

## Non-alcoholic fatty liver disease and psoriasis: So far, so near

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### Abstract

Psoriasis is a chronic inflammatory immune-mediated skin diseases which is frequently associated to comorbidities. Non-alcoholic fatty liver disease (NAFLD) is defined as an excessive accumulation of triglycerides in hepatocytes and includes a wide spectrum of liver conditions ranging from relatively benign steatosis to non-alcoholic steatohepatitis with fatty infiltration and lobular inflammation and to cirrhosis and end-stage liver disease. Actually, psoriasis is considered a systemic diseases associated to comorbidities, as metabolic syndrome and NAFLD is seen the hepatic manifestation of the metabolic syndrome. The possible link between psoriasis, obesity and metabolic syndrome, which are known risk factors for NAFLD has been

recently documented focusing in the crucial role of the adipose tissue in the development of the inflammatory background sharing by the above entities. According to recent data, patients with psoriasis show a greater prevalence of NAFLD and metabolic syndrome than the general population. Moreover, patients with NAFLD and psoriasis are at higher risk of severe liver fibrosis than those with NAFLD and without psoriasis. The link between these pathological conditions appears to be a chronic low-grade inflammatory status. The aim of this review is to focus on the multiple aspects linking NAFLD and psoriasis, only apparently far diseases.

**Key words:** Psoriasis; Non-alcoholic fatty liver disease; Adipose tissue; Adipocytokines; Biologic therapies; Non-biologic therapies

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**Core tip:** The review focuses on the multiple pathogenetic aspects of the possible link between psoriasis and non-alcoholic fatty liver disease (NAFLD) emphasizing the most recent scientific data. The importance of the multidisciplinary approach to patients affected by psoriasis is underlined and the therapeutic options to treat concomitant psoriasis and NAFLD is discussed evaluating the risk benefit of both biologic and non-biologic therapies.

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### INTRODUCTION

Psoriasis is an immune-mediated, chronic, and inflam-

matory disease with an estimated prevalence of 2%-3% in the worldwide<sup>[1]</sup>.

Recent evidence have shown that psoriasis is not only the disease of the skin surface but a complex entity with multi-systemic involvement and with a deep influence on patients' quality of life, morbidity and mortality<sup>[2]</sup>.

In particular, psoriasis is frequently associated to the so-called "psoriatic comorbidities", including arthropathy, uveitis, inflammatory bowel diseases and a cluster of medical conditions known as metabolic syndrome<sup>[3]</sup> (Figure 1).

According to the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATPIII), a patient is affected by metabolic syndrome, if he/she shows at least three of these following criteria: Abdominal obesity, defined as waist circumference  $\geq 102$  cm in men and  $\geq 88$  cm in women; Triglycerides plasma levels  $\geq 150$  mg/dL; high-density lipoproteins (HDL) cholesterol plasma levels not more than 40 mg/dL in men and 50 mg/dL in women; Blood pressure more than 130 mmHg (systolic) and 85 mmHg (diastolic); Fasting plasma glucose levels more than 100 mg/dL<sup>[4]</sup>.

Non-alcoholic fatty liver disease (NAFLD) is defined as the hepatic excessive accumulation of triglycerides in patients without a history of potus<sup>[5,6]</sup>.

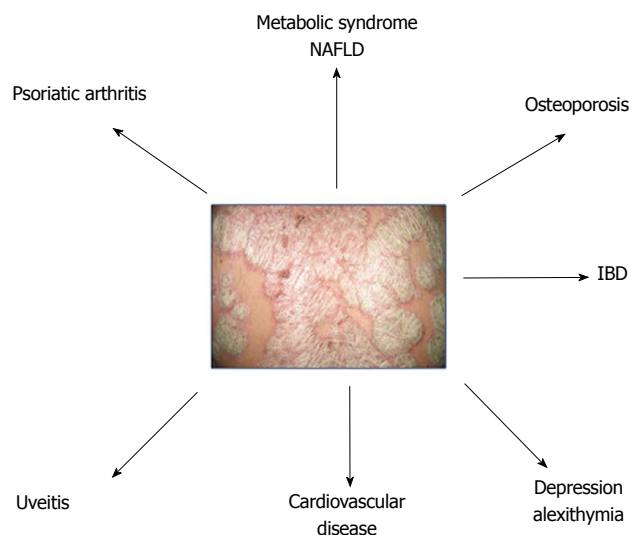
NAFLD include a wide variety of liver conditions ranging from relatively benign steatosis, consisting in fatty infiltration, to non-alcoholic steato-hepatitis (NASH) with fatty infiltration and lobular inflammation and to cirrhosis and hepatocellular carcinoma<sup>[7,8]</sup>.

NAFLD is currently the most common chronic liver disease in Western countries with a prevalence of 10%-25% and, it is now seen as the most frequent liver disorder, in particular in obese people<sup>[9]</sup>. Actually, NAFLD is strictly linked to the MetS being its hepatic manifestation<sup>[10]</sup>. It is known that metabolic syndrome is associated either to psoriasis and to NAFLD, thus it could be reasonable that both entities could be present in an individual simultaneously<sup>[11]</sup>. This review provides an overview on the most recent findings on the possible link between NAFLD and psoriasis, evaluating the common underlying physio-pathogenic process and the role of systemic drugs on their management.

## NAFLD: THE MULTIPLE HITS HYPOTHESIS

The liver plays a central role in lipid metabolism, importing serum free fatty acids (FFA), storing and exporting lipids and lipoproteins. Although the NAFLD pathophysiology has not been completely elucidated, the so called "multiple-hit hypothesis" describes it as a complex, two-step liver injury<sup>[12]</sup>.

The first hit is characterized by hepatic triglyceride accumulation contributing to steatosis; therefore, steatotic liver appears to be more vulnerable to the



**Figure 1 Comorbidities in psoriasis.** NAFLD: Non-alcoholic fatty liver disease. IBD: Inflammatory bowel diseases.

"second hit" of adipokine-induced liver injury, oxidative and endoplasmic reticulum stresses, mitochondrial dysfunction, and hepatic apoptosis, which subsequently promote the transition from simple steatosis to steatohepatitis<sup>[13-16]</sup> (Figure 2). Insulin resistance (IR) appears to exert a central role in both the first and second hits<sup>[17]</sup>. Insulin is an anabolic hormone that regulates glucose metabolism, gene expression, energy homeostasis and enzymatic functions<sup>[18]</sup>. The phosphatidylinositol 3-kinase (PI3K)-AKT pathway and the Ras-mitogen activated protein kinase (MAPK) pathway are the two most important pathway that are involved in insulin-mediated functions<sup>[17,18]</sup>.

In particular, the inhibition of gluconeogenesis and the uptake of glucose is linked to PI3K-AKT, while cell proliferation and differentiation depend on the interaction between MAPK and PI3K-AKT.

Liver, adipose tissue and skeletal muscle are the most important insulin-target tissues<sup>[17,18]</sup>. In the liver, insulin regulates the glucose metabolism, while in the adipose tissue it reduces the hormone sensitive lipase activity with the subsequent inhibition of the free fatty acid efflux out of adipocytes<sup>[17,18]</sup>.

A subject is considered insulin resistant when his or her insulin mediated glucose uptake by muscle and adipose tissue is impaired. As a compensatory mechanism, beta cells in the pancreas start to secrete increased amounts of insulin to maintain normoglycemia, leading to hyper-insulemia<sup>[19]</sup>.

In the adipose tissue, insulin allows free fatty esterification and triglyceride fat storage. When insulin resistance develops, free fatty acids are inappropriately shifted to non-adipose tissues, as the liver. Moreover, the hepatic lipogenesis and the activation of pro-fibrotic cytokines are mediated by hyperinsulinemia<sup>[20,21]</sup>.

Insulin resistance and hyperinsulinemia increase the excretion of triglycerides by the liver, resulting in elevated serum levels of triglycerides<sup>[20,21]</sup>.

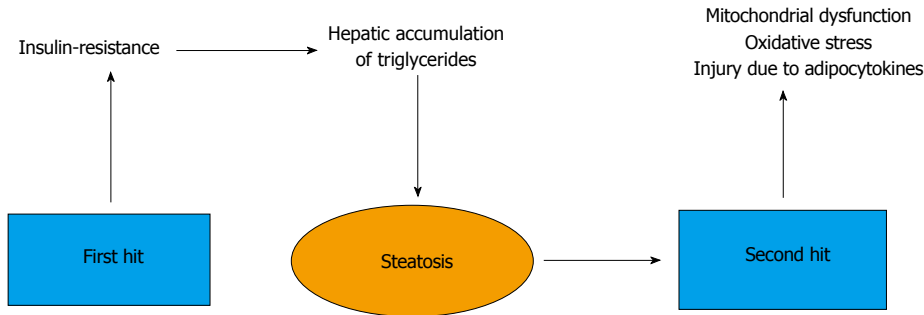


Figure 2 Non-alcoholic fatty liver disease and the two hits hypothesis.

In summary, different mechanisms are implicated in the hepatic triglyceride storage, as the increased triglyceride or FFA synthesis, the reduced FFA transport from the hepatocytes, an excessive transport of FFA to the liver or an abnormal dietary intake of FFA<sup>[22-24]</sup>.

Thus, this lipids' (tryglicerides and FFAs) accumulation in the liver leads to lipotoxicity and consequently to the mitochondrial disfunction and the oxidative stress, which represent the further liver damage<sup>[17]</sup>.

Many studies demonstrated a direct link between NAFLD and cardiovascular disease: inflammation, oxidative stress, insulin resistance, ectopic adipose tissue distribution, dyslipidemia, endothelial dysfunction, and adipocytokines are considered the common and shared pathogenetic processes<sup>[21,22]</sup>.

## PSORIASIS: A SYSTEMIC DISEASE

Epidermal hyperproliferation, abnormal keratinocyte differentiation, angiogenesis and activated CD4<sup>+</sup> and CD8<sup>+</sup> T-cell infiltrates in the dermis and epidermis are the most common detectable histologic features in psoriasis<sup>[25]</sup>.

The pathogenesis of psoriasis is characterized by the involvement of both innate and adaptive immunity. In the beginning of the inflammatory process, NK cells play an important role releasing pro-inflammatory cytokines; subsequently the Th1-Th17 interaction is crucial in the amplification of the flogosis<sup>[26]</sup>.

Clinically, psoriasis is characterized by sharply demarcated erythematous plaques covered by silvery-white scales preferentially on the elbows, knees, scalp, umbilicus and lumbar area<sup>[27,28]</sup>.

### Psoriasis and cardiovascular risk

Approximately 80% of psoriatic patients have limited disease, involving < 10% body surface area, but approximately 20% have more extensive skin involvement. Although psoriasis is rarely life-threatening, it exerts an important impact on patients' quality of life, similar to that caused by diabetes, cancer or heart disease<sup>[29-31]</sup>.

The underlying low and persistent inflammatory status with increased levels of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-6, seems to be

responsible of the metabolic dysregulation in psoriasis<sup>[32]</sup>.

Cardiovascular risk factors, such as diabetes, hypertension, dyslipidemia and obesity, are more prevalent in patients affected by psoriasis; moreover it has been suggested that the chronic inflammatory nature of psoriasis is also a contributing and potentially an independent risk factor for the development of cardiovascular disease<sup>[33]</sup>.

Recent evidence have demonstrated that psoriasis may represent an independent risk factor for cardiovascular morbidity and mortality: the cardiovascular risk is increased of about almost three times in patients affected by moderate to severe psoriasis, particularly in young people. For this reason, patients with severe psoriasis appear to have a reduced life expectancy of about 6-year<sup>[34]</sup>.

Furthermore, recent data have demonstrated that NAFLD may be linked to increased risk of cardiovascular events independently from conventional risk factors<sup>[35,36]</sup>.

Many evidences have shown that psoriatic patients have altered lipid metabolism with high levels of plasma cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, very low-density lipoprotein cholesterol, and decreased HDL cholesterol and antioxidant capacity. This dyslipidemic profile could precede the development of psoriasis<sup>[37]</sup>.

In 1994, Offidani *et al*<sup>[38]</sup> evaluated the lipid profile in children affected by psoriasis, demonstrating higher levels of plasma total cholesterol and no significant changes of plasma triglycerides<sup>[38]</sup>. Moreover, high percentage content of total cholesterol and of the cholesterol/protein ratio in LDL and in HDL was found with an alteration of their fluidity.

Raised levels of LDL and decreased levels of HDL cholesterol are responsible of coronary artery disease and of mortality for cardiovascular disease<sup>[39]</sup>.

### Psoriasis and hypertension

Hypertension shows an higher prevalence in patients affected by psoriasis compared with controls, thus a link between hypertension and psoriasis has been postulated<sup>[37]</sup>.

The increased production of angiotensinogen by adipose tissue, subsequently converted to angiotensin

II through angiotensin converting enzyme (ACE) could represent the central causative element of the hypertension in psoriatic patients<sup>[40]</sup>. It has been demonstrated an increase of ACE serum levels in psoriatic patients<sup>[37,40]</sup>. Angiotensin II is responsible for kidney salt retention and, acting as vasoconstrictor, for vascular tone regulation; moreover, it stimulates T-cell proliferation promoting inflammation and atherosclerosis<sup>[40]</sup>.

The association between hypertension and psoriasis may also be attributed to the increased oxidative stress in psoriatic patients: greater levels of reactive oxygen species can damage endothelium-dependent vasodilation<sup>[40]</sup>.

Furthermore, endothelin-1 could be involved in hypertension pathogenesis of psoriatic patients. Endothelin-1 is produced by keratinocytes and it promotes blood vessels vasoconstriction with consequently blood pressure increase. In lesional skin and in serum of psoriatic patients, endothelin-1 expression appears to be altered correlating to psoriasis disease severity<sup>[40]</sup>.

### Psoriasis and prothrombotic state

Metabolic syndrome and psoriasis have been associated to a pro-inflammatory and/or pro-thrombotic state probably related to elevated serum levels of PAI-1, fibrinogen and reactive C-protein (RCP). IL-6 induces RCP increase and it has been shown to be predictive of future cardiovascular disease (CVD) in healthy subjects. Moreover, the risk of in patients with either diabetes or MetS is significantly increased in the presence of elevated RCP levels<sup>[37]</sup>.

McDonald *et al.*<sup>[41]</sup> have shown that the global risk of arterial and venous diseases appeared to be 2.2 times higher in psoriatic patients compared with control patients affected by different skin diseases<sup>[41]</sup>. Another study conducted in a large cohort of psoriatic patients have underlined that the risk of CV mortality was 50% higher compared to the general population<sup>[42]</sup>.

These data were confirmed by Lin *et al.*<sup>[43]</sup>, who detected that patients affected by psoriatic arthritis (PsA) had an increased prevalence of metabolic syndrome with significantly greater carotid intima-media thickness compared to patients with psoriasis only. Furthermore, greatest CIMT measurements were detectable in PsA patients with metabolic syndrome compared to PsA patients without metabolic syndrome and psoriasis patients with or without metabolic syndrome<sup>[43]</sup>.

## PSORIASIS AND NAFLD: EPIDEMIOLOGY

Recent studies focused on the possible link between psoriasis, obesity and metabolic syndrome, which are known risk factors for NAFLD<sup>[44]</sup>.

It is known that, after the age of 40 years, the psoriatic patients have a higher prevalence of metabolic syndrome and an increased risk for the each components of MetS than controls<sup>[11]</sup>.

Moreover, the association between psoriasis and MetS is directly correlated to the severity of psoriasis and it is independent from the presence of obesity in psoriasis<sup>[45-47]</sup>. Considering that metabolic syndrome is detected both in NAFLD and psoriasis, it is likely that these two pathological entities can coexist in the same patient<sup>[11]</sup>. Lonardo *et al.*<sup>[48]</sup> in 2001 firstly documented three cases of concomitant psoriasis and NASH, confirmed by liver biopsy. All patients were obese or overweight and showed MetS components. In an Italian prospective observational study, the prevalence NAFLD in psoriatic patients was significantly increased, compared to general Italian population<sup>[49,50]</sup>.

Furthermore, NAFLD was unrelated to the severity of the skin disease, but logistic regression showed that patients with psoriasis and NAFLD showed a higher risk of psoriatic arthritis. This aspect could reflect the actions of pro-inflammatory cytokines in both diseases. Moreover, psoriatic patients with NAFLD had also significantly higher AST/ALT ratio and higher non-invasive fibrosis scores compared with controls with NAFLD not associated with psoriasis. AST/ALT ratio has proven to be an independent predictive factor for liver fibrosis in patients with NAFLD<sup>[25]</sup>.

Consequently, the risk of severe liver fibrosis is higher in patients affected by both NAFLD and psoriasis than patients with only NAFLD. These two parameters are considered independent predictors of liver fibrosis in NAFLD patients<sup>[49,50]</sup>.

These data were confirmed by Gisondi *et al.*<sup>[51]</sup> in a case-control study, who assessed the frequency and characteristics of NAFLD in patients with chronic plaque psoriasis vs healthy controls. Among 130 psoriatic patients, up to nearly half (47% vs 28% of controls) resulted affected by NAFLD, which was strongly related to psoriasis severity according to Psoriasis Area Severity Index (PASI) score. Moreover, patients with psoriasis and NAFLD showed metabolic syndrome and higher serum C-reactive protein<sup>[51]</sup>.

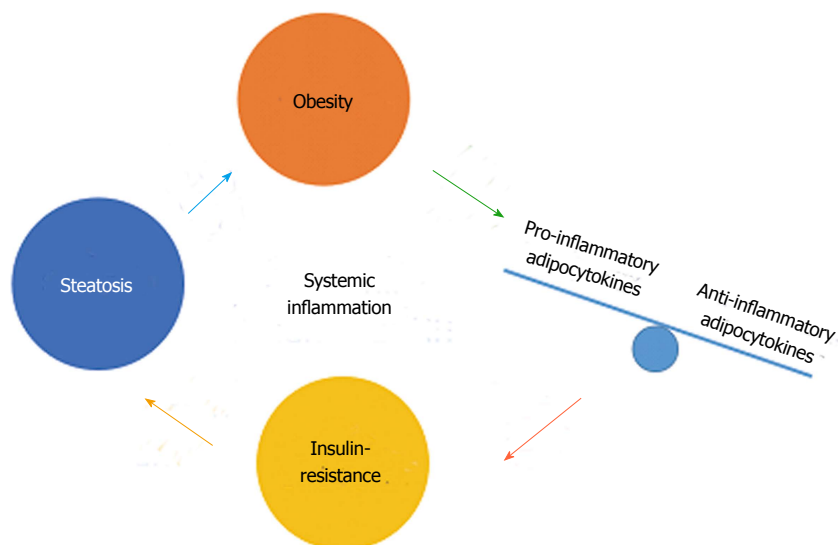
Van der Voort *et al.*<sup>[52]</sup> in 2013 conducted a large prospective population-based cohort study in subjects up to 55 years. Among 2292 participants, 118 (5.1%) were affected by psoriasis and the prevalence of NAFLD was 46.2% in psoriatic patients compared with 33.3% of participants without psoriasis. Thus, after adjustment for alcohol consumption, smoking status, presence of MetS components and alanine aminotransferase, psoriasis remained a significant predictor of NAFLD<sup>[52]</sup>.

## PSORIASIS AND NAFLD: THE PATHOGENIC LINK

The pathogenesis of both NAFLD and psoriasis seems to be multifactorial and complex and the precise link between these two entities has not completely elucidated. It could be speculated that a low, chronic and persistent inflammatory status may be the



Figure 3 The vicious circle.



"primum movens" linking NAFLD and psoriasis.

It is known that psoriasis and obesity are strictly associated: obesity seems to predispose to psoriasis and psoriasis seems to increase the risk of obesity. A recent meta-analysis of epidemiological studies was evaluating the associations between psoriasis and obesity have evidenced that an 1.46 or and 2.23 or for obesity among patients with mild psoriasis and severe psoriasis respectively. One incidence study found that psoriasis patients have a HR of 1.18 for new-onset obesity. Thus, psoriatic patients showed a higher prevalence and incidence of obesity directly correlated to the severity of psoriasis itself<sup>[6,53,54]</sup>. It is known that the increasing prevalence of NAFLD parallels the rise of obesity and its complications<sup>[55]</sup>. Thus, psoriasis and NAFLD could be linked by obesity itself, which may contribute to the development of further MetS components and comorbidities<sup>[55]</sup>.

As psoriasis and NAFLD, obesity is considered a persistent and low-grade inflammatory process<sup>[4,56]</sup>.

The adipose tissue accumulation seems to lead to adipocyte hypertrophy and hyperplasia with a sort of local ischemia; subsequently an inflammatory process and the release of pro-inflammatory chemokines start, attracting macrophages which amplify and spread the inflammatory process in neighboring adipocytes<sup>[57,58]</sup> (Figure 3).

Subcutaneous and central fat (omental and intra-abdominal) are the two most important part of the adipose tissue; the central one, also called visceral adipose tissue (VAT), is considered more metabolically active than the subcutaneous fat. A higher risk of developing insulin resistance and of MetS components is detected in patients affected by central obesity than patients with excess of subcutaneous fat<sup>[59-61]</sup>.

The energy storage, the endocrine role and the participation in the immune system are three important actions of the VAT<sup>[62]</sup>.

Thus, excess adipose tissue results in an unbalance between pro- and anti-inflammatory cytokines and the

increased inflammatory stimuli is responsible for the starting of the persistent low-grade inflammation<sup>[4,58,59]</sup>.

Adipocytokines are bioactive molecules able to modulate appetite-energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure and lipid metabolism by autocrine, paracrine and endocrine way. Furthermore, they play a crucial role in the pathogenesis of metabolic syndrome. Among adipocytokines, TNF- $\alpha$ , IL-6, leptin, visfatin, resistin appear to exert a pro-inflammatory effect, whereas adiponectin has anti-inflammatory properties<sup>[58,59,62]</sup>.

The pathogenesis of both psoriasis and NAFLD is strictly dependent on the above cytokines<sup>[63]</sup>.

Adipocytes and stromal-vascular cells are responsible for the secretion of TNF- $\alpha$ ; adipose tissue TNF- $\alpha$  is not secreted in systemic circulation and acts both in autocrine and paracrine way. In adipose tissue, TNF- $\alpha$  mRNA correlates with body mass index, percentage of body fat and hyper-insulinemia; moreover, weight loss decreases TNF- $\alpha$  levels<sup>[63]</sup>.

TNF- $\alpha$  interfere with insulin action reducing the auto-phosphorylation of tyrosine residues of insulin receptor and phosphorylation of insulin receptor substrate 1 (IRS-1), thus contributing to the first hit of NAFLD<sup>[37,64]</sup>. In addition, the production of adiponectin is inhibited by TNF- $\alpha$ <sup>[65]</sup>.

Finally, a positive correlation between TNF- $\alpha$  and BMI had been shown, and a higher serum levels was reported in patients with NAFLD<sup>[66,67]</sup>.

TNF- $\alpha$  plays a crucial role in the pathogenesis of psoriasis: in fact, psoriatic patients show elevated serum levels of TNF- $\alpha$  which positively correlate with PASI<sup>[68]</sup>. Moreover, TNF- $\alpha$  levels and plasma levels of adiponectin are negatively correlated<sup>[69-71]</sup>.

In psoriasis, TNF- $\alpha$  increases keratinocyte proliferation, pro-inflammatory cytokines' production, expression of vascular endothelial cell adhesion molecules, angiogenesis. In obese adipose tissues, the release TNF- $\alpha$  directly participate in the macrophage recruitment and lipolysis creating and perpetuating a

**Table 1** Role of adipocytokines in non-alcoholic fatty liver disease and psoriasis

Adipocytokines		Psoriasis	NAFLD
Anti-inflammatory	Adiponectin	↓ Promotes anti-inflammatory cytokines	↓ Increase insulin-sensitivity
Pro-inflammatory	IL-6	↑ Keratinocyte proliferation	↑ Contributes to insulin-resistance
	TNF- $\alpha$	↑ (1) Keratinocyte proliferation; (2) Angiogenesis; and (3) Promotes expression of adhesion molecules; and (4) Increase pro-inflammatory cytokines	↑ Contributes to insulin-resistance; Increase hepatic fibrogenesis
	Leptin	↑ (1) Keratinocyte proliferation; (2) Promotes Th1 responses; and (3) Angiogenesis	↑ (1) Leptin-resistance; and (2) Contributes to hepatic fibrogenesis
	Resistin	↑ Increase pro-inflammatory cytokines	↑ (1) Contributes to insulin-resistance; and (2) Controversial data on NAFLD
	Visfatin	↑	Not altered in early stage; Protection toward liver injury (?); Negatively correlated to TNF- $\alpha$
	Ghrelin	↑	↑

NAFLD: Non-alcoholic fatty liver disease.

vicious circle<sup>[72]</sup> (Table 1).

Adiponectin is an anti-inflammatory adipocytokine secreted by adipocytes acting as an insulin-sensitizing hormone. Moreover, adiponectin seems to down-regulate the synthesis of TNF- $\alpha$  in fat tissue and in heart muscle cells, to inhibit the production of IL-8, vascular adhesion molecule-1, and reactive oxygen species in endothelial cells and to stimulate the synthesis of IL-10<sup>[73]</sup>. Data on literature have demonstrated a negative correlation between adiponectin serum levels and body mass index (BMI)<sup>[73-78]</sup>. Obesity, type 2 diabetes, coronary disease, hypertension and non-alcoholic fatty liver disease in obese patients are associated to low plasma and serum levels of adiponectin<sup>[73,77,78]</sup>.

Moreover, it has been shown that serum adiponectin values were lower in patients affected by both psoriasis and NAFLD than in patients affected by psoriasis without hepatic involvement. This aspect could be linked to the adiponectin-mediated suppression of type 1 T helper cell-cytokines preventing psoriasis-prone individuals from developing disease until obesity and other factors antagonize its effects<sup>[79,80]</sup> (Table 1). Among pro-inflammatory adipocytokines, IL-6, leptin and resistin seem to be involved in the pathogenesis of both hepatic steatosis and psoriasis<sup>[81]</sup>.

Leptin regulates the appetite and body weight: scientific evidence have underlined higher leptin levels in obese patients with a sort of leptin resistance, just as in type 2 diabetes, where insulin resistance is observed<sup>[81-83]</sup>.

Furthermore, leptin resistance could promote the development of NAFLD by reducing intracellular lipid levels in skeletal muscle, liver and pancreatic beta cells. In patients affected by psoriasis, leptin serum levels are higher and psoriasis itself represents

an independent risk factor for hyperleptinemia. In psoriasis, leptin seems to enhance the synthesis of Th1 cytokines, to reduce the synthesis of Th2 and to mediate proliferative and anti-apoptotic processes in T-cells<sup>[84]</sup>.

Furthermore, there is a positive correlation between leptin serum levels and BMI<sup>[85,86]</sup> (Table 1). Resistin is a dimeric protein able to induce the synthesis of TNF- $\alpha$  and IL-12 and to increase blood glucose and insulin concentrations. It has been shown that psoriatic patients have elevated levels of resistin that is positively correlated with PASI index<sup>[85,87]</sup>. As resistin is a pro-inflammatory cytokine, it could be hypothesized that resistin might be involved in the pathogenesis of MetS in psoriatic patients<sup>[85,88]</sup>. Actually, it has not been completely elucidated the precise role of resistin in obesity, NAFLD and insulin resistance and/or diabetes<sup>[63]</sup> (Table 1).

Visfatin is a pro-inflammatory and insulin-mimetic adipocytokine contributing to glucose and lipid metabolism. The role of visfatin in NAFLD is debated. Recent study detected that although plasma visfatin levels are not altered in the first stages of NAFLD, it is inversely associated with TNF- $\alpha$ , suggesting its possible protective role against liver damage in this widespread disease. Data on the possible role of visfatin on psoriasis are insufficient<sup>[89]</sup> (Table 1).

Ghrelin has been suggested to be involved in metabolic syndrome, and obesity, type 2 diabetes and hypertension are associated to decrease levels of ghrelin. In NAFLD, it has been demonstrated that an imbalance in adiponectin, leptin, and ghrelin seems to be associated with more severe hepatic disease<sup>[90]</sup>. Moreover, serum ghrelin concentration is correlated with a low risk of developing NAFLD<sup>[91]</sup>.

In patients with psoriasis, serum level of ghrelin

was higher, although not statistically significant, than those of the control group, with a strong negative correlation with PASI score<sup>[92]</sup> (Table 1).

IL-6 is an inflammatory cytokine involved both in psoriasis and NAFLD. It regulates the migration of T cells into the epidermis, the growth and differentiation of dermal and epidermal cells<sup>[68]</sup>.

Obesity, inadequate glucose tolerance, and resistance to insulin are positively correlated with IL-6 serum levels; body weight reduction is associated with decreased IL-6 concentration<sup>[93,94]</sup>.

In psoriatic patients, serum levels of IL-6 are significantly increased with a positive correlation with PASI score<sup>[85]</sup>.

Moreover, a negative correlation between IL-6 and adiponectin plasmatic levels in obese patients has been observed; obese patients with psoriasis show a statistically significant increase of IL-6 compared to control group<sup>[87,95-97]</sup> (Table 1).

The role of IL-17 in pathogenesis of both psoriasis and NAFLD has been recently elucidated. Although the precise role has not completely clarified, elevated levels of IL-17 have been reported in obese patients and type 2 diabetes<sup>[98]</sup>.

T cells of adipose tissue can produce IL-17, and adipogenesis and glucose metabolism are regulated by IL-17. In NAFLD, Th17 and IL-17 seem to promote the evolution from simple steatosis to steatohepatitis. Finally, in psoriasis IL-17 induces IL-6 expression in keratinocytes; moreover severity of psoriasis is positively correlated with elevated serum levels of IL-17<sup>[98]</sup>.

However, in addition to the emerging role of adipose tissue in pathogenesis of psoriasis and NAFLD, it is also possible that NAFLD itself might contribute to the psoriasis severity by releasing of inflammatory mediators from inflamed liver, as C-reactive protein, reactive oxygen species, IL-6 and other pro-inflammatory cytokines. These inflammatory mediators are remarkably higher in patients with NAFLD than in those without<sup>[99,100]</sup>.

## CONVENTIONAL PSORIATIC TREATMENTS AND LIVER FUNCTION IMPLICATIONS

Successful treatment is imperative in order to improve signs and symptoms of psoriasis, and to improve physical or psychological distress. According to the European consensus mild psoriasis is defined as BSA < 10 and PASI < 10 and DLQI < 10 and moderate-to-severe as BSA > 10 or PASI > 10 and DLQI > 10. There is an agreement that mild psoriasis should preferentially be treated with topical therapy and, in case of inadequate response, UV-light should be added. In case of moderate-to-severe psoriasis systemic therapy should be initiated<sup>[101-104]</sup>.

Methotrexate (MTX), cyclosporine A (CsA) and

retinoids are common and efficacious systemic agent used for the treatment of moderate to severe psoriasis, but their long-term use is hindered by safety concerns and, in particular, by the risk of hepatotoxicity. A recent retrospective review conducted on 710 patients with moderate to severe psoriasis treated with MTX have shown that a high proportion (57.6%) of patients on MTX had deranged transaminases<sup>[105]</sup>.

MTX-mediated liver toxicity does not show specific histological aspects being similar to those of NASH. Moreover, metabolic syndrome and NASH are associated with several risk factors for methotrexate-mediated liver damage, as obesity, diabetes, and hyperlipidemia. Thus, the use of MTX in psoriatic patients should be carefully monitored for the possible worsening of a pre-existing steatohepatitis<sup>[24]</sup>. Thus, in MTX users, FibroTest can accurately predict the presence of liver fibrosis and the Fibroscan significantly predict the absence of significant liver fibrosis<sup>[106]</sup>. CsA is a potent immunosuppressor used for organ transplantations and various autoimmune disorders; one of the most detectable side effects is hepatotoxicity<sup>[107]</sup>. Acitretin is a synthetic retinoid which could induce liver toxicity by impairing mitochondrial phosphorylation efficiency without affecting the membrane potential<sup>[108]</sup>. Increased serum hepatic enzyme levels have been observed in approximately 25% of patients treated with acitretin but no clinically significant biopsy-proven hepatotoxicity was found after two years intermittent acitretin therapy<sup>[24]</sup>.

## ERA OF BIOLOGICS AND LIVER IMPLICATIONS

In recent years, the so-called biological therapies or biologic respond modifiers have led to a revolution in the treatment of moderate to severe psoriasis. Currently approved biological products for psoriasis treatment fall into two main classes: cytokine modulators and biologics targeting T cells<sup>[109]</sup>.

These treatments include fusion of proteins and monoclonal antibodies that target the T cells or specific inflammatory cytokines<sup>[110]</sup>.

TNF- $\alpha$  inhibitors link the TNF- $\alpha$  blocking its activity and reducing the interactions between immune cells and keratinocytes. Currently, three anti-TNF- $\alpha$  are been approved for the treatment of psoriasis: Infliximab, Adalimumab and Etanercept<sup>[110]</sup>. In literature, 20 cases of autoimmune hepatitis triggered by anti-TNF- $\alpha$  therapy have been reported to date. The median time and the number of doses of anti-TNF- $\alpha$  drugs to the onset of liver damage were 2 mo and 3 times, respectively. After the onset of liver damage, anti-TNF- $\alpha$  therapy was discontinued in all cases and six were treated with corticosteroid, with or without azathioprine. All cases had good response to the therapies, and the liver damage was resolved within approximately 3 mo in five cases.

However, it is difficult to distinguish a drug-induced autoimmune hepatitis (drug induced AIH) from a de novo autoimmune hepatitis (AIH) because the clinical, biochemical, serological, and histological patterns may be overlapping. Furthermore, patients treated with biological agents may have various forms of simultaneous autoimmune disease and ANAs before treatment. Moreover, about 3% of AIH cases had psoriasis as a concurrent autoimmune disease<sup>[110]</sup>.

Despite the pathogenesis of AIH triggered by anti-TNF- $\alpha$  therapy remains unclarified, some hypotheses had been postulated: TNF- $\alpha$  itself could contribute to the development of AIH and/or it could be linked to reactive metabolites of the anti-TNF- $\alpha$  drugs which are recognized by the immune system as neoantigens<sup>[111,112]</sup>.

Ustekinumab is a human monoclonal antibody approved for the treatment of psoriasis binding the p40 subunit of IL-12 and of IL-23, preventing their interaction with the cell surface IL-12R $\beta$ 1 receptor and subsequently inhibiting IL-12- and IL-23-mediated cell signaling, activation, and cytokine production. No data are reported about the role of Ustekinumab on liver function<sup>[113,114]</sup>.

## PSORIASIS, METS AND NAFLD: TOWARD COMMON THERAPEUTIC STRATEGIES?

Psoriasis is now perceived as a systemic disorder with skin manifestation and associated comorbidities responsible for increased morbidity and mortality. Thus, a multidisciplinary approach in the prompt diagnosis of psoriasis-related comorbidities and in their managements appear useful to obtain an appropriate tight control of psoriasis from an early stage<sup>[53,101]</sup>.

Given that TNF- $\alpha$  shows a pivotal role in psoriasis and related comorbidities, there could be a rationale in the use of TNF- $\alpha$  inhibitors in their treatment<sup>[11]</sup>.

### *The effect on psoriatic therapies on adipocytokines*

Data on literature show conflicting results about the role of psoriatic treatments on adipocytokines' levels. Ozdemir *et al.*<sup>[92]</sup> have demonstrated that, after cyclosporine treatment, a significant increase was seen in the serum level of adiponectin and resistin, not correlated to disease parameters<sup>[92]</sup>.

About the possible biologics' action on adipocytokines' levels, Shibata *et al.*<sup>[115]</sup> demonstrated an increased in adiponectin and IL-6 level after infliximab treatment. We have recently demonstrated that Adalimumab and Etanercept could be able to rebalance, but not normalize, adipocytokines' levels, mainly related to a reduction of pro-inflammatory ones rather than an increase of adiponectin<sup>[62]</sup>.

### *The effect of biologic response modifiers on blood lipids*

About lipid profiles, total cholesterol, triglycerides

are not significantly modified by Infliximab<sup>[116,117]</sup>. Conversely, another study have shown that Infliximab modifies plasma lipid and lipoprotein levels in patients with rheumatoid and psoriatic arthritis resulting in a more atherogenic profile and significantly increasing triglyceride levels and lowering HDL cholesterol<sup>[118]</sup>.

A retrospective study reviewing the medical records of 45 patients affected by psoriasis treated with Etanercept for 24 wk showed no statistically significant modifications on the lipid profile<sup>[119,120]</sup>.

Moreover, Puig *et al.*<sup>[121]</sup> emphasized that Etanercept treatment may provide some potentially favorable modulation of insulin sensitivity, HDL-C, Apo A1 and Apo B:Apo A1 ratio<sup>[121]</sup>. Finally, an *in vitro* study focused that the use of Etanercept can lead to a reduction in lipid peroxidation and an improvement in HDL antioxidant and anti-inflammatory properties<sup>[122]</sup>.

### *Biologic response modifiers and insulin resistance*

Few data are available about the role of TNF- $\alpha$  inhibitors on insulin resistance. A study conducted by Marra *et al.*<sup>[123]</sup> have evidenced that the use of Etanercept, in patients affected by psoriasis, can improve insulin sensitivity, by a sort of modulation of the inflammatory background. Similarly, an improvement in insulin sensitivity has been obtained 120 minutes after the Infliximab infusion to up to one year<sup>[41,123]</sup>.

Anecdotal cases of psoriasis with diabetes developing unpredictable hypo- or hyperglycemia has been reported after treatment with TNF- $\alpha$  inhibitors; this aspect resolved after the drug discontinuation<sup>[41]</sup>.

### *Biologic response modifiers and body mass index*

Significant weight gain of about 2 kg in 1 year and the increase of BMI has been reported in patients affected by psoriasis and psoriatic arthritis after long-term use of TNF-alpha inhibitors<sup>[41,71]</sup>.

Gisondi *et al.*<sup>[124]</sup> demonstrated that BMI and body weight were significantly increased in patients treated for 7 mo with infliximab compared with those treated with Ustekinumab.

### *Biologic response modifiers and NAFLD*

There are few data on the role of biological response modifiers on NAFLD. The only study on this topic was a retrospective case-control study in patients with psoriasis, metabolic syndrome, and NAFLD, conducted by Campanati *et al.*<sup>[25]</sup>. The authors found that the risk of developing hepatic fibrosis, shown by change in the AST/ALT ratio, was significantly correlated with insulin sensitivity assessed with the HOMA index and the QUICKI. However, the correlation coefficients between the above parameters were less than 0.1: this could be explained by the fact that the development of hepatic fibrosis in NAFLD depends on multiple factors not only by insulin resistance. Moreover, Etanercept attenuated insulin resistance, patients gained significant weight with increases in the waist-hip-ratio and BMI during



treatment, and these changes could themselves represent risk factors for the development of hepatic fibrosis in NAFLD<sup>[25]</sup>.

## CONCLUSION

Despite the relationship between NAFLD and psoriasis needs to be further investigated, data on literature show that psoriatic patients show an increased prevalence of NAFLD.

Moreover, NAFLD and psoriasis seem to be related to an increased cardiovascular risk, probably linked to the common low and persistent inflammatory state.

No specific pharmacological treatments should be suggested to these patients, as lifestyle modification and dietary recommendations, can play an important role in the treatment of metabolic complications of psoriasis<sup>[125]</sup>.

In fact, investigations have assessed the effect of weight-loss on psoriasis and conclusively found that the severity of psoriasis can be significantly improved. The most convincing data are derived from bariatric surgery where the majority of patients show a significant improvement of psoriasis severity<sup>[101]</sup>. However, there is no data yet available that demonstrates a lasting effect of weight loss measures on psoriasis severity/activity after the intervention. It could be underline that a significant weight loss can lead to significant improvements in circulating levels of leptin, and adiponectin with a possible action and inflammatory state<sup>[126]</sup>.

Improvement of insulin resistance and insulin sensitivity and a significant reduction in systemic inflammation could be obtained by the use of TNF- $\alpha$  inhibitors<sup>[118-124]</sup>. Thus, given that biological therapies present the potentiality to reduce the TNF- $\alpha$ -related metabolic comorbidities in psoriatic patients, further prospective studies are needed on this issue. Finally, evaluating the coexistence of NAFLD in psoriatic patients, dermatologists should consider methotrexate and other conventional therapies for psoriasis as possible triggers of liver disease in this population.

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