PSORIASIS AND COMORBIDITIES

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ABSTRACT

Psoriasis is a chronic inflammatory disease which is a result of complex interactions between genetic, environmental, and immunological factors. Psoriasis is now accepted as a systemic disorder accompanied by comorbidities rather than simply a cutaneous disease. Psoriasis has been associated with a number of systemic diseases such as diabetes mellitus, obesity, hypertension, metabolic syndrome, cardiovascular mortality, psoriatic arthritis, Crohn's disease, ulcerative colitis, pulmonary disease, psychiatric disorders, and malignancies referred to as comorbidities. Although the causal relationship between comorbidities and psoriasis has not been completely clarified yet, it seems that shared genetic susceptibility, common environmental factors, and/or overlapping inflammatory pathways may be potential biological links underlying this association. The presence of comorbid diseases is important since it is associated with a significantly reduced life span and a significant deterioration in life quality. It is also important to keep in mind that the comorbidities and drugs used to treat them have an impact on the choice of antipsoriatic treatment. Besides, systemic treatment of psoriasis with certain drugs may impact the comorbid conditions. Therefore, it is necessary for physicians to recognise these concomitant diseases early and to arrange management options. In this article, the current literature about psoriasis-associated comorbidities and treatment approaches will be discussed.

Keywords: Psoriasis, obesity, metabolic syndrome, comorbidity.

INTRODUCTION

Psoriasis is a chronic, hyperproliferative, immune-mediated, and inflammatory skin disease affecting approximately 1-3% of the population worldwide.[1,2] Chronic plaque psoriasis, the most common form of psoriasis vulgaris, is characterised by sharply demarcated erythematous papules and plaques with scales and with various distribution, severity and course.[1-3] Today there is increasing evidence to substantiate that psoriasis is not just a disease of the skin but a systemic inflammatory disease.[4-8]

Psoriasis results from interaction between an individual's genetic susceptibility, specific environmental factors, and immune mechanisms.[1,8-12] T cells, dendritic antigen-presenting cells, and cytokine networks are recognised as playing a major role in the pathogenesis of psoriasis.[11] The majority of T cells infiltrating in psoriasis were assumed to belong to the T-helper cell (Th)1 subset. Recently, not only has aberrant activation of dendritic cells in skin been found to play a critical role but evidence also points to a role for both Th1 and Th17 cells in the pathogenesis of psoriasis due to elevated levels of many specific inflammatory cytokines.[9,11,12] In particular, Th1 and Th17 cells are expanded and stimulated to release inflammatory cytokines, including tumour necrosis factor alpha (TNF-α), interferon (IFN)-gamma, interleukin (IL)-17 and IL-22. These cytokines contribute to changes that enhance and perpetuate psoriasis. The continuous inflammation proceeds step-by-step inducing systemic inflammation cascade. Sustained skin inflammation is sufficient to induce secretion of other cytokines from subcutaneous fat cells, endothelial cells and other inflammatory cells, leading to endothelial dysfunction, vascular

inflammation, thrombosis and systemic inflammation[10,12,13] (Figure 1). 'Psoriatic march' is a recently defined term and has been used to describe this process developing in a step-wise manner.[8,10]

As demonstrated in many studies, psoriasis is described as an immune mediated inflammatory disease that is connected with a range of comorbidities.[6,8,11,14,15] Numerous studies have evaluated the increased prevalence of comorbid diseases in psoriatic patients, including obesity, diabetes mellitus, metabolic syndrome, cardiovascular disease (CVD), Crohn's disease, ulcerative colitis, non-alcoholic fatty liver disease, psychiatric illness, sleep apnoea, chronic obstructive pulmonary disease (COPD), and malignancy.[4,5,7,9,11,15-21] Below, we will overview these comorbidities briefly.

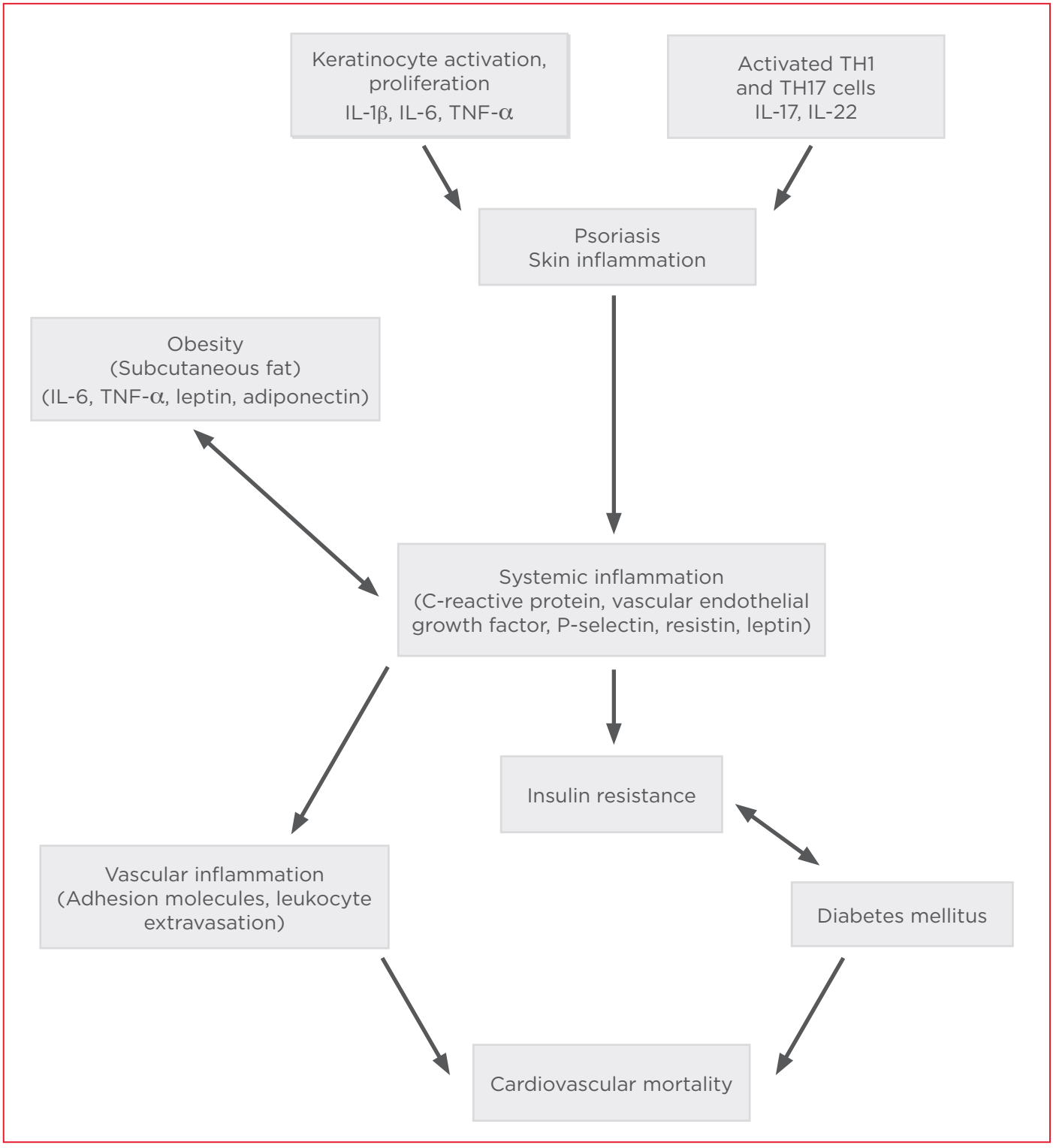

Figure 1. Simplified mechanism of systemic inflammation and consequent events.

OBESITY AND METABOLIC SYNDROME

Recently, a strong association between increased adiposity, obesity, and psoriasis has emerged.[4,5,8] Several studies have shown a significant association between increased body mass index (BMI) and psoriasis.[22-25] In addition to obesity, patients with psoriasis are more likely to have metabolic syndrome.[4-7,15-17]

It is now clear that intra-abdominal fat is not merely an inert mass but an active metabolic and endocrine organ, secreting adipocytokines, promoting inflammation, and affecting glucose metabolism and vascular endothelial biology.[26,27] Subcutaneous fat cells (adipocytes) produce proinflammatory cytokines under the influence of inflammatory mediators such as TNF-α that is produced by the skin. Primary cytokines that are produced by adipocytes include IL-6, TNF-α, plasminogen activator inhibitor type 1 (PAI-1), leptin and adiponectin, each of which plays multiple roles in inflammation, metabolism and endothelial cell function.[26,27] Besides, adipocytes bear Toll-like receptors that behave as a component of innate immunity and allow an immediate response to foreign pathogens and release cytokines.[27] As systemic inflammation continues and with increasing BMI, adiponectin is downregulated while leptin and resistin are upregulated, which induces insulin resistance and causes endothelial cells to produce adhesion molecules, promoting a hepatic release of both fibrinogen and C-reactive protein, and augmenting the procoagulant effects on platelets.[8,17,26,27] These drive the process with consequences of metabolic syndrome.

Several studies have shown that psoriasis may be linked to obesity, however, controversy still exists as to whether obesity is a result or a causative factor of psoriasis.[6,11,16] Either way, this strong association makes psoriasis an important healthcare issue.

Insulin Resistance/Diabetes Mellitus

Psoriatic patients have been found to be more insulin-resistant and to have impaired glucose tolerance and higher fasting insulin levels than healthy ones.[28-33] A large observational study by Brauchli et al.[31] demonstrated an increased risk of incident diabetes mellitus in patients with psoriasis when compared with a psoriasis-free study group. Among 1,061 incident cases of diabetes mellitus, 59% had a history of psoriasis. Also, they indicated that the risk was higher for patients with a longer psoriasis history.

Coto-Segura et al.[30] reported a recent study involving observational studies assessing the relationship between psoriasis or psoriatic arthritis and type 2 diabetes mellitus; their findings supported the association between psoriasis, psoriatic arthritis and type 2 diabetes mellitus. Another study reported by Armstrong et al.[32] recently demonstrated an increased prevalence and incidence of diabetes and indicated that this association is stronger among patients with severe psoriasis.

A study by Cohen et al.[33] supported previous reports of an association between psoriasis and diabetes mellitus. The age-adjusted proportion of diabetes was found to be significantly higher in psoriasis patients as compared to the control group. A possible explanation for the association between psoriasis and diabetes is the presence of chronic inflammation that occurs due to secretion of TNF-α and other proinflammatory cytokines such as IL-1 and IL-6, which precipitate both psoriasis and diabetes.

Metabolic Syndrome

Metabolic syndrome is a combination of central obesity, dyslipidaemia, insulin resistance, and elevated blood pressure, which has been associated with an increased risk of CVD beyond traditional risk factors.[4,5,7] The metabolic syndrome is an important driver of adverse cardiovascular outcomes.[34,35] Although the pathophysiology of all components of metabolic syndrome has not been clarified completely, it is accepted to be a heterogeneous and a complex disorder, developing on the basis of insulin resistance which is due, in large part, to the action of increased levels of proinflammatory factors, such as TNF-α, that are central to the pathogenesis of psoriasis.[9,17,19,26]

Multiple epidemiologic studies have consistently demonstrated higher prevalence of metabolic syndrome in patients with psoriasis.[4,5,9,18-21] This association is valid for mild severity psoriasis and it is independent from the tendency of psoriatic patients to be obese.[4] Dose-response relationships between more severe psoriasis and higher prevalence of metabolic syndrome components were recently established.[5]

The underlying pathophysiology linking psoriasis and metabolic syndrome may involve overlapping inflammatory pathways and genetic predisposition. Chronic inflammation and dysregulation of cytokines not only promotes epidermal hyperplasia in psoriasis, but may also antagonise insulin signalling, alter adipokine expression, and mediate insulin resistance and obesity.[36]

Abdominal obesity and insulin resistance are considered underlying risk factors for the development of metabolic syndrome.[5,11,33]

Non-Alcoholic Fatty Liver Disease

The relationship between non-alcoholic fatty liver disease (NAFLD) and psoriasis severity has been established. NAFLD is found to be highly prevalent among psoriasis patients, where it is closely associated with obesity and metabolic syndrome.[37-41] Gisondi et al.[39] have demonstrated a higher frequency of NAFLD in 130 patients with plaque psoriasis when compared with the control group (47% versus 28%). Patients with psoriasis and NAFLD also had higher serum C-reactive protein concentrations, greater severity of psoriasis, and revealed a higher frequency of metabolic syndrome than those with psoriasis alone. Miele and coworkers[37] prospectively examined the prevalence and characteristics of NAFLD in 142 patients with psoriasis and found NAFLD in 59.2% of the patients. The study revealed that NAFLD in psoriasis patients was significantly correlated with metabolic syndrome.

The proposed mechanism underlying these two disorders may involve common pathways. As NAFLD is thought to be an expression of metabolic syndrome in the liver, a degree of persistent inflammation with secretion of cytokines (TNF-α, IL-17/23) which induces the development of insulin resistance and metabolic syndrome is also implicated in the development of NAFLD.[40-42]

Cardiovascular Diseases

Psoriasis is now thought to be an independent risk factor for coronary artery disease and acute myocardial infarction (MI).[43] The risk of developing ischaemic heart disease and cerebrovascular disease has been reported to be higher in patients with moderate-to-severe psoriasis than in the general population.[43-45]

Several factors are associated with a higher risk of CVD, such as age, high blood pressure, obesity, smoking, dyslipidaemia, physical inactivity, and psychological stress. Many of these factors are also prevalent in psoriatic patients, which effects the severity of psoriasis.[8,11,16,18,44,46-48] Several studies demonstrated higher prevalence of CVD such as MI, thrombophlebitis, pulmonary embolism, and cerebrovascular disease in patients with psoriasis, and an increased mortality.[43-53] Furthermore, it has been pointed out that the presence of psoriasis as an independent risk factor for the development of atherosclerosis[5] and MI, after controlling for different variables and risk, was found to be higher in young patients with severe psoriasis.[43,44]

Kimball and coworkers[45] estimated the 10-year risk of coronary heart disease and stroke in 1,591 patients with psoriasis and found a significantly higher cardiovascular risk in patients with psoriasis when compared with general population, with a risk that was 28% greater for coronary heart disease and 11.8% greater for stroke.

Gelfand et al.[43] examined the incidence of MI among patients with and without psoriasis. They identified 130,976 patients with psoriasis and 556,995 in the corresponding control group, followed-up for a mean of 5.4 years. The authors showed that patients with psoriasis had a higher incidence of MI compared with control patients, and that patients who had severe psoriasis had the highest rate.

The mechanistic link between psoriasis and this observed increase in cardiovascular comorbidities has not been fully defined. However, it is clear that the chronic inflammation plays an important part in the pathogenesis of many metabolic and vascular diseases.[8,11,13] An increased risk of atherosclerosis in patients with inflammatory diseases such as systemic lupus erythematosus and rheumatoid arthritis has been demonstrated.[54,55] Inflammation was shown to be a key factor in atherogenesis, providing a unifying mechanism for explaining the association between atherosclerosis.[8,10,21]

Shared inflammatory pathways, including Th1-mediated inflammation, alterations in angiogenesis and endothelial dysfunction, may link the pathogenesis of psoriasis with the development of atherosclerosis and CVD.[13,23,43,44]

Crohn's Disease and Ulcerative Colitis

Crohn's disease and ulcerative colitis have been demonstrated to be significantly higher in patients with psoriasis than in the normal population, suggesting the possibility of a genetic link and chronic inflammation.[56-58] Cohen et al.[56] examined the prevalence of inflammatory bowel disease in 12,502 patients with psoriasis and 24,287 age and sex matched control group members. They found a significantly higher prevalence of both Crohn's disease and ulcerative colitis in psoriasis patient group compared with the control group. These associations are biologically plausible, as systemic inflammation and TNF-α plays an important role in all three diseases.[56]

Psychiatric Diseases

Psoriasis is a physically, socially, and psychologically disabling disease that negatively impacts quality of life.[3,59-67] Psoriasis impairs ability in daily activities that require the use of hands, walking, sitting and standing for long periods of time, occupational performance, sexual activities, and sleep; many also experience rejection which causes a feeling of stigmatisation.[62,63]

Psoriasis patients reported significantly higher degrees of depression and more body cathexis problems. In addition, the risk for developing psoriasis increased significantly in patients with moderate and severe depression. There is also a relationship between symptom severity and low affective expression.[63,65]

Krueger and coworkers[59] assessed patients' perspectives on the impact of psoriasis and a self-administered questionnaire was applied to patients. 79% of the patients reported that psoriasis had a negative impact on their lives and 40% felt frustrated with the ineffectiveness of their current therapies.[59] The study by Sampogna et al.[66] included 936 patients with psoriasis. The problems most frequently experienced by the patients were shame, anger, worry, and difficulties in social life. Dominguez and coworkers' study[67] included 86,880 females and the participants reported anti-depressant use and completed a scale. They found that depression was associated with an increased risk of incident psoriasis. Compared to women in the non-depressed group, women who reported either having high depressive symptomatology or who were on anti-depressants had 1.59 times relative risk of developing subsequent psoriasis. Sleep quality is also disturbed in patients with psoriasis due to itching and problems with depression and mood status.[68] Therefore, evaluation and treatment of psoriasis must include psychosomatic approaches in clinical practice.

Chronic Obstructive Pulmonary Disease

Dreiher et al.[69] compared 12,502 psoriatic patients with 24,287 healthy controls, in terms of presence of COPD, and demonstrated a higher prevalence of COPD in patients with psoriasis. A multivariate logistic regression model demonstrated that psoriasis was significantly associated with COPD, after controlling for confounders including age, sex, socioeconomic status, smoking, and obesity.[69] Another recently performed study from Taiwan supported similar results that psoriasis patients were at a greater risk of developing COPD with significantly lower COPD-free survival rates than the comparison cohort.[70]

Obstructive Sleep Apnoea Syndrome

Keeping in mind that psoriasis is associated with obesity and CVD, it is likely that psoriasis can be related to obstructive sleep apnoea syndrome (OSAS). Recent studies have reported that the frequency of OSAS was found to be higher in patients with psoriasis than the normal population.[71,72] Karaca et al.[71] demonstrated OSAS in 54.5% of patients with psoriasis. They also found higher psoriasis area severity index (PASI) in the OSAS group than in the non-OSAS group. Papadavid et al.[72] explored the association between OSAS and psoriasis in their study and found that psoriasis patients with OSAS presented more frequent snoring and had lower sleep quality compared with those without OSAS. They also reported that OSAS was associated with increased BMI and hypertension in psoriasis patients.

Malignancy

The relationship between psoriasis and increased cancer risk is still debated. Gelfand et al.[73] reported a study of 2,718 patients and their results indicated that patients with psoriasis are at increased risk for developing lymphoma. The limitations of this study were that 10% of the population studied was above 65 years old and the rate of lymphoma included the patients treated with methotrexate. A recently reported meta-analysis of epidemiological studies, including

1,080 articles, indicated that there may be an increased risk of some solid cancers such as lung, in psoriasis, especially in smokers and alcohol users; however, the large heterogeneity between these studies regarding study population and follow-up constitute the limitation of this report.[74] Chen et al.[75] investigated 3,686 patients with psoriasis and found that 116 had incident cancers. The 7-year cumulative incidence of cancer among psoriasis patients was 4.8%. Certain cancers including urinary bladder, oropharynx/larynx, liver/gallbladder, and colon/rectum were found to be significantly associated with psoriasis. The limitation of this study is that it does not contain information regarding severity of psoriasis, status of smoking, and alcohol use. Another study of Prizment and coworkers[76] revealed that with age-adjustment, psoriasis was associated with increased risk of lung, colon, and total cancer. After adjustment for smoking, only the association for colon cancer remained statistically significant.

Other Diseases

Although it has not been clarified whether the association of autoimmune diseases with psoriasis is a simple coincidence or is a pathogenic relationship, there have been several reports that indicate this co-occurrence. Bullous pemphigoid, systemic lupus erythematosus, myasthenia gravis, multiple sclerosis, Sjögren's syndrome, Hashimoto's thyroiditis, parkinsonism, dermatitis herpetiformis, pemphigus vulgaris, linear immunoglobulin A dermatosis, and vitiligo have been reported.[77-82] Recent data suggest that Th17 cells play an important role in the pathogenesis of a diverse group of immune-mediated diseases.[12]

MANAGEMENT OF A PSORIATIC PATIENT

The presence of comorbidities has important implications in the approach to patients with psoriasis. Systemic anti-psoriatic agents such as cyclosporine could negatively affect cardio-metabolic comorbidities such as hyperlipidaemia, hypertension and hyperhomocysteinaemia and may have important interactions with drugs commonly used by psoriatic patients.[4,11,22,25] TNF-α seems to be a particularly attractive target as it is known to induce endothelial cell dysfunction, insulin resistance and atherosclerosis.[8,10] Biological agents targeting TNF-α constitute a relatively new and efficient approach to psoriasis. The recent findings that the risk of MI is reduced in patients with rheumatoid arthritis who respond to anti-TNF-α therapy compared to non-responders, support the hypothesis that the anti-inflammatory effect of TNF-α blockers might reduce the cardiovascular risk potentially also in psoriasis patients.[11,83,84] Use of TNF-α inhibitors for psoriasis was associated with a significant reduction in MI risk and was associated with non-statistically significant lower MI incident rate compared with treatment with oral agents/phototherapy.[85] Therapeutic intervention by use of anti-inflammatory drugs including methotrexate and TNF-α antagonists seem to diminish the risk.[5,9] Torres et al.[18] reported three cases of psoriasis with metabolic syndrome that improved without using any systemic and/or topical antipsoriatic treatments, just by strict diet, antihypertensive-anti-lipid and anti-diabetic treatments. These data also suggest that the treatments of these patients not only improve the skin lesions but also control the inflammation associated with the psoriasis. Therefore, it is important that the dermatologist systematically seeks these concomitant pathologies among psoriatic patients and discontinuation of smoking and alcohol consumption should be encouraged.

CONCLUSION

Psoriasis is considered as a chronic, immune-modulated inflammatory disease. In this article, not only a summary of the evidence for a link between psoriasis and comorbidities is presented but also the main concepts regarding psoriasis are discussed. As mentioned during this article, recent literature brings a new point of view to psoriasis, which is a chronic recurrent disease with inflammatory state, including its association with severe comorbid conditions. This association has important clinical implications for the management of psoriasis: patients with psoriasis should be routinely screened for metabolic syndrome in a multidisciplinary manner and treated promptly and effectively, while clinicians should also monitor treatment efficacy and safety in patients with comorbid psoriasis and metabolic syndrome. Finally, patients should be encouraged to correct their cardiovascular risk factors, in particular obesity and smoking habits. Further research will be necessary to establish the directionality of this association and to demonstrate the effect of treatment on these comorbid diseases.

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