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REVIEW ARTICLE

Managing the Patient with Psoriasis and Metabolic Comorbidities

Francesco Bellinato[1] · Martina Maurelli[1] · Davide Geat[2] · Giampiero Girolomoni[1] · Paolo Gisondi[1]

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Abstract
Epidemiological data demonstrate strong associations between psoriasis and metabolic comorbidities, including obesity, hypertension, diabetes mellitus, dyslipidemia, and non-alcoholic fatty liver disease. The presence of metabolic comorbidities significantly influences the selection and effectiveness of pharmacological treatments. Some drugs should be prescribed with caution in patients with metabolic comorbidities because of an increased risk of adverse events, while others could have a reduced effectiveness. The aim of this narrative review is to highlight the challenges that healthcare professionals may face regarding the management of psoriasis in patients with metabolic comorbidities. In the first part of the article, the epidemiological association between psoriasis and metabolic comorbidities and their pathogenetic mechanisms is summarized. The second part describes the efficacy and safety profile of conventional and biologic drugs in patients with selected metabolic comorbidities including obesity, non-alcoholic fatty liver disease/hepatic steatosis, and diabetes. Finally, the role of pharmacological and non-pharmacological interventions, such as diet, alcohol abstinence, physical activity, and smoking avoidance is discussed. In conclusion, the choice of the best approach to manage patients with psoriasis with metabolic comorbidities should encompass both tailored pharmacological and individualized non-pharmacological interventions.

Key Points

There is a strong association between psoriasis and metabolic comorbidities, including obesity, hypertension, diabetes mellitus, dyslipidemia, and fatty liver disease.

The presence of metabolic comorbidities significantly influences the selection and effectiveness of pharmacological treatments.

Pharmacological and non-pharmacological interventions, such as a low-calorie diet, alcohol abstinence, physical activity, and smoking avoidance, could be very useful in the global management of patients with psoriasis with metabolic comorbidities.

1 Introduction

An emerging role of epidemiological studies is to report associations between psoriasis and several disorders in addition to the well-documented association with psoriatic arthritis (PsA) [1]. In particular, the cluster of interconnected conditions defining the metabolic syndrome, including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, and hyperglycemia, is known to be closely linked with chronic plaque psoriasis [2]. The presence of metabolic comorbidities significantly influences the selection and effectiveness of pharmacological treatments. Some drugs should be prescribed with caution in patients with metabolic comorbidities because of an increased risk of adverse events, while others could have a reduced effectiveness. The objective of this narrative review is to highlight the challenges that healthcare professionals may face regarding the management of psoriasis in patients with metabolic comorbidities. To this aim, we summarize the efficacy and safety profile of conventional and biologic drugs in patients with selected metabolic comorbidities and we discuss the role of pharmacological and non-pharmacological interventions.

✉ Paolo Gisondi
paolo.gisondi@univr.it

[1] Section of Dermatology and Venereology, Department of Medicine, University of Verona, Piazzale A. Stefani 1, 37126 Verona, Italy

[2] Department of Dermatology, Spedali Civili, Brescia, Italy

2 Epidemiology Data Supporting the Association Between Psoriasis and Metabolic Comorbidities

The strength of these associations has been repeatedly confirmed by several observational studies. A cross-sectional study reported that the prevalence of metabolic syndrome correlated directly with psoriasis body surface area [3]. A meta-analysis of 12 studies found a pooled odds ratio (OR) of 2.26 (95% confidence interval [CI] 1.70–3.01) for the association of metabolic syndrome with psoriasis [4]. The analysis of the separate components of metabolic syndrome found the strongest association with obesity, suggesting that the adiposity is the main factor behind the association between psoriasis and metabolic syndrome. Not only obesity, but also body mass index (BMI), hip circumference, and waist-hip ratio are independent risk factors for psoriasis. Several studies have found that psoriasis risk increases alongside with BMI [5, 6] and two recent studies provided evidence for a causal link between obesity and psoriasis through Mendelian randomization [7, 8]. These findings ultimately confirm that a higher BMI is a causal risk factor for psoriasis. Furthermore, obesity is associated with greater psoriasis severity and a reduced response to systemic treatments. Conversely, loss of excess weight through a low-calorie diet and/or bariatric surgery improves the response to systemic pharmacological treatments and improves patients' metabolic profile [9].

Regarding hypertension, a higher prevalence of arterial hypertension among individuals with psoriasis has been also reported [10]. In a meta-analysis, the risk of hypertension increased progressively, with an OR of 1.49 for severe psoriasis and 1.30 for mild psoriasis [11]. Individuals with both psoriasis and hypertension tend to experience an early onset of psoriasis and a higher prevalence of PsA [12].

The presence of metabolic syndrome indicates a clustering of risk factors that collectively contribute to an elevated risk of cardiovascular diseases. In fact, different studies indicate an increased risk of multiple cardiovascular disorders among patients with psoriasis. The OR of ischemic heart disease, cerebrovascular disease, and peripheral vascular disease was found to be 1.78 (95% CI of 1.51–2.11), 1.70 (95 % CI 1.33–2.17), and 1.98 (95 % CI 1.32–2.82), respectively. There is also a correlation between the severity of psoriasis and the rate ratios (RRs) for atrial fibrillation (a predominant cardiac arrhythmia associated with stroke); patients with severe psoriasis have a RR of 1.63, while those with mild psoriasis have a RR of 1.31 [13].

Regarding type 2 diabetes mellitus, the hypothesis that psoriasis may be associated with type 2 diabetes was first made by Brownstein in 1966 and Binazzi et al. in 1975, and since then several observational studies have assessed this association with psoriasis, showing a higher risk with greater severity of psoriasis [14–16]. Diabetic patients with psoriasis appear to be more likely to experience microvascular and macrovascular complications compared with patients without psoriasis [2]. In a meta-analysis of 44 observational studies, the pooled OR was determined to be 1.76 (95% CI 1.59–1.96), with the highest risk for patients with PsA (OR 2.18, 95% CI 1.36–3.50) and in those with severe psoriasis [17]. In addition, another meta-analysis of five cohort studies found a 38% increase in the risk of diabetes among patients with PsA, with an incidence rate of 13.4 per 1000 patient-years [18]. Furthermore, an atherogenic lipid profile was reported among patients with psoriasis, compared to patients without psoriasis. According to a systematic review, most of the studies found a significant association between psoriasis and dyslipidemia, with ORs that ranged from 1.04 to 5.55 [19]. Higher odds of dyslipidemia were reported in patients with severe psoriasis compared with patients with mild disease, and dyslipidemia itself may be a risk factor for developing psoriasis [20]. According to a European ancestry genome-wide association study-based Mendelian randomization study, psoriasis and blood lipids have a causal link. In particular, robust causal associations between low-density lipoprotein-cholesterol and triglyceride levels and psoriasis were found, although not with high-density lipoprotein-cholesterol. A reverse Mendelian randomization analysis also showed a causal association between psoriasis and low-density lipoprotein-cholesterol, but not with triglycerides [21]. Ultimately, non-alcoholic fatty liver disease (NAFLD) is a common liver disease that ranges from mild forms of steatosis up to steatohepatitis. A recent meta-analysis showed that psoriasis was associated with prevalent NAFLD (OR 1.96, 95% CI 1.70–2.26). Of note, patients with psoriasis with NAFLD had a higher mean Psoriasis Area and Severity Index (PASI) than their counterparts without NAFLD [22]. Moderate-to-severe psoriasis may be an independent risk factor for chronic kidney disease and end-stage renal disease. A cohort study found that severe psoriasis may be associated with chronic kidney disease and end-stage renal disease with hazard ratios of 1.93 (95% CI 1.79–2.08) and 4.15 (95% CI 1.70–10.11), respectively [23]. A systematic review and meta-analysis estimated a risk of incident chronic kidney disease and end-stage renal disease significantly increased among patients with psoriasis with the pooled RR of 1.34 (95% CI 1.14–1.57) and 1.29 (95% CI 1.05–1.60), respectively [24].

Several studies have reported associations between psoriasis and other emerging comorbidities such as cancer, especially T-cell lymphoma [25], pneumopathies such as chronic

pulmonary disease and obstructive sleep apnea, peptic ulcer disease, hyperuricemia/gout, osteoporosis, and sexual dysfunction. Some of these findings need to be confirmed in larger studies.

3 Shared Pathomechanisms Between Psoriasis and Metabolic Comorbidities

The pathomechanisms underlying the association between psoriasis and metabolic comorbidity can be summarized in: genetic predisposition, shared inflammatory pathways, and common risk factors [1]. Patients with psoriasis have an increased likelihood of possessing specific common genetic variants (i.e., FUT2, UBE2L3, SH2B3, CDKAL1, and apolipoprotein E) that have multi-faceted functions explaining their dual role in susceptibility to psoriasis and cardio-metabolic comorbidities. Four genome-wide significant loci with evidence of colocalization and shared directions of effect between psoriasis and diabetes have been identified. The proteins coded by genes in these loci (ACTR2, ERLIN1, TRMT112, and BECN1) signal through nuclear factor-κB signaling [27]. In addition, studies have consistently demonstrated that psoriasis and metabolic comorbidities share common underlying immunological mechanisms, particularly related to the activation of T-helper 1 and T-helper 17 cells [1]. Inflammatory mediators released from psoriatic lesions, including tumor necrosis factor (TNF)-α, interferon (IFN)-α, IFN-γ, interleukin (IL)-1, IL-6, and IL-17, can have systemic effects that contribute to atherogenesis (Fig. 1). Recent investigations conducted on human tissues have revealed a significant overlap in the transcriptomes of psoriasis and atherosclerosis, particularly those dependent on TNF-α and IFN-γ, thereby establishing a connection between the two diseases [28]. A psoriasis systemic inflammatory state may also fuel inflammation in adipose tissue. In turn, psoriatic adipose tissue contains various immune cells that can influence cardiometabolic diseases [29]. Among these, T cells, dendritic cells, neutrophils, mast cells, and adipose tissue macrophages contribute to obesity and insulin resistance. The release of adipokines, as chemerin, adiponectin, resistin, visfatin, and C-reactive protein by macrophages and T cells infiltrating visceral adipose tissue can explain the association between obesity and systemic inflammation. Adipokines are elevated in the serum of patients with psoriasis [30], and can contribute to the development of insulin resistance [31]. An association between obesity and PsA has been also observed; in particular, metabolic syndrome and adipokine levels correlate with skin and joint disease activity [32]. Psoriasis-related inflammation could also trigger the progression from a normal liver to NAFLD [33]. Pro-inflammatory cytokines and adipokines, including TNF-α,

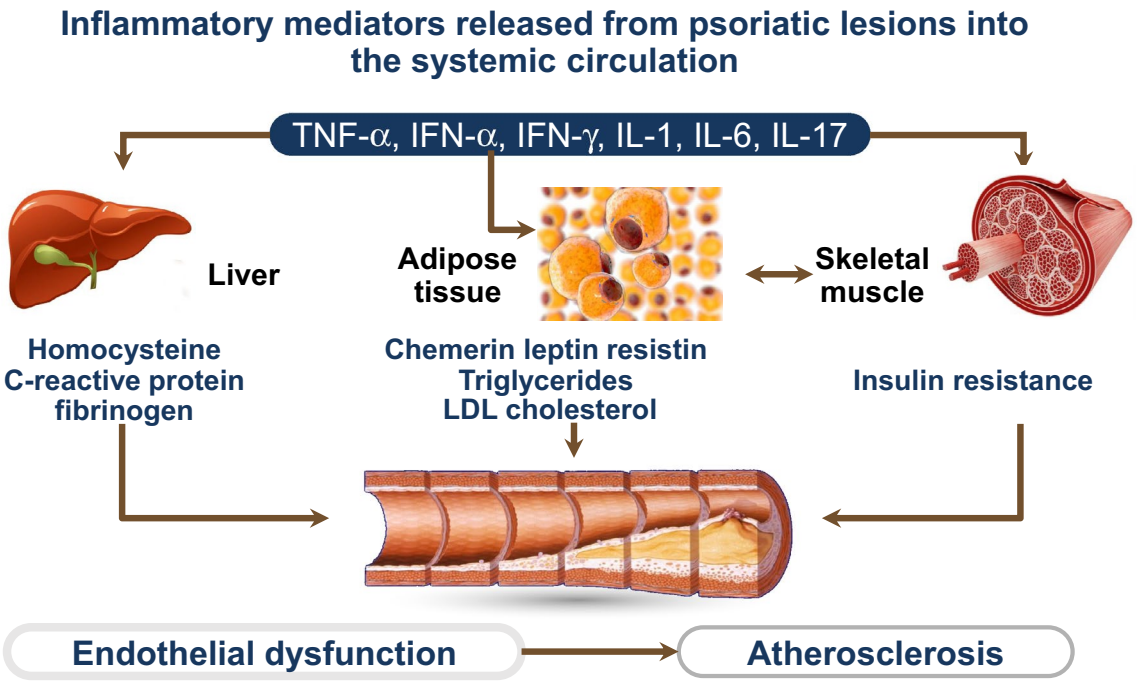

Fig. 1 Cross-talk between psoriatic lesions and liver, adipose, and muscular tissue involving different mediators (i.e., adipokines, tumor necrosis factor [TNF]-α, interferon [IFN]-α, [IFN]-γ, interleukin [IL]-1, IL-6, and IL-17) that stimulate the production of homocysteine, C-reactive protein, and fibrinogen from the liver; chemerin, leptin, resistin, triglycerides, and low-density lipoprotein (LDL)-cholesterol from the adipose tissue; and promote insulin resistance in the skeletal muscle. These mediators could promote endothelial dysfunction and atherogenesis

play pivotal roles in the pathogenesis of both psoriasis and NAFLD, as well as in the progression of NAFLD to non-alcoholic steatohepatitis. Insulin resistance is also strongly involved in the development of NAFLD, as it promotes an increased free fatty acid flux from visceral adipose tissue into the liver, thereby increasing hepatic neolipogenesis. Hepatic fat accumulation may further aggravate systemic and hepatic insulin resistance and promote increased hepatic glucose production. Adipokines, along with chemokines such as CXCL8 and CCL2 produced by visceral adipose tissue, can contribute to the formation of atherosclerotic plaques influencing endothelial cell function and interactions with immune cells. In addition to abdominal visceral fat, epicardial adipose tissue has been shown to be increased in patients with psoriasis and may contribute to an increased cardiovascular risk [34]. Indeed, epicardial adipose tissue has been suggested as a potential factor responsible for a distinctive pattern of cardiovascular disorders observed in psoriasis, including accelerated coronary atherosclerosis leading to myocardial infarction, atrial myopathy leading to atrial fibrillation, thromboembolic stroke, and ventricular myopathy leading to heart failure with preserved ejection fraction [35]. Finally, anxiety and depression are prevalent in patients with psoriasis and are potentially associated with unhealthy lifestyles such as alcoholism and smoking, which are well-known cardiovascular and metabolic risk factors [36].

4 Therapies Approved for Psoriasis and Their Potential Effects on Metabolic Comorbidities

The presence of metabolic comorbidities interferes with the selection and effectiveness of the treatments of psoriasis. In particular, some treatments should be prescribed with caution in these patients because of the increased risk of adverse events, and others could have a reduced effectiveness. Indeed, obesity is a negative predictor of efficacy for several systemic drugs, in particular those with a fixed dosage. Monitoring metabolic parameters, including blood glucose, glycated hemoglobin, lipid levels, creatinine, and liver enzymes is advisable in patients with psoriasis and metabolic comorbidities [37, 38].

4.1 Conventional Systemics

4.1.1 Methotrexate

Methotrexate should be prescribed with caution in obese patients because of the increased risk of liver toxicity, particularly in the case of long-term treatment and in the presence of other risk factors of liver toxicity such as heavy alcohol consumption, chronic hepatitis B and C, obesity, type 2 diabetes, hepatotoxic drugs, and hyperlipidemia [39–41]. Indeed, obesity is frequently associated with NALFD/non-alcoholic steatohepatitis that could predispose patients to liver fibrosis. The main clinical concern arises owing to the potential risk of significant liver fibrosis with prolonged methotrexate exposure, which has been estimated to occur in approximately 5% of patients (range 3.5–7%), with some reports linking fibrosis to the total cumulative dose [42]. Obese patients have been considered vulnerable candidates to methotrexate therapy according to an international eDelphi study to reach consensus on the methotrexate dosing regimen in patients with psoriasis, along with elderly individuals, individuals with kidney renal dysfunction, ulcerative colitis, a history of hepatitis, a lack of compliance, gastritis, diabetes, previous cancer, and congestive heart failure [39, 40]. In these settings, it is suggested to start with a lower dosage of 7.5–10 mg/week. Moreover, liver elastography or liver biopsy has been proposed for obese patients at baseline (within 2–6 months of starting treatment) and at cumulative doses of 1.0–1.5 g of methotrexate [41]. Ultimately, the efficacy of methotrexate in obese patients is lower compared with lean or normal weight patients, with a reduced PASI75 response [42].

4.1.2 Cyclosporine

Regarding cyclosporine, arterial hypertension as well as hyperlipidemia are common adverse events, hence its use in patients with metabolic comorbidities may be contraindicated because of the worsening of these metabolic disorders [43, 44]. Type 2 diabetes concurrent with psoriasis does not affect the efficacy of cyclosporine treatment; therefore, there is no necessity to modify the standard dosage of the drug and therapy regimen [45]. However, cyclosporine could impair insulin sensitivity in the long term. Indeed, new-onset type 2 diabetes is a frequent complication after transplantation, in particular in kidney allograft recipients treated long term with cyclosporine [46]. In addition, in obese patients, the dosage of cyclosporine needs to be adjusted to the body weight, thus leading to a higher risk of side effects and nephrotoxicity, such as obliterative vasculopathy of the afferent arteriole and tubulointerstitial fibrosis in advanced cases [47].

4.1.3 Acitretin

Acitretin therapy can cause hyperlipidemia, which is already frequent in obese individuals patients [32, 48]. As dyslipidemia is an additive cardiovascular risk factor in patients with diabetes, acitretin should be used with caution in such patients, as well in case of hypetriglyceridemia, alcoholism, and a history of pancreatitis [38–40].

4.1.4 Dimethyl Fumarate

Finally, dimethyl fumarate should be avoided in case of severe liver, kidney, and gastrointestinal tract diseases. In fact, gastrointestinal complaints, mainly diarrhea and increased stool frequency, are the most frequent adverse drug reactions during treatment [38–40]. However, metabolic comorbidities are not an absolute contraindication to dimethyl fumarate [38–40].

4.2 Biologics

Biologics approved for moderate-to-severe psoriasis include TNF-α inhibitors (adalimumab, etanercept, certolizumab pegol, infliximab), IL-12/23 inhibitors (ustekinumab), IL-17 inhibitors (ixekizumab, secukinumab, brodalumab, bimekizumab), and IL-23 inhibitors (guselkumab, risankizumab, tildrakizumab) [43].

4.2.1 TNF-α Inhibitors

Adalimumab, certolizumab pegol, and etanercept are used at a fixed dosage, whereas infliximab dosage is weight dosed (5 mg/kg). The efficacy of adalimumab is lower in obese patients, compared with normal weight patients [51]. There is evidence that the reduction in body weight leads to a better response to TNF-α inhibitors, as well to other systemic treatments [9]. Of note, TNF-α inhibitors may increase body weight, approximately of 1.5 kg, in a substantial number of patients [52]. The mechanism is unknown but a change in body mass composition has been shown with adalimumab, etanercept, and infliximab [52]. Tumor necrosis factor-α inhibitors, infliximab and etanercept might improve insulin resistance but this is still somewhat controversial [53–56]. Adalimumab has apparently marginal effects on insulin resistance, but it has been shown to improve laboratory parameters associated with non-alcoholic steatohepatitis [54]. An improvement in liver function tests has been observed also after treatment with infliximab [57, 58]. In contrast, some patients show liver toxicity with an elevation of serum liver enzymes as well as the development of NAFLD during TNF-α inhibitor treatment, with a normalization of liver enzymes after the cessation of therapy [59, 60]. Finally, congestive heart failure (New York Heart Association class III/IV) is an absolute contraindication to TNF-α inhibitor treatment because of an increased risk of heart failure exacerbation in some patients [38–40].

4.2.2 IL-12/23 Inhibitors

Ustekinumab dosage is partially weight based. In particular, the 45-mg dosage is indicated for patients with body weight < 100 kg, whereas the 90-mg dosage is indicated for those with a weight > 100 kg. Ustekinumab dose not increase the BMI in patients with psoriasis [61]. There are no studies addressing the possible role of ustekinumab in changing metabolic parameters [43].

4.2.3 IL-17 Inhibitors

While IL-17 inhibitors are highly effective both in normal weight and in obese patients [51], normal weight patients tend to have a better response and psoriasis clearance compared with obese patients [44]. Gerdes et al. showed weight reduction and no changes in lipid profiles and liver enzymes, but a reduction in uric acid levels, in patients treated with secukinumab for 52 weeks [62]. Results from phase III trials showed that ixekizumab had a neutral impact on cardiovascular and metabolic parameters including total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, very-low-density lipoprotein cholesterol, triglyceride, apolipoprotein A1, apolipoprotein B, or fasting glucose levels or for systolic/diastolic blood pressure [63].

4.2.4 IL-23 Inhibitors

Guselkumab and risankizumab are used at a fixed dosage, independently from body weight, and are not reported to increase body weight or to alter lipid and glucose metabolism [43]. Of note, risankizumab was found to be highly effective even in obese patients [52]. Tildrakizumab has two dosages: the 100-mg dosage is indicated for patients with body weight < 100 kg, whereas the 200-mg dosage is indicated for those with a weight > 100 kg. The effect of these drugs on metabolic parameters has not been investigated.

4.2.5 Small Molecules

Apremilast is an oral small molecule that inhibits phosphodiesterase 4. Apremilast could have beneficial effects on metabolic parameters. It may reduce body weight in a small fraction of patients, independently from its gastrointestinal side effects (nausea and diarrhea) and may improve glucose metabolism and enhance metformin activity [44, 53].

5 Pharmacological and Non-pharmacological Interventions Targeting Metabolic Comorbidities

Pharmacological interventions targeting metabolic comorbidities should be integrated in the global management of patients with psoriasis with metabolic comorbidities. As an example, statin therapy, commonly used to manage dyslipidemia, offers benefits beyond lipid control. Studies have shown that statins reduce all-cause mortality without

increasing adverse events in the general population undergoing primary prevention. Given the increased mortality risk observed in patients with psoriasis, some suggest that mortality should be considered a crucial endpoint in psoriasis management. Recent research indicates that statin therapy is associated with reduced mortality and cardiovascular events in patients with immune-mediated inflammatory diseases [64]. Through inhibition of the nuclear factor-κB pathway, glucagon-like peptide 1 receptor agonists could represent another useful pharmacological intervention. These drugs have shown improvements in PASI and weight/body mass index with no major adverse events in some small sample size studies [65]. Hematologic parameters to be screened and monitored in patients with psoriasis and metabolic comorbidities are reported in Table 1. Finally, non-pharmacological interventions such as diet and physical activity are also extremely beneficial to patients with psoriasis, as shown by a meta-analysis of six randomized controlled trials, which found that weight loss (following diet or physical activity) can improve psoriasis and PsA, and even prevent the onset of psoriasis in obese individuals [66–69].

5.1 Diet

Diet is an important non-pharmacological adjunct to the treatment of patients with psoriasis. The rationale of the impact of different dietary regimens may be related to their amount in anti-inflammatory compounds (e.g., some polyphenols and dietary fibers) and proinflammatory compounds (e.g., saturated fatty acids) [70, 71]. Indeed, diets rich in proinflammatory bioactive compounds have been linked to an increased incidence and severity of inflammatory disorders such as rheumatoid diseases and inflammatory bowel diseases [72, 73]. Conversely, healthy diets have not only been associated with a reduction in metabolic syndrome and cardiovascular events [73, 74], but also to a reduction in chronic systemic inflammation. For example, subjects who adhered to healthy diets were found to have significantly lower levels of serum IL-6 [73]. Regarding psoriasis, the role of diet on its severity has been the subject of a number of randomized clinical trials over the last decade (Table 2). In the largest trial by Naldi et al., which included 303 overweight or obese patients with psoriasis receiving systemic treatment, patients were randomized to either a low-caloric diet combined with physical exercise (intervention group) or informative counseling at baseline (control group) [74]. At 20 weeks, patients in the intervention group had a significantly higher mean PASI reduction and PASI50 response [74]. Of note, the fact that the intervention consisted of both diet and physical activity prevents the drawing of a definite conclusion on the relative role of diet alone. A recent multicenter survey showed that a significant percentage of obese patients with psoriasis are interested in participating in nutritional programs to reduce excess body weight, they are well aware of the negative effects of obesity on their health, whereas they are less informed of the impact of obesity on psoriasis [75].

5.2 Low-Calorie Diets

A few randomized clinical trials assessed the role of low-calorie diets in psoriasis. In a randomized, investigator-blinded trial, obese patients with psoriasis on a low-calorie diet in combination with low-dose cyclosporine (2.5 mg/kg/day) had a higher PASI75 response and a lower mean PASI and body surface area at 24 weeks compared with patients in the control group (low-dose cyclosporine alone) [9]. Similar to the study by Naldi et al. [74], subjects in the intervention group of this study were instructed to avoid alcohol and encouraged to perform moderate physical exercise. In another study, obese patients with psoriasis taking conventional or biologic drugs were randomly assigned to either an energy-restricted diet enriched in n-3 polyunsaturated fatty acids (intervention group) or their usual diet (control group) [76]. Patients in the intervention group achieved a significantly lower mean PASI than controls at the 3-month and 6-month follow-ups [76]. These findings were confirmed by a larger trial that included 262 obese patients with psoriasis treated with biologics who were randomized to a low-calorie diet or their normal diet; patients on the low-calorie diet experienced a significantly higher PASI75 response at 24 weeks [77]. Another randomized clinical trial that assessed a low-energy diet compared to a normal healthy diet in overweight or obese patients with psoriasis receiving systemic drugs showed a trend towards a greater mean PASI change in patients on the low-energy diet versus controls (− 2.3 vs

Table 1 Hematologic parameters advisable to be screened and monitored in patients with psoriasis and metabolic comorbidities

Complete blood count	Hemoglobin, white blood cell count, platelet count
Glucose levels	Fasting glucose, glycated hemoglobin
Lipids	Total cholesterol, low-density lipoprotein, high-density lipoprotein, triglycerides
Liver enzymes	Alanine transaminase, aspartate transaminase
Renal function tests	Serum creatinine, blood urea nitrogen, glomerular filtration rate

Table 2 Randomized clinical trials that evaluated the impact of diet on plaque psoriasis severity

Study	Study design	Number of patients	Duration	Intervention	Additional therapy allowed	Main results
Schultz et al. [89], 2020	RCT-IB	25	24 wk	Balanced protein-to-fat-to-carbohydrate ratio diet (intervention) vs usual diet (controls)	Topical treatments	No difference in PASI vs controls
Naldi et al. [74], 2014	RCT-IB	303	20 wk	Diet and exercise (intervention) vs informative counseling at baseline (controls)	Systemic treatments	Median PASI reduction at 20 wk: 48% vs 25.5% ($p = 0.02$) PASI50 at 20 wk: 49.7% vs 34.2% ($p = 0.006$)
Al-Mutairi et al. [76], 2014	RCT	262	24 wk	Low calorie diet (≤1000 kcal/day) (intervention) vs normal diet (controls)	Biologics	PASI75 at 24 wk: 85.9% vs 59.3% ($p < 0.001$)
Guida et al. [77], 2014	RCT-IB	44	6 mo	Energy-restricted diet enriched in n-3 polyunsaturated fatty acids (intervention) vs usual diet (controls)	Systemic treatments (MTX, CsA, biologics)	Mean ± SD PASI at 3 mo: 5.3 ± 4.3 vs 7.8 ± 4.1 ($p < 0.05$). At 6 mo: 2.6 ± 3.0 vs 7.8 ± 1.9 ($p < 0.05$)
Jensen et al. [78], 2013	RCT	60	16 wk	Low energy diet (800–1000 kcal/day) for 8 wk, then 1200 kcal/day for further 8 wk (intervention) vs normal healthy diet (controls)	Systemic treatments	Mean change in PASI at 16 wk: −2.3 vs −0.3 ($p = 0.06$)
Del Giglio et al. [79], 2012	RCT-IB	42	24 wk	Low-calorie diet (intervention) vs normal diet (controls)	None (patients previously taking MTX, stopped during study)	No significant difference in psoriasis severity vs controls
Kimball et al. [88], 2012	RCT	30	12 wk	Ornish diet vs South Beach diet (interventions) vs no dietary intervention (controls)	nb-UVB phototherapy	PASI75 at 12 wk: 83% (Ornish diet) vs 56% (South Beach diet) vs 38% (controls) [$p = 0.30$ between the two diet groups]
Gisondi et al. [9], 2008	RCT-IB	61	24 wk	CsA + low-caloric diet (intervention) vs CsA alone (controls)	None	PASI75 at 24 wk: 66.7% vs 29.0% ($p < 0.001$)

CsA cyclosporin A, *IB* investigator blinded, *MTX* methotrexate, *mo* month, *PASI* Psoriasis Area Severity Index, *RCT* randomized controlled trial, *SD* standard deviation, *UVB* ultraviolet B, *wk* week

0.3), although this difference was not statistically significant ($p = 0.06$) [78]. Conflicting findings were reported in a study by Del Giglio et al. [79], which included 42 obese patients with psoriasis who had been previously treated with methotrexate and had reached a PASI75 response by the time of enrollment. Methotrexate was discontinued, and patients were assigned to either a low-calorie or normal diet in order to investigate whether a low-calorie diet was able to maintain remission. In the following 24 weeks, psoriasis severity worsened in both groups with no significant difference between them [79].

5.3 Ketogenic Diets

Very-low calorie ketogenic diets have only recently been studied in psoriasis and appear promising, although more studies are required to draw definite conclusions. A very-low calorie ketogenic diet has been studied in patients with psoriasis by Castaldo et al. [6] who conducted a single-arm open-label trial in overweight or obese drug-naïve patients with psoriasis who underwent a 10-week, two-phase program consisting of a very-low calorie ketogenic diet for 4 weeks followed by a balanced, hypocaloric Mediterranean-like diet for 6 weeks. At 10 weeks, the mean PASI change was − 10.6 (95% CI − 12.8 to − 8.4; $p < 0.001$), with PASI50 and PASI75 achieved by 97.3% and 64.9% respectively [6]. In another study by the same author, 30 overweight or obese patients with psoriasis underwent a very-low calorie ketogenic diet for 4 weeks, after which clinical and biochemical parameters (including IL-2, IL-4, IL-1β, TNF-α, IFN-γ) and the metabolomic profile were assessed [80]. At 4 weeks, PASI was reduced by approximately 50% while IL-2 and IL-1β levels were reduced [80].

5.4 Mediterranean Diet

A Mediterranean diet was found in several studies to play a protective role in psoriasis [81–83]. A cross-sectional study by Barrea et al. reported that patients with psoriasisc have a lower adherence to the Mediterranean diet compared with age-matched, sex-matched, and BMI-matched controls [84]. In that study, psoriasis severity and C-reactive protein were negatively associated with the consumption of extra virgin oil and fish [84]. Other studies based on self-administered questionnaires confirmed the lower adherence to the Mediterranean diet of patients with psoriasis compared with controls [85]. Interestingly, a questionnaire cohort study (35,735 participants) found an inverse relationship between the adherence to the Mediterranean diet and having severe psoriasis [85]. A possible explanation for the beneficial role of the Mediterranean diet in psoriasis could be related to the anti-inflammatory properties of dietary fibers, antioxidants, polyphenols, and monounsaturated fats contained in extra virgin olive oil (an important source of monounsaturated fatty acids) [86]. In particular, monounsaturated fatty acids were found to be a predictor of psoriasis severity [86]. Furthermore, consumption of fish oils rich in omega 3 and moderate alcohol consumption [87], which are part of the Mediterranean diet, may also contribute to its beneficial effects in psoriasis.

5.5 Other Diets

Whilst low-calorie diets were the most studied, other diets have also been investigated. A small trial assessed two diets, the Ornish and South beach diets, in obese patients with psoriasis undergoing phototherapy [88]. After 12 weeks, the mean PASI improvement for the Ornish diet, South Beach diet, and control (non-dietary) group was 78%, 72%, and 71%, respectively ($p = 0.30$ Ornish vs South Beach diet, no comparison between dietary vs non-dietary group was performed) [88]. Furthermore, a small trial (25 patients) investigated a balanced protein-to-fat-to-carbohydrate ratio diet compared to the usual diet but did not find a significant difference in PASI between the two groups at 12 weeks [89]. Last, Michaëlsson et al. studied the effect of a gluten-free diet in 33 patients with anti-gliadin antibody-positive and six anti-gliadin antibody-negative psoriasis. Patients with anti-gliadin antibody-positive psoriasis experienced a significant PASI reduction after 3 months of a gluten-free diet (5.5 ± 4.5 to 3.6 ± 3.0) and 60% had worsening of psoriasis after returning to the ordinary diet [90]. Conversely, psoriasis severity was not affected by the gluten-free diet in patients with anti-gliadin antibody-negative psoriasis, suggesting that the benefits of gluten-free diets on psoriasis are limited to patients who have evidence of gluten sensitivity or celiac disease [90].

In conclusion, there is substantial evidence that diets aimed at lowering weight may improve psoriasis severity in obese patients, as concluded by a Cochrane review assessing lifestyle changes for treating psoriasis [91]. Hence, weight-loss measures including diets as well as physical activity should be initiated in all overweight and obese patients alongside pharmacological treatment. In this regard, weight-loss coaching—either in person or online—can be extremely helpful to these patients [92].

5.6 Alcohol Abstinence

Alcohol consumption is more prevalent in patients with psoriasis than in the general population [93, 94]. Regrettably, alcohol was shown to negatively impact psoriasis severity and its treatment. As to the former aspect, a study on study on 29 patients with moderate plaque psoriasis found that alcohol consumption evaluated through questionnaires and an alcohol-specific blood biomarker (i.e.,

phosphatidylethanol) correlated significantly with the PASI score [95]. These findings were confirmed by a study ofn 146 patients with psoriasis evaluating alcohol consumption using the Alcohol Use Disorder Identification Test (AUDIT) questionnaire [96]. In that study, regular drinkers (AUDIT score > 8) had more severe psoriasis than patients with an AUDIT score < 8 ($p < 0.05$) [96]. Furthermore, a study conducted on 95 patients with psoriasis, which investigated the link between alcohol consumption and psychological distress, also found a modest but significant association between psoriasis severity and weekly alcohol consumption ($r = 0.27$, $p = 0.02$) [97].

Alcohol also negatively impacts the treatment of psoriasis. First, an elevated alcohol intake can increase the toxicity of conventional systemic agents, particularly methotrexate-associated hepatotoxicity [98]. Furthermore, high alcohol consumption is associated with decreased efficacy of psoriasis treatments. A prospective cohort study conducted on 266 patients with psoriasis (134 treated with biologics and 132 with conventional systemic agents) found alcohol misuse to be significantly associated with a poor response to treatment [99]. Similarly, an observational study on 150 patients with psoriasis treated with a topical agent alone or in combination with methotrexate found the therapeutic outcome (PASI75 at 3 months) to be hampered by alcohol, tobacco, or smoking habit, high stress profiles, obesity, and female sex [100]. Furthermore, a study on 180 patients with psoriasis treated with biologics identified alcohol consumption (along with smoking, HLA-Cw6 negativity, and late-onset psoriasis) as a risk factor for treatment failure in the subgroup of patients who had used at least two biologics [101].

At the cellular level, alcohol may negatively affect psoriasis by promoting keratinocyte differentiation and inducing the production of inflammatory cytokines by immune cells [102]. In the murine model of imiquimod-induced psoriasiform dermatitis, chronic alcohol consumption was associated with epidermal thickening and increased cutaneous expression of Th17-related cytokines [102]. In vitro studies also showed that the expression of CCL20 (a Th17-recruiting chemokine crucial in psoriasis) was induced in murine epidermal keratinocytes when the medium was supplemented with ethanol [102]. Furthermore, alcohol was shown to induce IFN-γ release in lymphocytes and increase TNFα production from peripheral blood monocytes and macrophages [102].

In conclusion, given the harmful effects of alcohol in patients with psoriasis, alcohol consumption should be addressed in all patients with psoriasis [96]. Screening tools, such as AUDIT, AUDIT-Concise (AUDIT-C), and CAGE (Cut, Annoyed, Guilty and Eye) have been validated in psoriasis and represent simple yet effective tools [103]. Furthermore, interventions encouraging alcohol reduction are extremely valuable in patients with psoriasis, as reduced alcohol consumption can lead to a reduction in psoriasis severity and cardiovascular risk [103].

5.7 Physical Activity

Numerous large cross-sectional and cohort studies have found that the number of subjects engaging in physical activity is significantly lower among patients with psoriasis [104–109]. Among those studies, an analysis of data from the 2011–14 National Health and Nutrition Examination Survey (NHANES), which included 9174 Americans (232 self-reporting psoriasis), found that only 48.0% of subjects with psoriasis performed physical exercise to lose weight, as opposed to 62.4% of those without psoriasis ($p = 0.027$) [106]. In a German online survey of patients with psoriasis, only as few as 21.2% reported to be currently exercising for losing weight [105]. Reduced levels of physical activity among patients with psoriasis have also been confirmed by several smaller, both controlled and non-controlled survey studies [110–112]. Furthermore, several studies have shown that physical activity may even reduce the risk of developing psoriasis. For instance, a large prospective study that included 86,655 American female nurses found that vigorous physical activity was associated with a reduced risk of psoriasis (RR = 0.66, 95% CI 0.54–0.81; $p < 0.001$) [113]. Similarly, a Japanese population-based cohort study (487,835 participants) found that not exercising ≥ 1 h/ week and BMI were associated with psoriasis onset (hazard ratio 1.13, 95% CI 1.05–1.22 and hazard ratio 1.09, 95% CI 1.05–1.14, respectively) [114]. There is currently limited evidence as to whether physical activity is able to reduce psoriasis severity. The abovementioned randomized controlled trial by Naldi et al. [75] conduced on 303 overweight or obese patients with psoriasis found that a low-caloric diet combined with physical exercise reduced psoriasis severity at 20 weeks [75]. However, the specific role of physical activity is difficult to infer given that the intervention consisted of both diet and exercise. Despite the paucity of clinical trials, there are several reasons why physical activity should be encouraged in patients with psoriasis. First, physical activity can lead to weight loss in overweight and obese patients with psoriasis. Furthermore, physical activity may reduce the oxidative stress that characterizes psoriasis through the upregulation of anti-oxidant enzymes such as superoxide dismutase [115]. Physical activity might also reduce the levels of TNF-α and the expression of cell membrane adhesion molecules such as ICAM-1 and VCAM-1 and exerts epigenetic effects [115]. Ultimately, physical activity is associated with the improvement of the comorbidities associated with psoriasis, particularly the cardiovascular, metabolic, and psychological comorbidities. In conclusion, physical activity has several favorable effects on psoriasis and thus represents a cornerstone of non-pharmacologic treatments of psoriasis.

5.8 Smoking

Smoking has long been known to represent a risk factor for psoriasis, as shown by a meta-analysis that found a significant association between smoking and psoriasis (RR 1.88, 95% CI 1.66–2.13) [116]. A particularly strong association was confirmed between smoking and pustular psoriasis, OR = 5.3 (95% CI 2.1–13.0) [117]. Furthermore, despite some conflicting data, the majority of studies found an association between the level of smoking and psoriasis severity. For instance, a study on 818 patients with psoriasis found that heavy smoking (> 20 cigarettes/day) was associated with a more than twofold increased risk of more severe psoriasis (OR 2.2, 95% CI 1.2–4.1) compared with light smoking (≤ 10 cigarettes/day) [118]. Regarding psoriasis treatment, although conflicting evidence exists as to whether smoking is associated with associated with a worse response to treatment [119–122], a meta-analysis concluded that smoking negatively impacts the benefits of biologics on psoriasis [119]. Pathogenetically, the relationship between smoking and psoriasis may be explained by the formation of free radicals induced by smoking, which in turn stimulate pathways active in psoriasis such as mitogen-activated protein kinase, nuclear factor-κB, and JAK-STAT [123]. Furthermore, smoking triggers the production of reactive oxygen species with consequent skin damage, and prompts dendritic cells, macrophages, and keratinocytes to release cytokines that activate T lymphocytes [123].

In conclusion, smoking has a detrimental impact on patients with psoriasis as it not only worsens psoriasis severity but also its associated comorbidities, including cardiovascular diseases and inflammatory bowel diseases. Hence, smoking cessation should be strongly encouraged in patients with psoriasis who smoke.

6 Conclusions

A number of epidemiological studies support the association between chronic plaque psoriasis and the cluster of interconnected conditions defining the metabolic syndrome, including abdominal obesity, atherogenic dyslipidemia, hypertension, insulin resistance, and hyperglycemia. The physiopathology underlying this association is based on the genetic predisposition, shared inflammatory pathways, and common risk factors. The presence of metabolic comorbidities interferes with the selection and effectiveness of the treatments for psoriasis. While some treatments, such as methotrexate and cyclosporine, should be prescribed with caution in these patients because of an increased risk of adverse events, others like IL-17 and IL-23 inhibitors appear to have a safer profile. European guidelines on the systemic treatment of psoriasis are recommended as a specific reference for the management of patients with metabolic comorbidities. These guidelines outline specific screening and monitoring tests for each medication. Ultimately, non-pharmacological interventions including diet, physical activity, alcohol abstinence, and smoking avoidance, may be very useful in the global management of patients with psoriasis with metabolic comorbidities.

Declarations

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Conflict of interest Martina Maurelli, Francesco Bellinato, and Davide Geat have no conflicts that are directly relevant to the content of this article. Gisondi Paolo has been a consultant and/or speaker for AbbVie, Almirall, Amgen, Janssen, LEO pharma, Eli Lilly, Novartis, Pierre Fabre, Sandoz, Sanofi, and UCB. Girolomoni Giampiero served as a consultant and/or speaker for AbbVie, Abiogen, Almirall, Amgen, Biogen, Boeringher Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Genzyme, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, and UCB.

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