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Cardiometabolic Comorbidities and the Approach to Patients with Psoriasis

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Abstract. Psoriasis is a chronic inflammatory, immune-mediated skin disease, which may cause significant deterioration in the quality of life. Recent evidence indicates that psoriasis and psoriatic arthritis are frequently associated with cardiometabolic diseases including myocardial infarction, stroke, diabetes, obesity, dyslipidemia and non-alcoholic fatty liver disease. Although the causal relationship between cardiometabolic comorbidities and psoriasis has not yet been completely proven, it appears that obesity is a relevant risk factor for the development of psoriasis and metabolic syndrome. In addition, moderate to severe psoriasis itself is a risk factor for cardiovascular disease and the metabolic syndrome. Some common genetic traits as well as inflammatory mechanisms may underlie the development of psoriasis and cardiometabolic comorbidities. The presence of comorbidities has important implications in the global approach to patients with psoriasis. Traditional systemic anti-psoriatic agents could negatively affect cardiometabolic comorbidities, and may have important interactions with drugs commonly used by psoriasis patients. In contrast, the recent findings that the risk of myocardial infarction is markedly reduced in rheumatoid arthritis patients who respond to anti-TNF-α therapy compared with non-responders supports the hypothesis that the anti-inflammatory effect of TNF-α blockers might potentially reduce the cardiovascular risk also in psoriasis patients. Finally, patients with moderate to severe psoriasis should be treated promptly and effectively, should also be encouraged to drastically correct their modifiable cardiovascular risk factors, in particular obesity and smoking habit.

Key words: psoriasis, metabolic syndrome, obesity, cardiovascular risk.

ENFERMEDADES CARDIOMETABÓLICAS CONCOMITANTES Y ENFOQUE DE LOS PACIENTES CON PSORIASIS

Resumen. La psoriasis es una enfermedad cutánea inflamatoria e inmunológica que puede ocasionar un deterioro significativo de la calidad de vida.

La evidencia reciente señala que la psoriasis y la artritis psoriásica se asocian con enfermedades cardiometabólicas que comprenden el infarto de miocardio, el accidente cerebrovascular, la diabetes, la obesidad, la dislipemia y la esteatosis hepática de origen no etílico. Aunque la relación causal entre las enfermedades cardiometabólicas concomitantes y la psoriasis aún no se ha demostrado completamente, parece que la obesidad es un factor de riesgo relevante para el desarrollo de la psoriasis y del síndrome metabólico. Además, la psoriasis moderada o grave es, en sí misma, un factor de riesgo para la enfermedad cardiovascular y el síndrome metabólico. En el desarrollo de la psoriasis y las enfermedades cardiometabólicas concomitantes podrían subyacer algunos rasgos genéticos, así como mecanismos inflamatorios comunes. La presencia de enfermedades concomitantes tiene importantes implicaciones en la estrategia global de tratamiento de los pacientes con psoriasis. Los fármacos sistémicos antipsoriásicos tradicionales pueden influir negativamente en las enfermedades cardiometabólicas concomitantes y pueden presentar importantes interacciones con fármacos frecuentemente utilizados en pacientes con psoriasis.

En contraposición, los hallazgos recientes sobre la marcada disminución del riesgo de infarto de miocardio en pacientes con artritis reumatoide que responden a la terapia anti-TNF-α, comparados con los no respondedores, apoya la hipótesis de que el efecto antinflamatorio de los bloqueantes del TNF-α podría, potencialmente, reducir también el riesgo cardiovascular en los pacientes con psoriasis. Por último, los pacientes con psoriasis moderada a grave deben ser tratados rápida y eficazmente y se les debe animar a corregir radicalmente los factores modificables de riesgo cardiovascular, en particular la obesidad y el hábito tabáquico.

Palabras clave: psoriasis, síndrome metabólico, obesidad, riesgo cardiovascular.

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The Psoriatic March

Psoriasis is a chronic inflammatory skin disease affecting 2-3 % of the general population[1]. It is characterized by erythematous and scaling plaques, which are frequently itchy or painful. Genetic predisposition to psoriasis is complex, and includes aberrant innate and immune responses and abnormal reaction of keratinocytes to inflammatory signals[2]. Innate as well as adaptive immunity is crucial in the initiation and maintenance of psoriatic plaques[3-5]. Type 1 and type 17 T lymphocytes secreting, respectively, interferon-γ, IL-2, and IL-17 and IL-22 predominate in lesional skin and are essential for disease expression. In particular, intraepidermal CD8+ type 1 and dermal/epidermal CD4+ type 17 T cells appear to be the most relevant pathogenetic T cells[6-8]. These T cells act mostly by secreting cytokines including the above mentioned products as well as interferon-α, TNF-α, IL-1 and IL-6. Cytokines indirectly induce epidermal hyperplasia by stimulating the activation and/or secretion of autocrine growth factors from keratinocytes. Cytokine-activated keratinocytes secrete chemokines and cytokines for further attraction and activation of leukocytes, thus establishing vicious circles that perpetuate lesions. Among the earliest events in the innate immunity cascade driving psoriatic inflammation is the secretion of type I IFN by activated plasmacytoid dendritic cells (pDC), a special DC subset strategically positioned in pre-psoriatic symptomless skin, whose recruitment in psoriatic skin is strictly dependent on the chemerin/ChemR23 axis. Pro-chemerin is produced primarily by dermal fibroblasts, but also by mast cells and endothelial cells, and once secreted, it is activated by enzymes produced by neutrophils[9].

Other than being responsible for skin alterations, psoriatic cytokines can favour the development of psoriatic arthritis (PsA), and mediate a number of metabolic effects that in turn can favour the progression of insulin resistance, dyslipidemia and non alcoholic fatty liver disease (NAFLD)[10], hence directly and/or indirectly favouring the development of atherosclerosis. Therefore, moderate to severe psoriasis may increase the risk of cardiovascular diseases, configuring the so-called "psoriatic march" (fig. 1). As skin inflammation is largely reversible and natural progression might be attenuated or prevented, an early and effective psoriasis treatment could be effective in blocking the progression of the psoriatic march. On the other hand, it is also possible to hypothesize that metabolic comorbidities such obesity, NAFLD and metabolic syndrome might actively contribute to the severity of psoriasis through the release of pathogenetic mediators from the inflamed liver and/or visceral adipose tissues, including increased reactive oxygen species, elevated C reactive protein (CRP), IL-6 and adipokines, which also interface with thrombosis[11].

Psoriasis Comorbidities

The most common psoriasis comorbidity is PsA which affects up to one-third of patients with psoriasis[12,13]. It is a seronegative spondyloarthritis involving both the peripheral joints and the axial skeleton, and is usually associated with enthesitis, i.e the inflammation at tendon insertion. Enthesopathy has been reported to be also very common in psoriasis patients without clinical signs or symptoms of arthritis[14]. PsA runs a chronic fluctuating course, and about

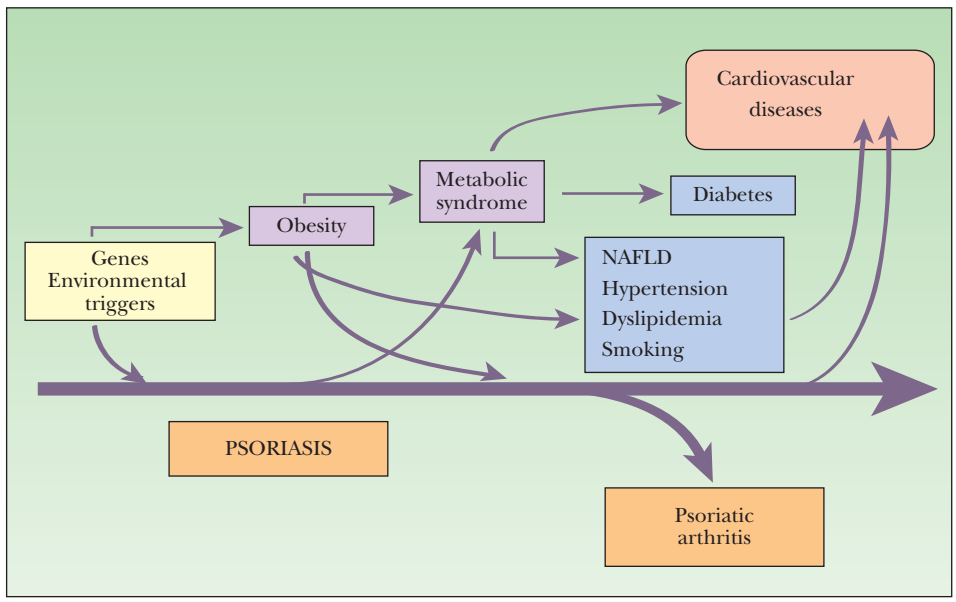

Figure 1. The psoriatic march. Genetic and environmental factors predispose to psoriasis and obesity. Obesity is a risk factor for both psoriasis and metabolic syndrome. However, inflammation associated with moderate to severe psoriasis can in turn favor insulin resistance, dyslipidemia, obesity and non alcoholic fatty liver disease (NAFLD), hence directly and/or indirectly fuelling atherosclerosis, and configuring the so-called "psoriatic march". Ultimately, moderate to severe psoriasis directly and indirectly increases the risk of cardiovascular diseases and mortality. Psoriasis also precedes the development of psoriatic arthritis.

20 % of the patients develop a very destructive and disabling form[15]. In addition, psoriasis has a major impact on patients' life and is associated with depressive symptoms in a relatively large proportion of patients[16]. 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 the higher risk of PsA[17].

Although already reported twenty years ago, recent large epidemiological studies have confirmed that chronic plaque psoriasis and PsA are associated with cardiometabolic disorders that confer an unfavourable cardiovascular risk profile, and a higher mortality rate[18].

Cardiometabolic Diseases Associated with Psoriasis

Atherothrombotic Diseases

Psoriasis patients show an increased risk of atherothrombotic diseases independently of concomitant 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 with 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[19]. 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 with the general population[20]. In contrast, psoriasis outpatients did not have an increased cardiovascular mortality risk. However, the most notable observation are two large retrospective cohort studies using the General Practice Research Database that involved almost 130,000 patients with psoriasis[21,22]. The General Practice Research Database is a large computerized database that contains longitudinal medical records from approximately 450 primary care practices throughout the United Kingdom. In these recent studies the risk of myocardial infarction was 1.29 (95 % confidence interval [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 independent of major risk factors identified in routine medical care. Consistent with the epidemiologic observations, other studies have shown that psoriasis is associated with atherosclerosis biomarkers. A cross-sectional study of 32 patients with severe psoriasis and 32 matched outpatient controls evaluated the prevalence of coronary artery disease using spiral computed tomography to measure coronary artery calcification. Severe psoriasis patients had a higher prevalence of coronary artery disease (CAD) compared with controls (59 % vs. 28 % respectively, $p < 0.02$), and had more severe CAD based on the coronary artery calcification scores[23]. Again, psoriasis independently predicted CAD when controlling for cardiovascular risk factors. Endothelial dysfunction is the critical early step in the process of atherogenesis, and it is commonly investigated by measuring arterial stiffness. Arterial stiffness has been found to be elevated in psoriasis patients independently of the other cardiovascular risk factors. In a cross-sectional study, we found that carotid femoral pulse wave velocity (PWVcf) was significantly higher in patients with psoriasis than in controls[24]. Difference was still significant after adjustment for age, gender, smoking status, hypertension and body mass index. Finally, there was a positive correlation between PWVcf and years of psoriasis duration, but not with disease severity[24].

Insulin Resistance/Type II Diabetes

Higher prevalence of insulin resistance and/or type II 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 53 and 40 % out of 17 patients with early (i.e. < 40 years) and late onset (i.e. > 40 years) psoriasis, respectively, which was significantly higher compared to 2.5 % in the controls[25]. Boehncke et al observed a significant correlation between psoriasis severity, insulin secretion and serum resistin levels, a cytokine known to be increased in insulin resistance, supporting the concept of insulin resistance as a consequence of severe chronic inflammation[26]. Indeed, Kaye et al found that psoriasis itself confers a risk of developing diabetes as the cumulative incidence of diabetes in the psoriasis cohort was higher than in the general population (hazard ratio 1.33; CI: 1.25-1.42)[27]. The association between psoriasis and type II diabetes is even stronger. Numerous cross sectional studies have shown that psoriasis, especially severe disease, confers a higher risk (up to 2.48) for diabetes[28,29]. The increased prevalence of diabetes in patients with psoriasis appears to be independent from traditional diabetes risk factors such as obesity and dyslipidemia[30]. Shared genetic background may also contribute to the susceptibility to both psoriasis and diabetes[31].

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 cholesterol[32,33]. Although the confounding effect of obesity and insulin resistance should be taken into account in evaluating this association, Mallbris et al found that patients 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, which suggests that dyslipoproteinemia in psoriasis might be genetically determined rather than acquired[34]. Indeed, apolipoprotein E gene polymorphism, which is strongly associated with hyperlipidemic states, has been reported in patients with chronic plaque and guttate psoriasis[35]. Moreover, isolated cases of lipoprotein glomerulopathy associated with apolipoprotein E3/3 in psoriasis have been reported[36].

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 with BMI. However, controversy still exists as to whether obesity is a result of psoriasis or a causative factor. A recent population-based study of patients with mild or severe psoriasis showed that the risk of obesity was significantly increased in psoriasis patients compared with healthy controls and strongly associated with disease severity (odds ratio [OR]: 1.27; 95% CI: 1.24-1.31 for mild psoriasis and OR: 1.79; 95% CI: 1.55-2.05 for severe psoriasis)[33]. In line with these findings, Herron et al found that psoriasis patients were almost twice as likely to be obese compared with the general population (34% vs 18%, respectively; p 0.001)[37]. Based on patient perception of body image before and at psoriasis onset, the investigators concluded that obesity appears 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 in psoriasis patients at disease onset versus controls[38]. 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 identify 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) of developing psoriasis, and those with a BMI > 29 kg/m^2 had an OR of 1.9 (95% CI: 1.2-2.8)[39]. A very large prospective cohort study on young women has confirmed that obesity precedes psoriasis, with the body weight being directly associated with the risk of developing psoriasis[40]. 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[41]. Very interestingly, it has been reported that the BMI negatively affect the short term clinical response to systemic treatments for psoriasis[42] and biologics with a fixed-dose regimen (etanercept, adalimumab, ustekimumab) may have a compromised efficacy in heavier individuals[43]. In line with these findings, we observed that a moderate weight loss (i.e. 6% of body weight) increases the responsiveness of obese psoriasis patients to a suboptimal dose of cyclosporine[44].

Metabolic Syndrome

The metabolic syndrome is a constellation of metabolic changes, in particular insulin resistance, which collectively confer a higher proinflammatory and prothrombotic risk[45]. The most widely accepted criteria for metabolic syndrome definition are 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) in men; > 88 cm (35 in) 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 mmHg or under treatment), and an elevated fasting glucose (> 110 mg/dl or under treatment)[46]. 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)[47]. However, when looking at individual components of the metabolic syndrome, only hypertriglyceridemia and abdominal obesity were significantly more prevalent in patients with psoriasis than in non psoriatic patients. Furthermore, hospitalized psoriasis patients vs. hospitalized melanoma patients in Germany were found to have 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[48]. 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[49,50].

Non Alcoholic Fatty Liver Disease

Non alcoholic fatty liver disease 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[51]. 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[52]. Accordingly, a huge number of individuals are at risk of developing advanced liver disease, including fibrosis and cirrhosis. There is now growing evidence suggesting that NAFLD may be also linked to increased risk of future cardiovascular events independently of conventional risk factors and metabolic syndrome components[53]. We found that the frequency of NAFLD –as diagnosed by patient history, blood sampling and characteristic ultrasonographic features– in patients with chronic plaque psoriasis is remarkably greater than that in non-psoriasis control subjects (47 % vs. 28 %; $p < 0.0001$), who were matched for age, gender and BMI[54]. Notably, the two groups also resulted comparable for the presence of the metabolic syndrome, possibly because they were matched for BMI. In addition, none of our psoriasis patients were 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 potential confounders such as age, gender, BMI, psoriasis duration and alcohol consumption. Although the 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 the highest insulin resistance are the ones who develop NAFLD. A 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[55]. 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 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[56]. 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[57]. Indeed, it was found that patients with psoriasis and NAFLD were more likely to have metabolic syndrome, and had significantly higher serum CRP and interleukin-6 levels, and lower serum adiponectin than those with psoriasis alone[54].

Cardiometabolic Comorbidities Change the Approach to Patients with Psoriasis

Systemic treatments for psoriasis including methotrexate, cyclosporine, retinoids and biologics, may contribute either to reduce or increase 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[58]. 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[59]. The presence of NALFD should be taken into great consideration when choosing therapy as acitretin, cyclosporine and methotrexate are potentially hepatotoxic and consequently could favour the progression from NAFLD to fibrosis and even cirrhosis. Cyclosporine can induce or worsen arterial hypertension, alter glucose tolerance and/or interfere with fatty acid metabolism favouring hyperlipemia[60]. Pharmacological treatment of dyslipidemia in psoriasis patients needs attention as statins could favour myolysis when associated with cyclosporine or retinoids. Also retinoids may increase serum cholesterol and triglycerides[61]. The occurrence of hypertrigliceridemia and hypercholesterolemia has also been occasionally reported in patients treated with anti-TNF-α agents, as well as increased liver transaminases, whereas true hepatitis has been a more rare but established event[62-64]. In addition, anti-TNF-α agents increase body weight in patients with psoriasis and Crohn's disease[65-67]. 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 observed in about 25 % of patients. We could not identify clinical parameters predicting this phenomenon.

Lifestyle modifications, including a low calorie diet, may supplement the pharmacological treatment of obese psoriasis patients. Indeed, we found that a moderate weight loss (i.e. 5 to 10 % of body weight) increases the responsiveness of obese patients with moderate to severe chronic plaque psoriasis to low doses of cyclosporine[44]. Weight

loss, through calorie restriction, induces decreases in insulin, leptin, C reactive protein and MCP-1, and increases adiponectin levels resulting in an anti-inflammatory effect.

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 with non-responders support the hypothesis that the anti-inflammatory effect of TNF-α blockers might improve the cardiovascular risk[68]. In particular, anti-TNF-α treatment has been shown to improve endothelial function as well as to reduce CRP serum levels in patients with rheumatoid arthritis[69]. Whether this effect could also be present and relevant in reducing thrombotic events in psoriasis patients needs to be investigated.

Concluding Remarks

Psoriasis is frequently associated with cardiometabolic disorders. The association between psoriasis and comorbidities is complex as the contributing mechanisms are largely unknown. The direct link between psoriasis and associated diseases is the presence of chronic inflammation and, in particular, elevated levels of multifunctional cytokines, such as TNF-α. Moreover, some common genetic traits may underlie the development of psoriasis and cardiometabolic comorbidities. However, statistical association does not prove causality and it could be speculated that impaired psoriasis-related quality of life may lead to unhealthy life style behaviours such as smoking, alcohol consumption, decreased physical activity and obesity which are independent risk factors for cardiovascular diseases[70]. However, by using multivariate regression analysis it has been reported that psoriasis may also act as an independent cardiovascular risk factor, but its impact is currently not measurable. Criteria are needed to identify which psoriasis patients are at higher risk of developing thrombotic events in order to select specific prevention strategies. Limited evidence suggests that psoriasis duration and severity are directly associated with an increased cardiovascular risk, but more appropriate biomarkers of disease severity are required. Moreover, further research is necessary to understand whether treatment of psoriasis could reduce the risk of atherothrombotic events, or, conversely, whether treatment of comorbidities improves psoriasis. We believe that psoriasis patients should be strongly encouraged to correct their modifiable cardiovascular risk factors, particularly obesity and smoking habits, and there is early evidence that this may also benefit psoriasis management[44]. On the other hand, if chronic inflammation is the driving force for premature atherosclerosis, psoriasis should be treated earlier and more effectively. Finally, cardiometabolic comorbidities change the approach to patients with psoriasis as it reinforces the need to treat the whole patient, reminding dermatologists that they are, above all, physicians with a special interest in the skin.

Conflict of interest
Authors have no conflict of interest to declare.

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