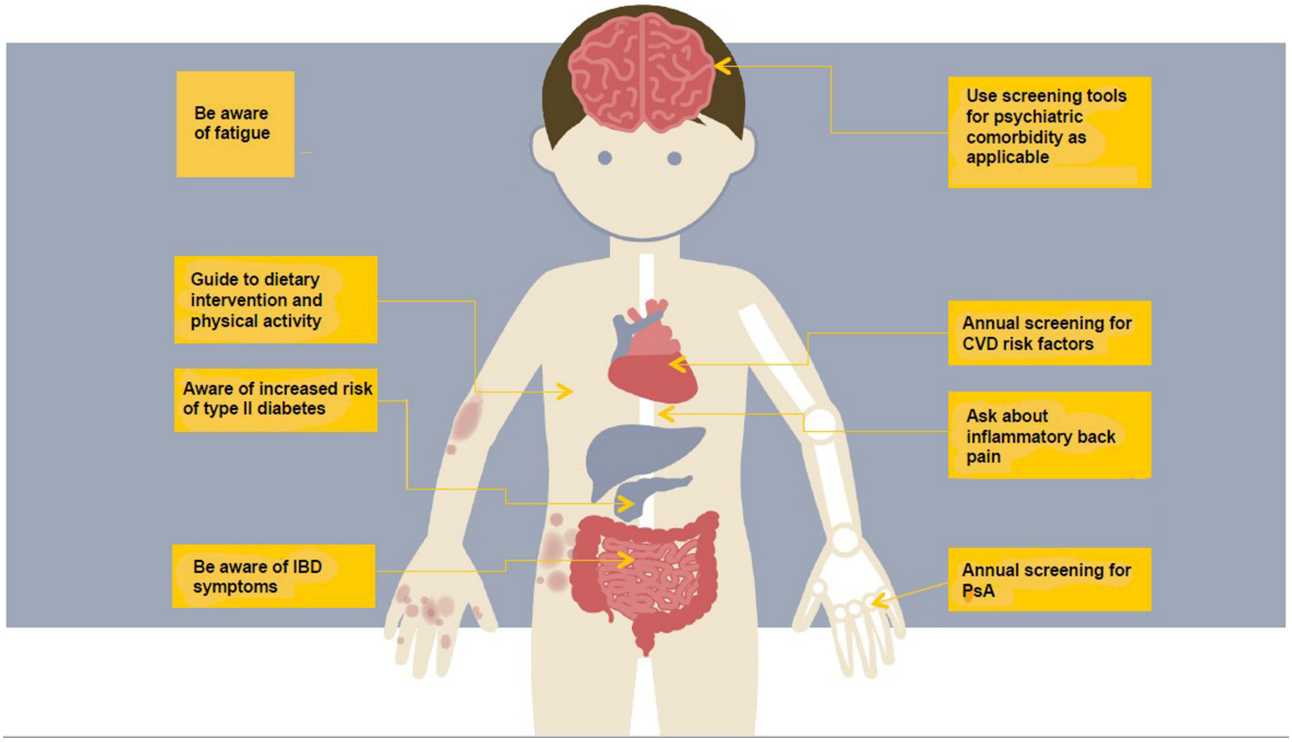

Figure 1 A brief overview of for the clinician's consideration, regarding psoriasis comorbidities. The reader is referred to Table 1 and the main text for further perspectives.

Furthermore, the British guideline recommends CVD risk assessment in adults with severe psoriasis at presentation and further cardiovascular assessment every five years.[27]

Even greater attention to co-morbidities may be warranted in young patients with psoriasis and patients with psoriasis with severe skin affection since they carry the largest risk of CVD.[3]

Adequate treatment of psoriasis activity has been suggested to reduce the risk of CVD. More specifically, biologic therapy, including TNF-alfa inhibitors, has been associated with, eg a reduced risk of major cardiac events, reduced coronary artery disease progression, and reduced vascular inflammation.[12,28–32] Other studies have found no reduction in risk of CVD, vascular inflammation or cardiovascular events.[33–37]

Lastly, studies have shown that dietary intervention and physical exercise may have a positive effect on the cardiovascular risk profile and the severity of psoriasis.[38,39] Improvement of the cardiovascular risk profile by dietary means is clinically relevant. In short, it is recommended to eat higher volumes of fruit, vegetables, fish, wholegrain and polyunsaturated fats (fish, nuts etc.). Simultaneously, consuming only limited amounts of red and processed meat and refined carbohydrates is recommended.[26]

Psoriatic Arthritis

Psoriatic arthritis (PsA) is an inflammatory, musculoskeletal, heterogenic disease that may include arthritis, enthesitis, dactylitis, axial disease and skin/nail disease.[40] PsA has a well-established association with psoriasis.[14,42–47] Approximately 70–80% of patients develop psoriasis before PsA. Simultaneous debut of psoriasis and PsA is seen in 10–15%, whereas PsA develops first in 10–15%.[48–50]

Importantly, a diagnostic delay of as little as 6 months is associated with peripheral joint damage and worse long-term functional outcome, and earlier treatment initiation is associated with a better clinical outcome.[51,52] Inhibition of structural damage progression has been shown for several biologics and underpins the need to initiate effective disease-modifying therapy in patients with active PsA.[53] Several effective treatments with proven efficacy in both psoriasis and PsA are available.[77]

The prevalence of PsA among patients with psoriasis depends on many factors, including geography, ethnicity and the applied diagnostic criteria. However, the prevalence of PsA is generally estimated to fall in the 20–30% range.[14,42–44,56–59]

Like psoriasis, PsA heavily affects patients' quality of life.[40,45,60] Despite the relatively extensive prevalence of PsA and its negative effect on quality of life, PsA remains difficult to diagnose and is therefore potentially undertreated.[44,45,61,62,63,64]

PsA is typically diagnosed clinically according to "CASPAR" (Classification for Psoriatic Arthritis) criteria.[64] These criteria include both clinical and paraclinical parameters. To diagnose a patient with PsA, the patient must have inflammatory joint disease and score at least three points on other parameters.[64,65] Despite widespread use of these criteria, PsA remains difficult to diagnose and differentiate from osteoarthritis.[66]

Even though PsA is a clinical diagnosis, numerous strides have been made to establish a single biomarker that may independently assist the physician in easily diagnosing PsA. Multiple candidate biomarkers have been suggested and investigated, but unfortunately none have so far proven successful in diagnosing PsA.[162,163] Aside from biomarkers and the clinician's assessments - screening questionnaires, ultrasound, x-ray and/or magnetic resonance imaging (MRI) may be used in the diagnostic process.[46,62,68,71,72,163]

A PsA screening questionnaire appears to be a feasible tool in the busy daily clinical practice of many dermatologists.[54] As to the choice of questionnaire, several validated questionnaires have shown good diagnostic performance.[54] These include for example Psoriasis Epidemiology Screening Tool (PEST),[71] The 4-item Psoriatic Arthritis Uncluttered Screening Evaluation (PURE-4),[72] Early Arthritis for Psoriatic Patients (EARP),[69] and Toronto Psoriatic Arthritis Screening (ToPAS).[73] However, the number of items, domains included, and how questions are presented varies between these questionnaires. A specific screening questionnaire can currently not be recommended unambiguously as the most useful for clinical practice in favor of the other listed above.

It is also relevant for the dermatologist to be aware that particular psoriasis phenotypes have been associated with an increased risk of PsA, these include nail dystrophy, perianal/intergluteal psoriasis and scalp lesions.[164] Furthermore, a high number of actively involved joints, either tender or swollen (defined as five or more); radiographic damage (joint destruction), in particular if there is also inflammation; elevated acute phase reactants; and extra-articular manifestations, in particular dactylitis reportedly predict a more aggressive disease progression.[76]

Successful/efficient treatment of patients with coexisting psoriasis and PsA requires a therapeutic approach with proven efficacy in both skin and joints. Methotrexate may be effective for psoriasis and peripheral PsA, and several biologics have been approved for both psoriasis and PsA, whereas others have not been approved or have failed to show efficacy in either skin or joints.[77] Combination therapy or combing systemic and adjunctive local therapy or, for example, non-steroid anti-inflammatory drugs (NSAIDS) is often required. Specific treatment recommendations may be found in the following references and must be aligned with national healthcare system-specific regulations.[77–79,161]

Thus, many well-tolerated and efficacious therapies are available. Priority should therefore be given to identifying PsA patients so that they may start relevant treatment, which decreases the risk of structural skeletal damage and potentially lowers the risk of long-term centralised pain syndromes.[45,165]

Other Immune-Mediated Diseases

Psoriasis is associated with an increased prevalence of other immune-mediated disease (IMID)s.[81,82] The mechanisms of this association are not fully understood, but many factors, for example, genetic and environmental factors, have been suggested.[82,83] Among other immune-mediated diseases associated with psoriasis are inflammatory bowel disease (IBD), rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome and systemic sclerosis.[14,81,82,84–87] We discuss only a selection of these below.

IBD, especially Crohn's disease (CD) and ulcerative colitis (UC), have been associated with psoriasis in several studies.[81,90–94,102] Psoriasis patients have been estimated to have a higher risk of CD than the general population, and the same applies to a lesser extent to UC.[14,91–94] This risk is particularly pronounced in patients with severe psoriasis.[91] Furthermore, IBD is typically diagnosed before psoriasis.[95]

Coexistence of IBD and psoriasis may require a combined effort by gastroenterologists and dermatologists as treatment modifications may often be necessary. Tumour necrosis factor inhibitor (TNFi) together with ustekinumab

have been approved for both IBD and psoriasis and may be a good treatment option. However, up to 5% of patients treated with TNFi may develop paradoxical TNFi-induced psoriasis.[96–98] Other treatment modalities used in IBD may not be effective in psoriasis, for example, vedolizumab and azathioprine. The widely used anti-interleukin (IL)-17 drugs for psoriasis are not recommended for patients with IBD.[77,94,99–101]

Mental Disorders

Mental disorders are well-known comorbidities to psoriasis, especially depression and anxiety.[14,103–109] The prevalence of mental disorders in patients with psoriasis is not easily estimated and has been estimated at 10–60%.[14,110–112]

Intuitively, being diagnosed with psoriasis may have a negative effect on a patient's mental state.[106,113–115] Additionally, an independent, increased risk of mental illness in patients with psoriasis has been shown.[105–108,115,116] The negative effect on quality of life paired with the independent, elevated risk of mental disorders has potential to create a vicious cycle.[108,117] However, of notice, the psychological impact does not always correlate with the clinical severity of the ongoing skin disease.[14] Moreover, psoriasis patients have an elevated risk of suicidal ideation and behaviour (SIB), including a potentially increased risk of completing suicide.[118–122]

Despite the well-established association between mental disorders and psoriasis, and the fact that early diagnosis of mental illness has proven important, mental disorders in patients with psoriasis are underrecognised and undertreated.[108,109,123,124] Screening for mental health disorders, especially in patients with psychiatric risk factors, and consideration of psychotherapy of patients with psoriasis are thus imperative.[105,111,117]

Multiple depression and mental health disorder questionnaires exist to aid the diagnosis of mental health disorders. Some well-known questionnaires are: the Beck Depression Inventory and the Spielberger State-Trait Anxiety Scale I–II.[118,166,167] To our knowledge, no specific questionnaires have proven superior.

However, dermatologists should be particularly attentive to females and younger and more severely affected patients with psoriasis since they have been shown to carry an increased risk of mental illnesses (including SIB).[105,113,118,122,127]

Studies have shown that biological treatment of psoriasis decreases symptoms of depression; however, treatment of psoriasis does not always equal better odds for remission of mental disorders.[14,106,109,116,121,128]

Other Comorbidities

Fatigue has been associated with multiple inflammatory diseases, including psoriasis.[129] Fatigue may interfere profoundly with a patient's daily life.[129] The severity of fatigue correlates with the severity of psoriasis.[130] Studies have shown that up to 50% of patients with psoriasis had considerable fatigue.[129] Biological drugs used for the treatment of psoriasis consistently reported a small-to-moderate beneficial effect on fatigue independently of the type of drug.[131] In addition to optimal treatment of underlying disease activity, exercise programmes and supervised self-management programmes with cognitive-behavioural therapy or mindfulness may be beneficial in coping with fatigue.[132–134]

Ocular comorbidities, such as uveitis, has been found in a number of psoriasis patients.[135–137] Ocular comorbidities are important to diagnosis and treat, and can easily be overlooked.[135] The risk is elevated especially in patients with concomitant PsA as studies have shown that patients with PsA and severe psoriasis have a 2.4-fold higher risk of developing non-infectious uveitis than the general population.[138] Clinicians may screen patients with for example the Ocular Manifestations in Psoriasis Screening questionnaire.[135] Clinicians may also be aware of clinical characteristics of uveitis, including: eye redness, eye pain, light sensitivity, blurred vision, floaters and decreased vision.[139]

Epidemiologic studies have indicated that psoriasis is associated with an increased risk of various types of cancer and increased cancer mortality, although results are conflicting and no full consensus on the matter exists.[140] Lymphoma has been studied for its possible association with psoriasis. Thus, some studies have found a slightly increased risk of lymphoma and cutaneous lymphoma among patients with psoriasis,[141–146] whereas other studies have found that when systemic psoriasis treatment was taken into account, the risk was not significantly higher than in the general background population.[147]

Some studies report that psoriasis is associated with a lower socioeconomic status in general and some that a correlation exists between the severity of psoriasis and a lower socioeconomic status.[148–150] Clinicians should therefore

consider adopting a holistic approach to patients with psoriasis to avoid patients establishing a negative spiral by which disease causes further socioeconomic decline.[168]

Patients with psoriasis have also been shown to have an increased risk of non-alcoholic fatty liver disease (NAFLD), which in part may be attributed to the increased risk of metabolic syndrome and obesity in psoriasis patients[151–154] and the existence of a Hepato-Dermal Axis has been proposed.[155]

Furthermore, NAFLD has been associated with reduced eGFR in psoriasis patients.[156]

Treatment-Related Pitfalls

A noteworthy number of psoriasis patients are treated with biologics and other systemic immunomodulators, which may, in some cases, alter the risk of certain illnesses. Such illnesses should not be considered comorbidities to psoriasis and consequently not directly related to psoriasis. However, although not in scope for this review, they remain important considerations for the clinician and are therefore mentioned briefly below: Biologics do not seem to increase the risk of cancer, although some studies have indicated a slightly higher risk for TNF-inhibitors than for newer biologics and methotrexate.[157] The risk of non-melanoma skin cancer is elevated for both anti–TNF agents and non-biologics and may be affected by previous treatment with psoralen and ultraviolet A (PUVA) therapy and photo-therapy.[169]

Methotrexate is among the first-line systemic treatment options for psoriasis in many countriesMethotrexate treatment may be associated with a number of side-effects including an increased risk of liver damage.[151,170]

Biologics are associated with slightly increased risk of infections, and anti-IL17 agents are associated with an increased risk of mucocutaneous candidiasis.[171] Risks of serious infections are generally slightly higher for patients on anti-TNF than on anti-IL17 and anti-IL23 agents.[158] Increased awareness of infections and candidiasis and prescription of relevant treatment are warranted in patients on biologics and other immunomodulators.[158,171]

Conclusion

Psoriasis is associated with an increased risk of several comorbidities including cardiovascular disease, psoriatic arthritis, mental disorders and other immune-mediated diseases, and these associations require the treating physician's attention.

A holistic approach to patients with psoriatic disease is recommended; a focus not only on skin symptoms but on all aspects of the disease including comorbidities may improve disease management and prevent long-term mental and physical impairment. Arguably, attention to comorbidities may improve the quality of life of some patients with psoriasis. Managing all comorbidities associated with psoriasis may constitute a considerable task for the clinician. The use of screening tools may possibly help discover patients in need of referral to other specialties or for further investigation.

Throughout this article, we have attempted to provide relevant considerations and guidance for physicians providing care for patients with psoriasis.

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