Cardio-metabolic comorbidities of psoriasis

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Summary

Psoriasis is a cutaneous inflammatory chronic disease affecting 2-3% of the Italian population. A number of studies have allowed to identify a significant association between psoriasis and several comorbidities. The most frequent comorbidities are psoriatic arthropathy, chronic inflammatory bowel diseases (Crohn’s disease and ulcerative colitis), hepatic steatosis and metabolic syndrome, i.e. the simultaneous presence of hypertension, obesity, dyslipidemia, hyperglycemia and/or diabetes. When choosing a psoriasis treatment clinicians should take into consideration several objective and subjective parameters, including disease severity, presence of comorbidities, treatment expectations and fear for adverse events. The traditional systemic drugs may negatively interfere on comorbidities. Cyclosporin, for example, may favor or worsen hypertension, while methotrexate can be hepatotoxic, especially in case of prolonged therapies. Biological agents are a therapeutic option which allows for a good disease control in the long term also in patients showing important comorbidities. Safety data collected in patients with psoriasis are rather reassuring. However, it is important to consider the possible adverse events and to carefully monitor the patients in order to minimize risks.

KEY WORDS: psoriasis; comorbidities; therapy; metabolic syndrome.

Table 1 summarizes the most common comorbidities of psoriasis.

<table>
<thead>
<tr>
<th>Comorbidities of psoriasis</th>
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<tr>
<td>• Ocular inflammation (Iritis/Uveitis/Episcleritis)</td>
<td>• Psychosocial burden (Reactive depression, Higher suicidal ideation, Alcoholism)</td>
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<tr>
<td>• Crohn’s disease</td>
<td>• Metabolic Syndrome (Arterial Hypertension, Dyslipidaemia, Insulin resistant diabetes, Obesity)</td>
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<tr>
<td>Ulcerative Colitis</td>
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<tr>
<td>• Psoriatic Arthritis</td>
<td>• Generalised Pustular and Palmoplantar psoriasis</td>
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<tr>
<td>7-30%</td>
<td>40-50%</td>
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<tr>
<td>• Spondyloarthopathies</td>
<td></td>
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<tr>
<td>• Nail psoriasis</td>
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A significant association between waist and visceral adipose tissue has been demonstrated – the adipose tissue being accumulated mainly in the liver – which in turn is an independent cardiovascular risk factor. Fat accumulation in the liver is defined as steatosis: it can be either pure, presence of fat only, or steatosis associated with inflammation and fibrosis, the so-called steatohepatitis, possibly leading to cirrhosis. If some drugs, i.e. methotrexate, are used in obese patients who suffer from pure steatosis and drink alcohol, progression from pure steatosis to steatohepatitis can be accelerated. This is a crucial
factor that should be taken into consideration in the clinical practice. This acceleration is also associated with cardiovascular risk. Is this situation common in psoriatic patients? Prevalence of pure steatosis in patients with psoriasis is 48% (15). Patients with moderate-to-severe psoriasis who consult dermatologists frequently show this hepatic metabolic situation. From the pathogenetic point of view, obesity is a metabolic disease but also an inflammatory disease involving several body regions, including adipose tissue, liver, pancreas, muscles and also brain (16). A hypothalamic inflammation may also occur, i.e. the brain can become insensitive to the anorexia-inducing stimulus of leptin, a satiety signaling adipocytokine. Therefore, overweight or obese subjects tend to eat excessively because they lack the leptin-induced satiety stimulus induced. Also brain inflammation can have relevant sequelae.

However, if psoriasis is a skin disease and the inflammation affects the skin, which is the link with the systemic involvement? Some inflammatory markers have been identified which are increased in patients with psoriasis independently from arthritis. These include C-reactive protein (CRP) which is the easiest to measure: it tends to decrease when the psoriasis is effectively treated, but CRP decrease is not sufficient to reduce the cardiovascular risk (17). Other inflammatory biomarkers are interleukin 6, adiponectin (15) and other adipocytokines, including chemerin which not only has a pro-inflammatory action, and is strictly associated with obesity, with tryglicerides value, but is also a chemotactic factor for plasmocytoid dendritic cells, which are not normally seen in healthy skin, but are attracted in the pre-psoriatic skin by chemerin. Also resistin is increased in psoriatic patients: it is an adipocytokine, an independent marker of insulin-resistance (18).

Another interesting topic which is currently studied is uric acid activity; uric acid has a protective antioxidant action at low concentrations, but can be toxic also for the endothelium at high concentrations. Preliminary data seem to show that the prevalence of hyperuricemia in psoriatic patients is 19%, significantly higher than in the general population. Moreover, it is thought that there are some mediators which are intrinsically released by keratinocytes and are associated with psoriatic inflammation, involving not only skin, but also other body organs, including liver, muscle or fat tissue, with a systemic impact at the endothelium level and consequent triggering of cardio-metabolic comorbidities (Figure 1).

Some papers have confirmed that independently from all cardiovascular risks, psoriatic patients have an endothelial dysfunction, regardless of their smoking status, obesity, diabetes and other risk factors (19). The concept of psoriatic march (Figure 2) – inherited from other systemic immune-mediated diseases like SLE – involves a number of factors, including metabolic syndrome, smoking status, diabetes and hypertension and supports an increased incidence of cardiovascular events as well as cardiovascular mortality, in particular in case of moderate-to-severe psoriasis (20).

An item to add to this list which is important in the clinical practice is vitamin D dosage, being particularly poor in patients with psoriasis. The prevalence of vitamin D deficiency is on average 55%, but if it is measured during the winter, it may be as high as 81% in patients with psoriasis. This is the reason why in the clinical practice it should be measured and balanced in case of deficiency (18).

Also from the genetic point of view, data is emerging on the pathogenic association between psoriasis and cardio-metabolic comorbidities: four European and American independent databases have confirmed ten

![Inflammatory mediators released from psoriatic lesions may have systemic effects](Figure 1 - Main inflammation mediators released by the psoriatic plaque and their systemic effects.)
metabolic-SNPs (single-nucleotide polymorphism) equivalent to punctiform mutations, which are common to psoriasis and cardio-metabolic comorbidities, including dyslipidemia and diabetes (21). Of note, three SNPs are located on chromosome 6 proximal to HLA: HLA cw6 is intrinsically associated with a higher risk of developing psoriasis. Moreover, a higher prevalence of cardiovascular events, especially at a young age, was observed in the parents of patients with psoriasis (22).

How much all this influences dermatologists’ activity? The first issue to be considered is that obesity is an independent risk factor for the development of psoriatic arthritis and psoriasis (23). Moreover, obesity can be considered as a risk factor for the development of methotrexate-induced hepatic toxicity and cyclosporine-induced renal toxicity, and generally patients with a high BMI (Body Mass Index) have a lower response to treatments, including biological agents (24, 25). Several studies have been published on the role of hepatic steatosis as a risk factor for methotrexate-induced hepatic toxicity (26).

The use of cyclosporine is independently associated with the risk for dyslipidemia, and methotrexate and infliximab with the risk for increased transaminases (27). Moreover, it is important to highlight the role of non-pharmacological interventions. A number of clinical trials demonstrates that a significant loss of body weight – i.e. that obtained by means of bariatric surgery – can improve psoriasis independently from drug treatment (28, 29). Moreover, it has been demonstrated that patients with psoriasis treated with low-dose cyclosporine, have a better response if a calorie-controlled diet is associated to drug treatment (30). The other important component of non-pharmacological interventions is physical activity. A wide American study on patients who were followed up perspective over a period of time demonstrated an inverse association between the risk of developing psoriasis over time and physical activity (31).

In conclusion, evidence suggests that psoriasis is associated with an inflammation which is not only cutaneous. This can be due to common genes between psoriasis and its comorbidities, and it is therefore appropriate to keep these comorbidities into consideration when choosing drug treatments.

References