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# Metabolic Comorbidities and Psoriasis

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**SUMMARY** Psoriasis is a chronic inflammatory, immune-mediated skin disease, which affects 2%-3% of the population worldwide. Chronic plaque psoriasis is frequently associated with metabolic diseases including diabetes, obesity, dyslipidemia, metabolic syndrome and nonalcoholic fatty liver disease. Although the causal relationship between metabolic comorbidities and psoriasis has not yet been completely proven, it appears that shared genetic links, common environmental factors and/or common inflammatory pathways may underlie the development of psoriasis and comorbidities. The presence of comorbidities has important implications in the global approach to patients with psoriasis. Traditional systemic antipsoriatic agents could negatively affect cardio-metabolic comorbidities, and may have important interactions with drugs commonly used by psoriatic patients. In contrast, the recent findings that the risk of myocardial infarction is reduced in patients with rheumatoid arthritis who respond to anti-TNF-α therapy compared to non-responders, supports the hypothesis that the anti-inflammatory effect of TNF-α blockers might reduce the cardiovascular risk potentially also in psoriasis patients. Finally, patients with moderate to severe psoriasis should be treated promptly and effectively, and should be encouraged to drastically correct their modifiable cardiovascular risk factors, in particular obesity and smoking habit.

**KEY WORDS:** psoriasis, metabolic syndrome, obesity, nonalcoholic fatty liver disease

## INTRODUCTION

Psoriasis is a chronic inflammatory disease most commonly manifested by skin lesions on the elbows, knees, scalp, genitals, and trunk that has been estimated to affect 1% to 3% of the population worldwide (1). Psoriasis is currently considered an immune-mediated inflammatory disorder (IMID), alongside other entities such as rheumatoid arthritis, Crohn's disease or multiple sclerosis. Despite their distinct clinical presentation, these diseases share common features such as the chronic course, their inflammatory nature and several pathogenetic mechanisms, including a so-called Th1-like cytokine milieu in the affected tissue, dominated by interferon alpha and gamma along with TNF-alpha, interleukins (IL) 2, 22 and 17 (2). Another shared feature of IMIDs is the association with other diseases, in particular cardiovascular diseases. The morbidities more commonly associated to psoriasis include psoriatic arthritis (PsA) and Crohn's disease, which share with psoriasis some common pathogenic mechanisms; psychological morbidities which are related

to the burden of the disease on the quality of life, and metabolic diseases, which are the main object of this review (Table 1).

A more common psoriasis comorbidity is PsA, which affects up to one-third of patients with psoriasis (3). It is a seronegative spondyloarthritis involving both peripheral joints and axial skeleton, and usually begins as enthesitis, i.e. the inflammation at tendon insertion. Enthesopathy has been reported to be very common also in psoriasis patients without clinical signs or symptoms of arthritis (4). PsA runs a chronic fluctuating course, and about 20% of patients develop a very destructive and disabling form (5). Psoriasis precedes the development of PsA in the vast majority of patients, without correlation between skin disease severity and risk of developing PsA. A recent prospective study showed that scalp psoriasis, psoriasis of the intergluteal/perianal area and nail psoriasis confer a higher risk of PsA (6). In addition, psoriasis has a major impact on patients' life and is associated with a significant reduction of the quality of life and with depressive symptoms in a relatively large proportion of patients (7).

Although already reported twenty years ago, recent large epidemiological studies have confirmed that chronic plaque psoriasis and PsA are associated with cardio-metabolic disorders that confer an unfavorable cardiovascular risk profile, and a higher mortality rate (8). The association between psoriasis and comorbidities has been also confirmed in childhood patients (9). This study was conducted using a database of about 1.3 million of non selected individuals from a German statutory health insurance organization. The overall rate of comorbidities in psoriatic patients younger than 20 years was twofold compared with persons without psoriasis (14.4% *vs*. 7.2%; $P<0.01$). Juvenile psoriasis was associated with increased rates of hyperlipidemia, obesity, hypertension, diabetes mellitus, rheumatoid arthritis and Crohn's disease. Interestingly, hyperlipidemia, diabetes and hypertension were seen twice as often in patients with psoriasis as in controls.

## METABOLIC DISEASES ASSOCIATED WITH PSORIASIS

### Insulin resistance/type 2 diabetes

A higher prevalence of insulin resistance and/or type 2 diabetes in psoriasis has long been recognized but the extent and the potential mechanisms are still poorly understood. Impaired glucose tolerance based on glucose oral tolerance test was reported in 13.2% out of 53 and 40% out of 17 patients with early (<40 years) and late (>40 years) onset psoriasis, respectively, which was significantly higher compared to 2.5% in controls (10). Boehncke *et al*. observed a significant correlation between psoriasis severity and insulin secretion and serum resistin levels, a cytokine known to be increased in insulin resistance, supporting the concept of insulin resistance occurrence as a consequence of severe chronic inflammation (11). Indeed, Kaye *et al*. found that psoriasis itself conferred a risk of developing diabetes as the cumulative incidence of diabetes in the psoriasis cohort was higher than comparison data (hazard ratio 1.33; confidence interval (CI) 1.25-1.42) (12). The association between psoriasis and type 2 diabetes is even stronger. Numerous cross-sectional studies have shown that psoriasis, especially severe disease, confers a higher risk (up to 2.48) of diabetes (13). The increased prevalence of diabetes in patients with psoriasis appears to be independent of traditional diabetes risk factors such as obesity and dyslipidemia (14). The shared genetic background may also contribute to the susceptibility to both psoriasis and diabetes (15).

**Table 1.** Metabolic comorbidities in psoriasis patients

| |
|---|
| Insulin resistance/type 2 diabetes |
| Atherogenic dyslipidemia |
| Obesity |
| Metabolic syndrome |
| Nonalcoholic fatty liver disease |

### Atherogenic dyslipidemia

Multiple cross-sectional studies have consistently shown that psoriasis is associated with atherogenic dyslipidemia, i.e. elevated serum plasma concentrations of triglycerides, very low density lipoprotein (VLDL) and low density lipoprotein (LDL) as well as low serum concentration of high-density lipoprotein (HDL) cholesterol (16,17). Although the confounding effect of obesity and insulin resistance should be taken into account in evaluating this association, Mallbris *et al*. found the patients to have an abnormal lipoprotein composition already at the onset of psoriasis independently of age, sex, body mass index (BMI), smoking, blood pressure and alcohol consumption, suggesting that dyslipoproteinemia in psoriasis might be genetically determined rather than acquired (18). Indeed, apolipoprotein E gene polymorphism, which is strongly associated with hyperlipidemic states,

Acta Dermatovenerol Croat
2010;18(4):297-304

has been reported in patients with chronic plaque and guttate psoriasis (19). Moreover, isolated cases of lipoprotein glomerulopathy associated with apolipoprotein E3/3 in psoriasis have been reported (20).

### Obesity

An association between increased BMI and psoriasis has been confirmed, suggesting that psoriasis patients are more frequently overweight or obese than the general population, and that the severity of psoriasis may be correlated to BMI. However, controversy still exists as to whether obesity is a result of psoriasis or a causative factor. A recent population-based study in patients with mild or severe psoriasis showed that the risk of obesity was significantly increased in psoriasis patients as compared with healthy controls and strongly associated with disease severity (odds ratio (OR): 1.27; 95% CI: 1.24-1.31 and OR: 1.79; 95% CI: 1.55-2.05, mild and severe, respectively) (21). In line with this findings, Herron *et al*. found that psoriasis patients were almost twice as likely to be obese compared with the general population (34% *vs*. 18%; *P*=0.001) (22). Based on patient perception of body image before and at psoriasis onset, the investigators concluded that obesity appeared to be a consequence of psoriasis. Further support for obesity as a consequence of psoriasis comes from a recent case-control study in which no differences in BMI were observed between psoriasis patients at disease onset and controls (23). In contrast, in a case-control study involving 560 patients with recently diagnosed (<2 years) psoriasis compared to 690 controls who had been recently diagnosed with other dermatological diseases, Naldi *et al*. identified obesity as an independent risk factor associated with psoriasis, accounting for 16% of all psoriasis cases at onset. Patients with a BMI of 26-29 kg/m$^2$ had an OR of 1.6 (95% CI: 1.1-2.1), and those with a BMI >29 kg/m$^2$ had an OR of 1.9 (95% CI: 1.2-2.8) of developing psoriasis (24). A very large prospective cohort study in young women confirmed that obesity preceded psoriasis, with body weight being directly associated with the risk of developing psoriasis (25). Obesity is indeed associated with a persistent low-grade inflammation characterized by increased levels of leptin, resistin, IL-6, TNF-α, IL-8 and MCP-1, which could fuel psoriasis inflammation (26). Very interestingly, it has been reported that BMI negatively affects short-term clinical response to systemic treatments for psoriasis (24) and biologics with a fixed-dose regimen (etanercept, adalimumab, ustekimumab) may have a compromised efficacy in heavier individuals (27). In line with these findings, we observed that a moderate weight loss (i.e. 6% of body weight) increased the responsiveness of obese psoriasis patients to a suboptimal dose of cyclosporine (28).

### Metabolic syndrome

The metabolic syndrome is a constellation of metabolic changes, in particular insulin resistance, which collectively confer a higher proinflammatory and prothrombotic risk (29). The most widely accepted criteria for metabolic syndrome definition have been issued by the Adult Treatment Panel III, which defines it as the presence of at least three of the following conditions: abdominal obesity (waist circumference >102 cm (40 in) men; >88 cm (35 in) women); elevated serum triglycerides (>150 mg/dL (1.7 mmol/L) or under treatment); low HDL cholesterol (men <40 mg/dL (1 mmol/L); women <50 mg/dL (1.3 mmol/L) or under treatment); elevated blood pressure (>130/85 mm Hg or under treatment), and elevated fasting glucose (>110 mg/dL or under treatment) (30). In a cross-sectional study, we found that psoriasis patients had a higher prevalence of metabolic syndrome *versus* general dermatology patients after controlling for sex and age (30.1% *vs*. 20.6%; OR 1.65; 95% CI 1.16-2.35) (31). However, when looking at individual components of the metabolic syndrome, only hypertriglyceridemia and abdominal obesity were more significantly prevalent in patients with psoriasis than in non-psoriatic patients. Furthermore, hospitalized psoriasis patients vs. hospitalized melanoma patients in Germany were found to have an increased prevalence of metabolic syndrome on the basis of a modified version of the WHO definition (OR 5.92; 95% CI 2.78-12.8) when adjusted for age and sex (32). Metabolic syndrome has features of a hypercoagulable state, consisting of increased levels of clotting factors (tissue factor, factor VII and fibrinogen) as well as inhibition of the fibrinolytic pathway, e.g., increased plasminogen activator inhibitor-1 and decreased tissue plasminogen activator activity. This prothrombotic state may reflect the effects of dysfunctional adipocytes, and inflammatory activation and changes at various levels of the coagulation system (33,34).

### Nonalcoholic fatty liver disease

Nonalcoholic fatty liver disease (NAFLD) is now regarded as the hepatic manifestation of the

metabolic syndrome, and represents the most common cause of abnormal liver function tests among adults in the United States and Europe (35). The prevalence of NAFLD has been estimated to be in the 20%-30% range in the general population in various countries and is almost certainly increasing (36). Accordingly, a huge number of individuals are at a risk of developing advanced liver disease, including fibrosis and cirrhosis. There is now growing evidence suggesting that NAFLD may be also linked to an increased risk of future cardiovascular events independently of the conventional risk factors and metabolic syndrome components (37). We found the frequency of NAFLD – as diagnosed by patient history, blood sampling and characteristic ultrasonographic features – in patients with chronic plaque psoriasis to be remarkably greater than that in non-psoriasis control subjects (47% *vs*. 28%; $P<0.0001$) matched for age, gender and BMI (38). Notably, the two groups were also comparable for the presence of the metabolic syndrome, possibly because they were matched for BMI. In addition, none of our psoriasis patients was treated with methotrexate, TNF-α antagonists or other potentially hepatotoxic medications. Another major finding of the study was that NAFLD was associated with the severity of psoriasis independently of the potential confounders such as age, gender, BMI, psoriasis duration and alcohol consumption. Although data do not allow to ascertain the directionality of the association between NAFLD and psoriasis, it could be speculated that proinflammatory cytokines and other factors that are overproduced in patients with psoriasis likely contribute to the development of insulin resistance, and that psoriasis patients with highest insulin resistance are the ones who get NAFLD. The leading role in the development of inflammation, insulin resistance and NAFLD in psoriasis patients is likely to be played by increased visceral adipose tissue, possibly through its multiple secreted factors such as free fatty acids, hormones, and adipocytokines (39). However, it is also possible to hypothesize that NAFLD might actively contribute to the severity of psoriasis through the release of pathogenetic mediators from the inflamed liver, including increased reactive oxygen species, elevated C-reactive protein (CRP), IL-6, and other proinflammatory cytokines. Importantly, several studies have shown that these potential mediators of vascular and skin injury are remarkably higher in patients with NAFLD than in those without it (40). The systemic release of proinflammatory/proatherogenic mediators from the steatotic liver is also one of the underlying mechanisms by which NAFLD may contribute to accelerated atherogenesis (41). Indeed, it was found that patients with psoriasis and NAFLD were more likely to have the metabolic syndrome, and had significantly higher serum CRP and IL-6 levels, and lower serum adiponectin than those with psoriasis alone (41).

## Concluding remarks

### Clinical relevance of the association between psoriasis and comorbidities

The concomitance of metabolic comorbidities has relevant consequences, which are included in the following sub-paragraphs.

### Patients with psoriasis are at a risk of developing cardiovascular accidents

Patients with psoriasis show an increased risk of atherothrombotic diseases independently of the concomitance of traditional cardiovascular risk factors. In the pivotal study by McDonald and Calabresi, the risk of arterial and venous vascular diseases (i.e. myocardial infarction, thrombophlebitis, pulmonary embolism and cerebrovascular accident) was 2.2 times higher among patients with psoriasis compared to patients with other dermatologic conditions. Disease duration did not appear to have an effect on the risk, but the extent of skin involvement was associated with a slightly higher risk in older age groups (42). More recent studies support these earlier observations. In a comparison of psoriasis inpatients from the Swedish Inpatient Registry, outpatients from the Swedish Psoriasis Association, and the general population, psoriasis patients who had at least one hospital admission for psoriasis from 1964 to 1995 incurred a 50% greater risk of cardiovascular mortality compared to the general population (43). In contrast, psoriasis outpatients did not have an increased cardiovascular mortality risk. However, the most notable observations are two large retrospective cohort studies using the General Practice Research Database that involved almost 130,000 patients with psoriasis (44,45). In these recent studies, the risk of myocardial infarction was 1.29 (95% CI 1.14-1.46) for 30-year-old patients with mild psoriasis and 3.10 (95% CI 1.98-4.86) for 30-year-old patients with severe psoriasis, and the hazard ratio for stroke was 1.06 (95% CI 1.0-1.1) and 1.43 (95% CI 1.1-1.9) for mild and severe psoriasis, respectively. The increased risk of myocardial infarction and stroke in psoriasis patients was

Acta Dermatovenerol Croat
2010;18(4):297-304

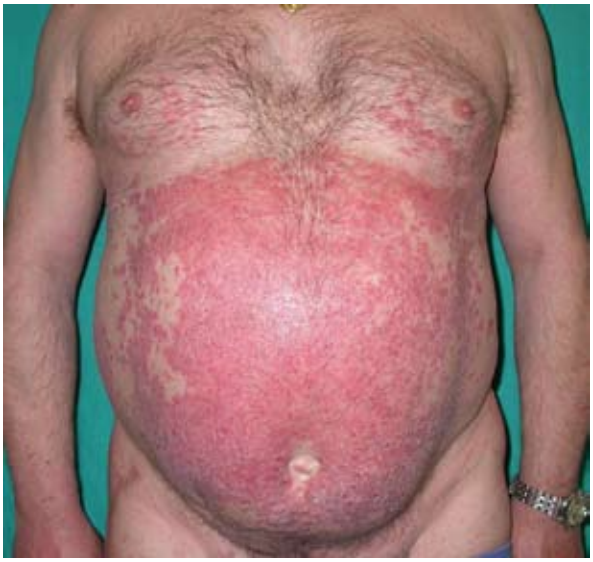

**Figure 1.** Phenotype of a typical patient with psoriasis and abdominal obesity associated with metabolic syndrome.

independent of the major risk factors identified in routine medical care. Indeed, severe psoriasis is associated with an increased risk of death from a variety of causes, with cardiovascular death being the most common etiology (8).

## The choice of systemic treatment for psoriasis is influenced by the concomitance of metabolic comorbidities

Systemic treatments for psoriasis including methotrexate, cyclosporine, retinoids and biologics may contribute either to reducing or to increasing the cardiovascular risk. Indeed, it has been reported that American veterans affected by psoriasis, psoriatic arthritis and rheumatoid arthritis treated with moderate doses of methotrexate have a reduced risk of major cardiovascular events compared to non-treated patients (46). This effect is possibly attributable to the anti-inflammatory effects of the drug. On the other hand, methotrexate use can induce hyperhomocysteinemia, which is an established risk factor for both arterial and venous thrombosis. Moreover, methotrexate should be chosen with caution in cases of overweight patients, high alcohol consumption, diabetes mellitus or viral hepatitis due to the increased risk of developing liver fibrosis (47). The presence of NAFLD should be taken into great consideration when choosing therapy, as acitretin, cyclosporine and methotrexate are potentially toxic for the liver and consequently could favor the progression from NAFLD to fibrosis and even cirrhosis. As far as cyclosporine is concerned, this drug can induce or worsen arterial hypertension, alter glucose tolerance and/or interfere with fatty acid metabolism favoring hyperlipemia (48). Pharmacological treatment of dyslipidemia in psoriasis patients warrants attention as statins could favor myolysis when associated with cyclosporine or retinoids. Also, retinoids may increase serum cholesterol and triglycerides. The occurrence of hypertriglyceridemia and hypercholesterolemia has been occasionally reported also in patients treated with anti-TNF-α agents, as well as increment of liver enzymes, whereas a true hepatitis has been a more rare but established event (49). In addition, anti-TNF-α agents increase body weight in patients with psoriasis and Crohn's disease (50). We observed that after 6 months of continuous anti-TNF-α therapy both with infliximab and etanercept, a relevant increase (4-10 kg) in body weight was recorded in about 25% of patients. We could not identify the clinical parameters predicting this phenomenon (51).

Although controversy still exists, the recent findings that the risk of myocardial infarction is markedly reduced by 6 months in rheumatoid arthritis patients who respond to anti-TNF-α therapy compared to non-responders supports the hypothesis that the anti-inflammatory effect of TNF-α blockers might improve the cardiovascular risk (52). In particular, anti-TNF-α treatment has been shown to improve endothelial function as well as reduce serum CRP levels in patients with rheumatoid arthritis (53). Whether this effect could be present and relevant in reducing thrombotic events also in psoriasis patients need to be investigated.

## Dermatologists need to manage comorbidities while treating psoriasis

In the light of the comorbidities associated with psoriasis, managing these patients should not be limited to their skin symptoms, but should also include an holistic approach. As in case of PsA, dermatologists are in the position to detect developing comorbidities early. All relevant measures can be taken in a simple way in outpatient setting. The comprehensive investigation of psoriasis patients should include measurement of pulse and blood pressure, determination of BMI, and measurement of fasting blood lipids and blood glucose. Moreover, the dermatologist should be aware of the importance of recommending the patient lifestyle modifications including a low calorie diet, which may supplement the pharmacological treatment

of obese patients. Weight loss, through calorie restriction, could improve metabolic comorbidities including decreasing insulin resistance, reducing serum lipids and reducing blood pressure levels. Furthermore, losing weight may improve psoriasis. Several case studies have shown that weight loss from gastric bypass surgery results in remission of psoriasis (54). Likewise, in a recent controlled study we showed that moderate weight loss (i.e. 5%-10% of body weight) increased therapeutic response to a low dose of cyclosporine in obese patients with moderate to severe chronic plaque psoriasis, suggesting that lifestyle modifications including a low calorie diet may supplement the pharmacological treatment administered to obese psoriasis patients (28). Weight loss, through calorie restriction, induces decreases in insulin, leptin, CRP and MCP-1, and increases adiponectin levels, resulting in an anti-inflammatory effect.

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