PSORIASIS: BEYOND THE SKIN

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Disclosure: Dr Ryan has acted as a consultant, advisor, or speaker for AbbVie, Dermira, Dr Reddy's, Janssen, Lilly, Medimetriks, Novartis, Regeneron-Sanofi, and UCB. Dr Kelly has declared no conflicts of interest.
Received: 27.07.17 **Accepted:** 19.12.17
Citation: EMJ. 2018;3[1]:90-95.

ABSTRACT

Previously considered as just a skin condition, psoriasis has come to be regarded as a complex, systemic inflammatory disorder that affects multiple other systems. The association of psoriasis with cardiovascular disease and the increased prevalence of cardiovascular risk factors in psoriasis patients is increasingly recognised. Psoriasis is also associated with sleep apnoea, chronic obstructive pulmonary disease, chronic kidney disease, and liver disease. Increased awareness by both patients and physicians of these associations is vital to maximise optimal health outcomes in psoriasis patients. Screening for associated comorbidities and implementation of appropriate interventions is necessary. Furthermore, there is a considerably increased prevalence of depression and anxiety in psoriasis patients that is often not detected by physicians. Patients should be opportunistically assessed and treated, or referred appropriately, for psychological and mental health issues. Further studies are required to expand our knowledge of the systemic manifestations of psoriatic disease, and to allow us to further improve the health outcomes of psoriasis patients.

Keywords: Cardiovascular risk, comorbidities, psoriasis, psoriatic arthritis (PsA).

INTRODUCTION

There is growing evidence that psoriasis is much more than just a disease of the skin, with several important systemic manifestations similar to those of other chronic inflammatory diseases. Psoriatic arthritis (PsA), an inflammatory arthritis, is a well-known extracutaneous manifestation of psoriasis. Other systemic manifestations of psoriasis have emerged over the last two decades. Psoriasis patients have a clinically significant increased risk of cardiovascular disease (CVD) and cardiovascular risk factors when compared with the general population.[1] There is also an increased prevalence of depression and anxiety among psoriasis patients.[2] Associations of psoriasis with chronic kidney disease (CKD), chronic liver disease, chronic obstructive pulmonary disease (COPD), and sleep apnoea have also been described.[3] Dermatologists should work in tandem with other specialists and primary care physicians to screen for these risk factors and treat them according to national and international guidelines.

An electronic search via PubMed and Google Scholar was undertaken for all studies regarding psoriasis-associated comorbidities. All randomised controlled trials, systematic reviews, meta-analyses, observational cohort studies, and case series were included; however, individual case reports were excluded. The results of the electronic search were analysed and are described below.

PSORIATIC ARTHRITIS

The most common extracutaneous manifestation of psoriasis is PsA. There is wide variation in the reported prevalence of PsA in psoriasis patients, varying from 6–42%.[4,5] Certain clinical features may suggest a slightly higher predisposition to PsA in patients, including scalp psoriasis, nail psoriasis (nail changes including pitting, onycholysis, onychoschizia, subungual hyperkeratosis, and oil spots), and a family history of PsA. Patterns of PsA include distal arthritis, asymmetric oligoarthritis, symmetric polyarthritis, arthritis mutilans, and spondyloarthritis. The average time from the manifestation of psoriasis to the onset of joint

disease is 7–12 years.[6-8] A delay in the diagnosis of PsA can impact on a patient's long-term outcome. Irreversible changes in the joint can occur within the first year of disease development in 40–60% of patients,[9] and therefore screening of psoriasis patients for PsA is pertinent at every visit. Patients should be asked about joint pain or back stiffness, particularly early in the morning or after a long journey. Morning stiffness lasting >30 minutes is a strong indicator of PsA.[10] Ideally a Psoriasis Epidemiology Screening Tool (PEST) questionnaire should be completed by psoriasis patients annually. There are no specific serological tests to confirm a diagnosis of PsA; however, radiography of joints can be useful to delineate the presence, extent, and pattern of joint damage. Radiographs, along with serology (rheumatoid factor and anti-cyclic citrullinated peptide), can also help to distinguish PsA from osteoarthritis or rheumatoid arthritis. All clinicians treating patients with psoriasis should not hesitate to refer them to a specialist.

CARDIOVASCULAR COMORBIDITIES

Beyond its association with PsA, the association between psoriasis and CVD has now been established and is an area of intensive research. There is considerable evidence that patients with moderate-to-severe psoriasis have an increased risk of conditions such as CVD, hypertension, hyperlipidaemia, obesity, diabetes, and metabolic syndrome.[1] Patients with psoriasis have higher rates of mortality when compared to the general population.[11] A seminal cohort study using the UK General Practice Research Database (GPRD) reported that patients with psoriasis had an increased adjusted relative risk for myocardial infarction after controlling for other cardiovascular risk factors, particularly in those with more severe psoriasis and in younger patients.[12] A similar study using the GPRD found the incidence of CVD risk factors, such as hypertension, diabetes, obesity, and hyperlipidaemia, was increased in psoriasis patients compared with the general population.[13] Recent studies examining the association of psoriasis and these cardiovascular risk factors have supported these findings.[14,15]

Studies have demonstrated that psoriasis patients are more likely to be obese; however, it is unclear whether obesity predates or is a consequence of psoriasis. A prospective study that followed 78,626 women for 14 years showed a positive correlation between increasing BMI and risk of incident psoriasis,[16] suggesting obesity may precede the development of the disease. A recent study examining children and adolescents with psoriasis showed that they are more obese compared to age and sex-matched controls. There was also a tendency towards central adiposity in psoriatic patients in this study.[17] Psoriasis patients have an increased incidence of dyslipidaemia, and important differences have been observed in lipoprotein size, particle composition, and cholesterol efflux mechanisms. These patients also have a lower level of high-density lipoprotein and an increased level of low-density lipoprotein; the proportion of these lipoproteins in psoriasis patients is similar to that of diabetic patients.[17] In psoriatic patients with an adverse lipid profile, statin therapy should be considered. Physicians should be vigilant to observe for liver toxicity in those patients prescribed both methotrexate and a statin.

A meta-analysis and systemic review suggested that the prevalence of diabetes was increased in psoriasis patients, with an odds ratio of 1.53 for mild disease and 1.97 for severe disease.[18] Percutaneous absorption of topical steroid treatments can lead to worsening of blood sugar control and diabetes. In rare cases, patients can develop iatrogenic Cushing's syndrome.[19] In a large meta-analysis looking at the prevalence of hypertension in 309,469 psoriasis patients, the odds ratio for hypertension in patients with mild psoriasis was 1.30, and 1.49 in those with severe psoriasis compared with healthy controls.[15]

Excess alcohol consumption and smoking are independent risk factors for the development of CVD and both are increased in psoriasis. A meta-analysis of 28 studies showed an association between psoriasis and current or former smoking, and suggested that smoking is an independent risk factor for the development of psoriasis.[20] Biochemically, cigarette smoking has been shown to increase the number of circulating T helper (Th)17 cells in the peripheral blood of psoriasis patients compared to non-smokers. Th17 cells are proposed to be one of the main drivers of psoriasis.[21]

All psoriatic patients require an annual lipid profile and glycated haemoglobin (HbA1c) or fasting glucose assessment for dyslipidaemia and diabetes or insulin resistance. They should have opportunistic blood pressure monitoring when attending appointments. There should be a low threshold to start cardioprotective medications; notably, beta blocker therapy for CVD can lead to

flares in psoriasis and is therefore best avoided. There are no dedicated guidelines for the management of coronary risk in patients with psoriasis and physicians should be mindful that scoring systems, such as the 10-year Framingham risk score, could significantly underestimate cardiovascular risk in these patients.[22]

There is debate as to the ability of biologic therapies to treat psoriatic comorbidities other than PsA. Some psoriatic registries have shown a reduced hazard ratio (0.26; 95% confidence interval: 0.12–0.56) for myocardial infarction for those patients treated with anti-tumour necrosis factor-α inhibitors compared with those not treated.[23] This was believed to be related to a reduction in inflammation and subsequent atherosclerosis. Following this, a double-blind placebo-controlled psoriasis trial of adalimumab that used positron emission tomography and computed tomography combined to measure vascular inflammation, did not show reduced vascular inflammation in adalimumab-treated patients.[24] Further studies are required to delineate the association of reduced cardiovascular risk in psoriasis patients treated with biologic therapies.

OTHER COMORBIDITIES

Psoriasis and Sleep Apnoea

There is increasing evidence showing an association between psoriasis and obstructive sleep apnoea (OSA). The association of OSA and psoriasis was first described in 1999.[25] Shalom et al.[26] looked at the prevalence of OSA in 12,336 patients with psoriasis and compared them to 24,008 age and sex-matched controls. The study found a significant association between psoriasis and OSA, which was still present following multivariate analysis adjusting for sex, ethnicity, BMI, COPD, hypothyroidism, hyperlipidaemia, and peptic ulcer disease.[26] A Danish study also looking at a population of psoriasis patients found that patients with more severe psoriasis and those with PsA had a greater incidence of OSA.[27] Karaca et al.[28] performed sleep studies on 33 patients with psoriasis and detected an increased frequency of OSA in psoriasis patients compared to that of the normal population.

Psoriasis and Chronic Obstructive Pulmonary Disease

A meta-analysis and systemic review identified four observational studies, with a total of 13,418 patients, looking at the association of COPD and psoriasis.[29] They found that psoriasis patients were at a much greater risk of developing COPD than the general population. This association was stronger among patients with more severe psoriasis.[29] The high prevalence of smoking among psoriasis patients further increases their risk of COPD.[20]

Psoriasis and Chronic Kidney Disease

Patients with moderate-to-severe psoriasis have an increased risk of moderate-to-advanced CKD independent of traditional risk factors. An epidemiological study using a UK primary care electronic medical records database identified 143,883 psoriatic patients and compared them to 689,702 patient controls. Patients who had received phototherapy, systemic, or biologic therapy were defined as having severe psoriasis. Patients with psoriasis were found to be more likely to develop CKD compared to controls. This increased risk was significant even after controlling for traditional risk factors for kidney disease (age, sex, diabetes, high blood pressure, high cholesterol levels, and use of non-steroidal anti-inflammatory drugs). Patients with severe psoriasis were almost twice as likely to develop CKD and were >4-times more likely to develop end-stage renal disease requiring dialysis.[30] PsA patients have a higher risk of CKD and end-stage renal disease compared to that of psoriasis patients.[31] Many systemic medications for psoriasis are excreted via the renal system, e.g., methotrexate. A lowered glomerular filtration rate can lead to decreased drug metabolism and drug toxicity. Renal function should be monitored via routine blood tests, blood pressure measurements, and urinalysis in all psoriasis patients, particularly those prescribed systemic treatments. Early detection is critical because once kidney disease develops it cannot always be reversed.

Psoriasis and Liver Disease

Liver fibrosis, like kidney disease, is generally asymptomatic and can go undetected until the condition becomes advanced. Non-alcoholic fatty liver disease (NAFLD) is the most common form of liver disease in developed countries. This form of liver disease denotes the presence of fat in the liver cells in the absence of excess alcohol consumption, which then leads to significant inflammation and liver fibrosis. The condition is closely linked to obesity and metabolic syndrome. Among a series of 130 psoriasis patients matched for BMI, age, and

sex with 260 healthy controls, psoriasis patients were found to have a higher rate of NAFLD following a liver ultrasound examination.[32] The psoriasis patients also had higher levels of C-reactive protein than controls.[32] Those psoriasis patients who had NAFLD also had higher interleukin-6 and adiponectin levels than those without disease.[32] A Dutch observational study of 2,292 people found 46.2% of psoriasis patients had a diagnosis of NAFLD compared to 33.3% of healthy controls.[33] This study did not control for BMI or metabolic disease. A study looking at the clinical features of NAFLD in psoriasis patients found NAFLD to be strongly associated with PsA.[34] Given that patients with PsA have higher levels of inflammatory cytokines than psoriasis patients without joint involvement, this is a credible association. The association between psoriasis and excessive alcohol intake is well-described. This confounds the already higher propensity of psoriasis patients to develop liver disease. Methotrexate, one of the first-line systemic treatments for psoriasis globally, is known for its propensity to cause liver fibrosis. In patients with no risk factors for hepatotoxicity, a cumulative dose of 3.5–4.0 g of methotrexate is acceptable. Beyond this dose, liver biopsy or possibly a switch of medications should be considered.[35] A systematic review of methotrexate and liver fibrosis in psoriasis patients found a 22% increased risk of any type of fibrosis on biopsy following the use of methotrexate.[36] There was also a trend towards methotrexate use and progression towards significant fibrosis, but this was not statistically significant. Duration and cumulative dose of methotrexate was not associated with fibrosis on biopsy. Psoriasis patients should have regular serum liver function tests, particularly those on systemic medication. All psoriasis patients on methotrexate should have regular procollagen-3 level tests, in addition to their regular liver function tests.[30]

THE PSYCHOSOCIAL BURDEN OF DISEASE

Patients with psoriasis may experience significant psychological and social disability. This varies among patients and does not always correlate with psoriasis severity; for example, a small patch of psoriasis on a young person's face compared to a large plaque on the back of an older person can have disproportionate effects on quality of life. Psoriasis patients may avoid some social situations, such as swimming, and can be restricted in their clothing choices, for example, avoiding wearing dark colours to minimise the appearance of skin flakes, wearing short sleeves, or shorts. Psoriasis patients also have a high risk of sexual dysfunction; patients with genital psoriasis report a lower frequency of intercourse, higher incidence of dyspareunia, and a worsening of their psoriasis following intercourse.[37] Unemployment levels are high among psoriasis patients; in a study of 5,604 psoriasis patients, 12% were unemployed. Of these, 92% cited psoriasis and/or PsA as the sole reason for not working.[38] A recent meta-analysis of 98 studies showed that the prevalence of depressive symptoms among psoriasis patients was 28%. The prevalence of clinical depression in this analysis was 12% using the International Classification of Diseases code.[39] Furthermore, psychological distress is also known to exacerbate psoriasis disease. A significant portion of patients report stress and distress as triggers for their psoriasis. In a review of 928,194 patients from 15 papers, the prevalence of anxiety was 48%, which was significantly higher than in healthy controls. Dermatology centres should screen patients for anxiety and depression at each clinic visit. Patients who may be suffering from depression should be referred to a specialist. Notably, fluoxetine, lithium, and some benzodiazepines used in the treatment of some mental illnesses can make psoriasis flare. Recent studies in mindfulness and cognitive behavioural therapy in psoriasis patients have shown significant improvements in mental health status and the clinical severity of their psoriasis.[40-42]

Up to 30% of psoriasis patients abuse alcohol. This can lead to a wide spectrum of health and social problems, including liver cirrhosis, ischaemic heart disease, atrial fibrillation, sudden death, cerebrovascular disease and stroke, acute and chronic kidney injury, peptic ulcers, depression, suicide, and anxiety. A large objective study found that mortality from alcohol-related causes was significantly higher in psoriasis patients than in the general population.[43] As previously noted, there is an increased incidence of NAFLD in psoriasis patients, which increases the adverse effects of excess consumption of alcohol on liver inflammation.[44] Excessive alcohol consumption can thus limit treatment options in these patients. Self-reported alcohol consumption often underestimates actual intake in psoriasis patients. Physicians should be aware that patients who abuse alcohol often evade detection until medical, legal, or social problems arise. Alcohol biomarkers,

such as erythrocyte mean cell volume, gamma-glutamyltransferase, and carbohydrate-deficient transferrin can assist in the detection of alcohol abuse. Screening questionnaires, such as AUDIT and CAGE, can also be helpful.[44] Alcohol excess in psoriasis is thought to be due to the psychological distress associated with the disease.[45] Studies have shown psoriasis patients who consume alcohol in excess have higher levels of anxiety.[39] Both smoking and alcohol consumption in excess have been shown to worsen psoriasis and decrease the efficacy of treatments.[46] Social behaviours, such as cigarette smoking and excessive alcohol consumption, are modifiable risk factors for both psoriasis and CVD. Psoriasis patients should be opportunistically counselled and supported to modify their behaviours.

CONCLUSION

Once thought of as merely a skin condition, psoriasis has come to be regarded as a complex systemic inflammatory disorder that affects multiple other systems, as described in this article. In recent years, the association of psoriasis with CVD is becoming increasingly recognised. There is also an association between psoriasis and sleep apnoea, COPD, CKD, and liver disease; thus, screening of psoriasis patients for these comorbidities and the implementation of appropriate interventions is necessary. Furthermore, depression and anxiety are very prevalent in psoriasis patients and often not detected by physicians; mental illnesses can be more difficult to assess and diagnose than systemic illnesses during a routine consultation. The use of validated questionnaires for depression and anxiety can be a useful screening method in the outpatient setting. It is vital that patients who are having mental health issues are treated and referred to appropriate specialists. Further studies are warranted to expand our knowledge of the systemic manifestations of psoriatic disease and to allow us to improve health outcomes in our psoriasis patients.

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