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METABOLISM (M DALAMAGA, SECTION EDITOR)

Deciphering the Association Between Psoriasis and Obesity: Current Evidence and Treatment Considerations

Kyriaki Paroutoglou[1] · Evangelia Papadavid[1] · Gerasimos Socrates Christodoulatos[2] · Maria Dalamaga[1,2]

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Abstract

Purpose of Review Obesity and psoriasis represent chronic inflammatory states that are interconnected in a vicious cycle, sharing also a degree of synergy. In this review, we aim to decipher the various lines of evidence supporting the bidirectional association between psoriasis and obesity highlighting their pathophysiologic connections as well as we attempt to strategize a therapeutic holistic approach for obese psoriatic patients.

Recent Findings Recent meta-analyses have shown that (1) genetically higher BMI increased the odds of psoriasis occurrence; (2) obesity is associated with higher incidence and prevalence of psoriasis as well as psoriasis severity; (3) obesity is associated with lower efficacy to anti-TNF agents and may predict biologic treatment discontinuation; and (4) weight loss through diet and physical exercise may improve pre-existing psoriasis and prevent from de novo psoriasis. Methotrexate, acitretin, and cyclosporine could worsen hypertension, liver steatosis, and dyslipidemia. Since infliximab and ustekinumab are weight adjusted, they may be ideal drugs to treat obese psoriatic patients. IL-17 inhibitors are very effective independently from body weight; however, they tend to present better clearance rates in normal weight patients. There is a paucity on weight data regarding the efficacious IL-23 inhibitors. Apremilast may induce weight loss as an adverse effect presenting also some beneficial metabolic actions. Finally, simvastatin and some antidiabetic drugs could decrease psoriasis severity.

Summary More mechanistic, observational studies and well-conducted RCTs are necessary to decipher the enigmatic link between psoriasis and obesity, and to provide evidence-based specific guidelines for the screening and management of obese psoriatic patients.

Keywords Adiponectin · Adipose tissue · Anti-TNF agent · Apremilast · IL-17 inhibitor · IL-23 inhibitor · Leptin · Obesity · Psoriasis · Resistin

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✉ Maria Dalamaga
madalamaga@med.uoa.gr

Kyriaki Paroutoglou
kparou@gmail.com

Evangelia Papadavid
papadavev@yahoo.gr

Gerasimos Socrates Christodoulatos
gerchristod82@hotmail.com

[1] 2nd Department of Dermatology and Venereology, School of Medicine, National and Kapodistrian University of Athens, Attikon General University Hospital, 1 Rimini Street, Chaidari, 12462 Athens, Greece

[2] Department of Biological Chemistry, School of Medicine, National and Kapodistrian University of Athens Medical School, 27 Mikras Asias Street, Goudi, 11527 Athens, Greece

Abbreviations

BMI	Body mass index
CI	Confidence interval
CVD	Cardiovascular disease
t2DM	Diabetes mellitus type 2
GLP-1	Glucagon-like peptide-1
GWASs	Genome-wide association studies
HMW adiponectin	High molecular weight adiponectin
HR	Hazard ratio
IFN	Interferon
IL	Interleukin
MD	Mean difference
MetS	Metabolic syndrome
NAFLD	Non-alcoholic fatty liver disease
OR	Odds ratio
OSAH	Obstructive sleep apnea/hypopnea
PASI	Psoriasis area and severity index

PsA	Psoriatic arthritis
RCT	Randomized controlled trial
RR	Relative risk
TNF-α	Tumor necrosis factor-α
SNPs	Single-nucleotide polymorphisms
WAT	White adipose tissue
WMB	Weighted mean difference
SMD	Standardized mean difference

Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease of the skin due to dysregulated epidermal cell proliferation as a response to an unknown or non-specific trigger [1]. It typically manifests as erythematous plaques with a silvery scale, often with involvement of the nails [2]. Psoriasis affects approximately 2–3% of the population in Europe and North America [3] with no predilection for gender, although men seem to suffer from more severe forms [4].

The etiology of psoriasis is multifactorial, including genetic and environmental factors [1–5]. The dysregulation of the innate and adaptive immune systems in psoriasis may lead to an inflammatory cycle involving resident T cells of the skin and pro-inflammatory cytokines such as interferon (IFN)-γ, tumor necrosis factor-α (TNF-α), interleukin (IL)-23, IL-17, and IL-22 [6–8]. In this inflammatory setting, IL-23-secreting cells, such as macrophages and myeloid dendritic cells, infiltrate psoriatic skin activating the expression of IL-17A and other pro-inflammatory cytokines produced by a plethora of immune cells comprising mainly T helper cells (Th17 cells), cytotoxic T cells, T γδ, and mast cells [5, 9]. This variety of cells plays an important role in the intensification of cutaneous inflammation, activating IL17A-induced keratinocyte response [9, 10]. Keratinocytes represent the key-responding cells to the cytokine milieu, secreting in turn chemokines, cytokines, and other peptides establishing thereby vicious inflammatory networks. Moreover, the white adipose tissue (WAT) situated under the skin could influence the cutaneous inflammation by producing cytokines and adipokines. The abnormal cutaneous and systemic secretion of cytokines and adipokines may contribute to the stimulation, differentiation, and proliferation of keratinocytes and immune cells leading to the development of psoriatic skin lesions [11, 12].

Five different clinical types of psoriasis have been described: chronic plaque psoriasis (psoriasis vulgaris), guttate psoriasis, inverse psoriasis, pustular psoriasis, and erythrodermic psoriasis [2]. Two-thirds of patients have mild psoriasis [13], while the management of more severe forms presents many challenges due to the chronicity, complexity, and the related comorbidities of the disease [14]. Conventional treatment of psoriasis includes topical treatment for mild to moderate psoriasis, with corticosteroid creams, vitamin D analogues, topical retinoids, calcineurin inhibitors, and phototherapy treatment, while systemic treatment for more severe forms includes acitretin, apremilast, cyclosporine, and methotrexate [1, 2]. In recent years, better understanding and decoding of the inflammatory cascade underlying psoriasis have led to the discovery and use of biologic agents [2, 15]. This has been a tremendous breakthrough and invaluable addition to the therapeutic options available for patients with severe psoriasis.

Apart from psoriatic arthritis (PsA), comorbidities of psoriasis include obesity and obesity-associated metabolic disorders, such as metabolic syndrome (MetS), dyslipidemia, hypertension, diabetes mellitus type 2 (t2DM), non-alcoholic fatty liver disease (NAFLD), obstructive sleep apnea/hypopnea (OSAH), and cardiovascular disease (CVD) [16–21]. There is emerging evidence suggesting an underlying shared chronic inflammatory process between psoriasis and obesity [12], while it is noteworthy to mention that some anti-psoriatic drugs may also influence obesity and obesity-associated comorbidities through their adverse effects [22]. In this review, we aim to decipher the various lines of evidence supporting the bidirectional association between psoriasis and obesity highlighting their pathophysiologic connections as well as we attempt to strategize a therapeutic holistic approach for obese psoriatic patients.

Material and Methods

We performed a literature search of the meta-analyses investigating the association between obesity and psoriasis. We used the databases PubMed and Scopus with the keywords "meta-analysis" and "obesity" and "psoriasis." We have also identified two Mendelian randomization (MR) studies showing a causal association between obesity and psoriasis. Table 1 depicts the list of meta-analyses delineating the association between psoriasis and obesity.

Investigating the Bidirectional Association Between Obesity and Psoriasis

The relationship between obesity and psoriasis has been demonstrated in animal studies. Employing an obese mouse model with psoriasiform dermatitis induced by imiquimod, it was shown that obesity may acutely aggravate the severity of psoriasiform dermatitis in mice [37]. Furthermore, mice expressed greater levels of psoriasis mediators, such as IL-22 and IL-17A and its downstream protein regenerating islet-derived 3γ, which has been implicated in psoriatic epidermal hyperplasia as a critical mediator [37]. These findings suggest that obesity may exacerbate psoriasiform dermatitis through upregulation of pro-inflammatory cytokines.

Table 1 List of meta-analyses analyzing the association between psoriasis and obesity

Meta-analysis	Number of studies	Number of individuals	Pooled OR and 95% CI or *p* values	Comments
Causal association between obesity and psoriasis (Mendelian randomization studies)				
Budu-Aggrey et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. *PLoS Med*. 2019;16(1):e1002739 [23••]	Individual-level data from the UK Biobank and the Nord-Trøndelag Health Study (HUNT), Norway Summary-level data from BMI and psoriasis GWASs	753,421	97 SNPs associated with BMI as a proxy for BMI MD in BMI of 1.26 kg/m^2 (95% CI 1.02–1.51) between adult psoriasis cases and controls MD in BMI of 1.55 kg/m^2 (95% CI 1.13–1.98) between psoriasis cases and controls in children 1.09 (95% CI 1.06–1.12) for higher BMI increasing the odds of psoriasis (9% increase in the odds of psoriasis per 1 kg/m^2 increase in BMI)	Genetically higher BMI increases the odds of psoriasis Little support to a possible causal effect of psoriasis genetic risk on BMI.
Ogawa et al. A transethnic Mendelian randomization study identifies causality of obesity on risk of psoriasis. *J Invest Dermatol* 2019; 139:1397–1400 [24]	Transethnic Mendelian randomization using GWAS results	13,229 case and 21,543 control European individuals 282 case and 426 control Japanese individuals	$p = 0.0093$ $p = 0.0069$	For Europeans, significant causality of genetically increased BMI on psoriasis risk For Japanese, significant causality of genetically increased BMI on psoriasis risk
Obesity predisposing to psoriasis				
Aune et al. Body mass index, abdominal fatness, weight gain and the risk of psoriasis: a systematic review and dose-response meta-analysis of prospective studies. *Eur J Epidemiol*. 2018;33:1163–1178 [25••]	7 prospective	17,636	Summary RR 1.19 (95% CI 1.10–1.28) for a 5 unit increment of BMI and psoriasis risk Summary RR 1.24 (95% CI 1.17–1.31) per 10 cm increase in waist circumference and psoriasis risk Summary RR 1.37 (95% CI 1.23–1.35) for 0.1 unit increment in waist-to-hip ratio and psoriasis risk Summary RR 1.11 (95% CI 1.07–1.16) per 5 kg of weight gain	Increased risk of psoriasis with higher BMI, waist circumference, waist-to-hip ratio, and weight gain 2–4-fold increase in the risk of psoriasis among those at the high end of each adiposity measures
Budu-Aggrey et al. Evidence of a causal relationship between body mass index and psoriasis: a Mendelian randomization study. *PLoS Med*. 2019;16(1):e1002739 [23••]	Individual-level data from the UK Biobank and the Nord-Trøndelag Health Study (HUNT), Norway Summary-level data from BMI and psoriasis GWASs	753,421	1.04 (95% CI 1.03–1.04) for 1 kg/m^2 increase in BMI	Higher BMI is associated with 4% higher odds of psoriasis
Psoriasis and prevalence/incidence of obesity				
Armstrong et al. The association between psoriasis and obesity: a systematic review and meta-analysis of observational studies. *Nutr Diabetes*. 2012; 2:e54 [22]	13 retrospective case-control 3 prospective case-control	2.1 million (201, 831 psoriasis patients)	1.66 (95% CI 1.46–1.89) for obesity among patients with psoriasis compared with controls HR of 1.18 (95% CI 1.14–1.23) for new onset obesity among psoriasis patients 1.46 (95% CI 1.17–1.82) for obesity among patients with mild psoriasis	Psoriasis patients present higher prevalence and incidence of obesity Patients with severe psoriasis present higher odds of obesity that those with mild psoriasis

Table 1 (continued)

Meta-analysis	Number of studies	Number of individuals	Pooled OR and 95% CI or *p* values	Comments
			2.23 (95% CI 1.63–3.05) for obesity among patients with severe psoriasis	
Miller et al. Meta-analysis of psoriasis, cardiovascular disease, and associated risk factors. *J Am Acad Dermatol.* 2013;;69:1014–24 [21]	75 retrospective case-control	503,686 psoriasis cases and 29,686,694 controls	1.8 (95% CI 1.4–2.2) for psoriasis associated with obesity defined by BMI 1.6 (95% CI 1.2–2.3) for psoriasis associated with obesity defined by abdominal fat	Psoriasis is associated with obesity defined by BMI and abdominal fat. This association was mainly seen in hospital-based studies than population-based studies
Weight loss and psoriasis severity				
Upala et al. Effect of lifestyle weight loss intervention on disease severity in patients with psoriasis: a systemic review and meta-analysis *Int J Obes*. 2015; 39:1197–1202 [26]	5 RCTs	878	MD − 2.49 (95% CI − 3.90 to − 1.08) in PASI scores in patients receiving weight loss intervention (dietary and lifestyle) compared with controls Pooled OR 2.92 (95% CI 1.39–6.13) for a 75% reduction in PASI score in the intervention group compared with the control group	Non-pharmacological, non-surgical weight loss intervention is related to a reduction in the severity of psoriasis in overweight or obese patients
Mahil et al. Does weight loss reduce the severity and incidence of psoriasis or psoriatic arthritis? A critically-appraised topic. *Br J Dermatol* 2019;181: 946–953 [27••]	7 RCTs 2 cohort studies	757	Mean change in PASI score, − 2.50 (95% CI − 4.09 to − 1.09) for weight loss following lifestyle interventions (diet or physical activity) compared with control In 2 cohort studies, bariatric surgery, particularly gastric bypass, lowers the risk of developing psoriasis (HR 0.52, 95% CI 0.33–0.81)	Weight loss may improve pre-existing psoriasis and may prevent de novo psoriasis in individuals with obesity
Obesity and response to biologics				
Singh et al. Obesity and response to anti-tumor necrosis factor-α agents in patients with select immune mediated inflammatory diseases: a systematic review and meta-analysis *PLoS One*. 2018;13(5): e0195123 [28•]	54 cohorts (22 cohorts for psoriasis/PsA)	19,372 patients with selected autoimmune disorders (23% obese)	Obese patients presented 60% higher odds of failing anti-TNF-α therapy (OR 1.60; 95% CI 1.39–1.83) Particularly, obese patients with psoriasis and/or PsA presented 57% higher odds of failing anti-TNF-α therapy (OR 1.57; 95% CI 1.30–1.89)	Obesity is a predictor of inferior response to anti-TNF-α agents in patients with selected immune-mediated inflammatory diseases, including psoriasis/PsA
Shan et al. Impact of obesity on the efficacy of different biologic agents in inflammatory diseases: a systematic review and meta-analysis. *Joint Bone Spine* 2019; 86: 173–183 [29]	6 cohorts	1625 patients with psoriasis (219) and PsA (1406) Obese patients ranged from 32 to 33.3%	Three out of four studies in psoriasis showed that obese patients had higher mean PASI and lower PASI90/75 response rate than normal or overweight patients Remission and good response rate do not seem to be affected by BMI in PsA. However, moderate/good response rate and adherence to anti-TNF-α agents were diminished by obesity in PsA	Obesity is associated with lower efficacy to anti-TNF-α agents
Mourad et al. Factors predicting persistence of biologic drugs in psoriasis: a systematic review and meta-analysis. *Br J Dermatol* 2019; 181: 450–458 [30•]	6 cohorts for obesity	9311	HR 1.21 (95% CI 1.10–1.32) for obesity predicting treatment discontinuation Obesity predicted lower rates of biologic persistence due to ineffectiveness in the etanercept (HR, 1.24 (95% CI 1.07–1.45)),	Obesity predicts biologic treatment discontinuation

Table 1 (continued)

Meta-analysis	Number of studies	Number of individuals	Pooled OR and 95% CI or *p* values	Comments
			ustekinumab (HR, 1.43 (95% CI 1.01–2.03)), and infliximab (HR, 2.38 (95% CI 1.49–3.81)) groups	
Adipocytokines and psoriasis				
Zhu et al. Leptin levels in patients with psoriasis: a meta-analysis. *Clin Exp Dermatol*. 2013;38:478–483 [31]	11 retrospective case-control	773 patients with psoriasis and 570 healthy controls	Higher leptin levels in patients with psoriasis compared with controls, WMD 7.24 (95% CI 4.55–9.93; $p < 0.001$	Hyperleptinemia is associated with psoriasis
Zhu et al. Adiponectin levels in patients with psoriasis: a meta-analysis *J Dermatol* 2013; 40: 438–42 [32]	9 case-control for adiponectin and 3 case-control for HMW adiponectin	389 cases and 360 controls for adiponectin and 132 cases and 132 controls for HMW adiponectin	Not significantly different adiponectin in cases than controls, SMD, − 0.151 (95% CI − 0.616 to 0.315; $p = 0.526$) Not significantly different HMW adiponectin in cases than controls, SMD, 0.999 (95% CI − 2.626 to 4.624; $p = 0.589$)	Adiponectin and HMW adiponectin may not be associated with psoriasis
Huang et al. Increased serum resistin levels correlate with psoriasis: a meta-analysis. *Lipids Health Dis* 2015; 16;14:44 [33]	9 case-control	421 psoriasis patients and 348 healthy control	Higher resistin levels were found in psoriasis patients compared with healthy controls, SMD 2.22 (95% CI 1.14–3.29, $p < 0.001$) Higher resistin levels were found in Asian (SMD = 3.27, 95% CI = 1.62–4.91, $p < 0.001$) and in Caucasian populations (SMD = 0.91, 95% CI = 0.28–1.54, $p < 0.001$)	Hyperrestinemia is associated with psoriasis in both Asian and Caucasian populations
Bai et al. Serum levels of adipokines and cytokines in psoriasis patients: a systematic review and meta-analysis. *Oncotarget* 2017;9: 1266–1278 [34•]	59 case-control 4 cross-sectional	2876 psoriasis patients and 2237 healthy controls	SMD − 0.90 (95% CI − 1.78 to − 0.02) for adiponectin levels in psoriasis patients compared with healthy controls SMD 0.74 (95% CI 0.46 to 1.02) for lipocalin-2 levels in psoriasis patients compared with healthy controls SMD 3.55 (95% CI 0.86 to 6.24) for chemerin levels in psoriasis patients compared with healthy controls SMD 1.97 (95% CI 0.58 to 3.37) for resistin levels in psoriasis patients compared with healthy controls	Serum adiponectin levels were significantly lower, whereas serum lipocalin-2, chemerin and resistin levels were significantly higher in psoriasis patients compared with controls No significant differences in serum levels of visfatin and omentin-1 were observed between psoriasis patients and healthy controls
Kyriakou et al. Serum leptin, resistin and adiponectin concentrations in psoriasis: a meta-analysis of observational studies. *Dermatology* 2017; 233: 378–389 [35]	38 retrospective case-control	5795	Higher leptin concentrations in psoriatic patients compared with controls, MD 5.64 ng/mL (95% CI 3.00–8.29, $p < 0.001$) Higher resistin concentrations in psoriatic patients compared with controls, MD 4.66 ng/mL (95% CI 2.62–6.69, $p < 0.001$) Lower adiponectin concentrations in psoriatic patients compared with controls, MD − 1.87 μg/mL (95% CI − 2.76 to − 0.98, $p < 0.001$)	Leptin and resistin concentrations were significantly higher, and adiponectin concentrations were significantly lower in patients with psoriasis compared with controls

Table 1 (continued)

Meta-analysis	Number of studies	Number of individuals	Pooled OR and 95% CI or *p* values	Comments
Kyriakou et al. Effects of treatment for psoriasis on circulating levels of leptin, adiponectin and resistin: a systematic review and meta-analysis. *Br J Dermatol* 2018; 179: 273–281 [36]	15–17 studies	532–782 patients with psoriasis	After treatment, no significant change in adiponectin was observed, SMD − 0.14 (95% CI − 0.34 to 0.05) After treatment, no significant change in adiponectin was observed, SMD 0.06 (95% CI − 0.09 to 0.20) After treatment, serum resistin was significantly lower than before treatment, SMD 0.50 (95% CI 0.20–0.79)	Treatment intervention reduces serum resistin but does not modify leptin or adiponectin concentrations

BMI, body mass index; *CI*, confidence interval; *GWASs*, genome-wide association studies; *HMW adiponectin*, high molecular weight adiponectin; *HR*, hazard ratio; *MD*, mean difference; *MR*, Mendelian randomization study; *OR*, odds ratio; *PASI*, psoriasis area and severity index; *PsA*, psoriatic arthritis; *RCT*, randomized controlled trial; *RR*, relative risk; *TNF-α*, tumor necrosis factor-α; *SNPs*, single-nucleotide polymorphisms; *WMB*, weighted mean difference; *SMD*, standardized mean difference

A number of meta-analyses have depicted an important bidirectional association between psoriasis and comorbid obesity, with growing evidence showing that obesity may be a predisposing factor for psoriasis while psoriasis patients present higher prevalence and incidence of obesity. In particular, a meta-analysis of 7 prospective studies including 17,636 participants has shown that higher BMI, waist circumference (WC), and waist-to-hip ratio (WHR) as well as weight gain were associated with an increased risk of psoriasis, with a 2–4-fold increase in the risk of psoriasis among those at the high end of each adiposity measures. In particular, there was a 19%, 24%, 37%, and 11% augmentation in the relative risk of psoriasis for each 5 unit increase in BMI, 10 cm increase in WC, 0.1 unit increment in WHR, and 5 kg of weight gain [25••]. A clear dose-response association has been observed between BMI, WC, WHR, and weight gain with psoriasis risk. Moreover, these results were in accordance with a previous meta-analysis of case-control and cross-sectional studies showing that obesity is associated with increased odds of psoriasis occurrence [22].

More importantly, a causal relationship between obesity and psoriasis has also been shown in two recent MR based on genome-wide association studies, using specific genetic polymorphisms associated with BMI as a proxy for BMI, which is less confounded than measured BMI [23, 24]. MR studies present many advantages in the delineation of a causal association. Based on the assumption of the random assortment of alleles from parents to offspring at conception, genetic variants can be used as unbiased proxy variables being unrelated to confounding factors and reverse causation [38]. Therefore, employing genetic variants as proxy variables for lifelong exposure in MR studies could circumvent residual confounding and reverse causation bias ameliorating causal inference. Based on the fact that the majority of known genetic variants are moderately related with BMI, multiple single-nucleotide polymorphisms (SNPs) are used for MR in order to evaluate the relationship between genetically determined higher BMI and psoriasis occurrence. From these studies, it was shown that, overall, genetically determined higher BMI is associated with a 9% increase in the odds of psoriasis per 1 unit increase in BMI in both children and adults [23••]. In a very recent transethnic MR study, this association was observed in both European and Japanese populations [24].

Similarly, on the other side of this bidirectional relationship, a large meta-analysis of 13 retrospective and 3 prospective case-control studies with 2.1 million participants showed a higher prevalence and incidence of obesity among patients suffering from mild and severe psoriasis. Particularly, patients with severe psoriasis presented greater odds of obesity occurrence than those with mild psoriasis [22]. On the contrary, from the previous MR study, there was little support for a potential causal association of psoriasis genetic risk on BMI [23••].

Interestingly, there is mounting evidence suggesting that non-pharmacological, non-surgical weight loss is associated with reduction in the severity of psoriasis, as expressed by psoriasis area and severity index (PASI) in overweight or obese patients [28–30]. Nevertheless, it should be underscored that BMI alone is not an accurate measure of determining adiposity [39, 40], and recent evidence has shown that individuals with normal BMI can still carry excess body fat which may be associated with psoriasis occurrence. Estimating body

fat distribution may be a more useful way of assessing obesity in these patients [41]. Weight loss following lifestyle interventions such as diet and/or physical exercise may improve pre-existing psoriasis and prevent de novo psoriasis in obese subjects [27••]. There is also evidence of a linear dose-response association, with more weight loss being related to higher improvements in psoriasis severity. Although the amelioration in psoriasis is small in magnitude (mean change in PASI − 2.50), it seems to be sustainable up to 64 weeks [42, 43]. The consequences of bariatric surgery on psoriasis and PsA severity have only been shown in small case series. However, in a meta-analysis of 2 large population-based cohort studies, it was shown that bariatric surgery, particularly gastric bypass but not gastric banding, may lower the risk of developing psoriasis and PsA [27••]. The observed superiority of gastric bypass over gastric banding could be due to higher postoperative weight loss using the former surgical procedure or to direct anti-inflammatory actions in gut microbiome and gastric hormones such as glucagon-like peptide-1 (GLP-1) [27••].

Pathophysiologic Connections Between Obesity and Psoriasis

Obesity and psoriasis represent chronic inflammatory states that are interconnected in a vicious cycle, sharing also a degree of synergy [44]. Recent research, which has brought better understanding into the multifaceted role of adipose tissue, has indicated that WAT, particularly visceral fat, acts as an endocrine organ producing pro-inflammatory cytokines and adipocytokines, leading to a dysregulation of the immune system and a chronic subclinical low-grade inflammation [45]. Adiposity is related with low-grade inflammation through oversecretion of pro-inflammatory cytokines. Particularly, activated macrophages in the adipose tissue stimulate adipocytes to secrete TNF-α, IL-1, IL-6, and IL-8, which could contribute to the development of psoriasis [46]. In addition to TNF-α production, adipose tissue may trigger inflammation through the secretion of adipocytokines [31, 33, 34, 47–49]. Adipocytokines are produced not only by adipocytes but also by other cells infiltrating the adipose tissue, mainly macrophages [50]. Interestingly, the adipocytokine leptin is secreted by the adipose tissue to signal satiety to the hypothalamus and increases energy expenditure by promoting lipolysis and reducing hepatic lipogenesis. Leptin also acts as an immunomodulatory molecule [31, 48, 51, 52]. Common obesity is associated with hyperleptinemia and leptin resistance. Psoriatic patients present hyperleptinemia independently from BMI, which is associated with increased occurrence of psoriasis [31, 48]. Leptin may increase keratinocyte proliferation and pro-inflammatory cytokine secretion, which are hallmarks of psoriasis [53]. Moreover, the skin of obese subjects is characterized by impaired barrier function, while impairment in lymphatic function could delay the clearance of pro-inflammatory mediators [34•].

Controversy exists regarding the role of the adipocytokine adiponectin in psoriasis (Table 1). Adiponectin is secreted mainly by adipocytes of the WAT. It influences a plethora of cell types, including adipocytes, monocytes, T lymphocytes, endothelial cells, and keratinocytes. Generally, adiponectin exerts anti-inflammatory properties inhibiting the secretion of pro-inflammatory cytokines such as TNF-α, IL-6, IL17, and IL-1, upregulating the production of anti-inflammatory cytokines like IL-10, and suppressing vascular inflammation via the downregulation of endothelial cell adhesion molecules [14, 54, 55]. The most recent meta-analyses have shown that psoriatic patients exhibit lower levels of adiponectin [34, 35]. However, in a previous meta-analysis of 9 case-control studies, adiponectin and its main biologic isoform HMW adiponectin were not significantly different in psoriatic patients than healthy controls [32]. This discrepancy may be attributed to the lower sample size of the latter meta-analysis. Similar to adiponectin, omentin-1, another anti-inflammatory adipocytokine that inhibits TNF-α-stimulated expression of pro-inflammatory cytokines, is suppressed in obesity. However, no significant differences in serum omentin-1 were observed between psoriatic patients and healthy controls in a recent meta-analysis [34•].

The most consistent findings regarding serum levels of adipocytokines in psoriasis were observed for resistin, a pro-inflammatory adipocytokine which is increased in obesity, insulin resistance, atherosclerosis, cardiovascular disease, acute inflammation, and cancer [50, 56–60]. Hyperresistinemia was associated with psoriasis occurrence in both Asian and Caucasian populations [33–35]. Moreover, resistin levels were correlated with psoriasis severity indexes in psoriasis patients. More importantly, resistin was the only pro-inflammatory adipocytokine that decreased after treatment for psoriasis [36]. Interestingly, another adipocytokine, chemerin, which may activate angiogenesis in psoriatic skin and induce chemotaxis of plasmacytoid dendritic cells and immature myeloid dendritic cells leading to skin lesions of psoriasis patients, was found elevated in psoriatic patients [34•].

Further research is required to elucidate the ontological role of adipocytokines in psoriasis which may represent the missing link between psoriatic skin inflammatory processes and metabolic alterations such as obesity and Mets. As adipocytokines are implicated in the “psoriatic march” and constitute biomarkers of obesity-related inflammation and cardiometabolic risk, it would be important to examine their contribution to the increased cardiovascular risk in psoriasis and to investigate whether their normalization may ameliorate cardiovascular risk [11, 12, 61].

Management Strategy of Psoriasis in Obese Patients

Therapeutic Aims, Weight Loss, and a Holistic Lifestyle Approach

Therapeutic aims in the management of obese psoriatic patients should include remission or improvement of psoriasis, greater and longer sustained response to systemic and biologic anti-psoriatic treatment, reduction of metabolic and other side effects of systemic treatment and decrease of the patients' cardiovascular (CVD) risk, generalized inflammation, and insulin resistance. In parallel, another aim would be the treatment cost reduction, eventually through the improvement of psoriasis severity and the savings due to the weight-adjusted dose changes of the required treatment [17, 28, 62–65].

Based upon the fact that diet with high caloric value, sedentary lifestyle, and emotional stress are some of the modifiable shared risk factors in both obesity and psoriasis, the importance of a holistic approach for obese psoriatic patients becomes evident [12]. Particularly, weight loss, especially through education on healthy diet, and physical activity are of paramount importance in psoriasis with comorbid obesity [26].

As mentioned previously, weight loss through dietary and lifestyle interventions was associated with reduction in psoriasis risk and severity in overweight or obese individuals [26, 27]. Individual studies have also suggested that adopting an anti-oxidant and anti-inflammatory diet such as the Mediterranean diet may reduce inflammation, C-reactive protein (CRP) levels, CVD risk, psoriasis risk, severity, and impairment of life quality in psoriatic patients [62, 66–69]. Weight loss through bariatric surgery for morbidly obese psoriatic patients has also been associated with significant reduction of psoriasis severity [70].

More importantly, recent meta-analyses depicted in Table 1 have shown that obesity is a predictor of inferior response to anti-TNF-α agents in patients with immune-mediated related disorders including psoriasis and PsA. Particularly, obese patients with psoriasis and/or PsA presented 57% higher odds of failing anti-TNF-α therapy [28•]. Moreover, obesity was associated with lower efficacy to anti-TNF-α agents in psoriasis but not PsA [29]. However, moderate/good response rate and adherence to anti-TNF-α agents were diminished by obesity in PsA [29].

Another meta-analysis of 6 cohort studies also found that obesity may be a predictor of biologic treatment discontinuation [30•]. Specifically, obesity predicted lower rates of biologic persistence due to ineffectiveness in the etanercept, ustekinumab, and infliximab groups [30•]. Finally, a more recent review of 3 retrospective and 1 prospective studies concluded that obese patients had significantly higher mean PASI and lower PASI 90/75 (i.e., a 90% or 75% decrease in PASI from baseline) response rate to biologic agents compared with normal or overweight patients [29].

Considerations in Choosing Anti-psoriatic Therapy in Obese Patients

Table 2 provides a list of the most common anti-psoriatic agents and their relevant implications in obesity-related comorbidities. Careful consideration of the comorbid disorders should be given in psoriatic patients to avoid the development or deterioration of metabolic conditions due to the potential adverse effects of anti-psoriatic agents [17, 63, 65, 71–74]. Therefore, it is recommended to perform regular screening for metabolic-related comorbidities such as t2DM, dyslipidemia, obesity, hypertension, Mets, NAFLD, and kidney disease and manage them accordingly as well as consult an appropriate specialist when indicated [63, 65, 74]. The European Academy of Dermatology and Venereology has recently published an updated position statement for the management of comorbidities in psoriasis, advising that treatment in such cases should be individualized and closely monitored depending on the patients' lifestyle and concomitant diseases [63]. It is suggested that patients on topical anti-psoriatic treatment should be assessed for comorbidities annually and patients on systemic treatment every 6 months. Furthermore, an extensive guidance is provided recommending targeted medical history for such comorbidities (personal and family history, etc.), specific physical examination, additional tests that should be performed in dermatology clinics for psoriatic patients, referral criteria to relevant specialties when comorbidities are identified, and advice on further management when a diagnosis of a comorbidity has been established [63]. It is important to consider the implications of anti-psoriatic agents, both conventional and biologics, in these comorbidities. Specifically, in patients with t2DM, it should be taken into account that cyclosporine and the anti-TNF-α biologic agent adalimumab may induce hyperglycemia, while acitretin may increase serum levels of cholesterol and triglycerides as well as cause glucose tolerance impairment [63, 65, 74]. During initiation of the anti-TNF-α biologic agent etanercept, patients on antidiabetic medications should be monitored closely for hypoglycemia, and upon its occurrence, their antidiabetic treatment needs to be adjusted [63, 65, 74]. In patients with obesity and other obesity-related disorders, adalimumab and cyclosporine may induce hyperlipidemia while treatment with acitretin may cause hypertriglyceridemia. Therefore, monitoring of serum lipid levels prior and after the initiation of treatment with these medications is advised [63, 65, 74]. Regarding hypertension, patients on cyclosporine, adalimumab, and the anti-TNF-α biologic agent infliximab should be regularly monitored as these agents are known to cause high blood pressure, while cyclosporine is contraindicated in patients with uncontrolled hypertension [63, 65, 74].

Table 2 Implications of anti-psoriatic therapies in obesity-related comorbidities

Comorbidities	Treatment						
	MTX	CSA	Acitretin	Anti-TNF-α agents	IL-12/23 inhibitors	IL-17 inhibitors	Apremilast
Diabetes mellitus type 2		Can cause hyperglycemia	May impair glucose tolerance and increase lipids	Adalimumab may cause hyperglycemia. Etanercept initiation may induce hypoglycemia in patients receiving insulin			Increases insulin sensitivity and metformin activity
Dyslipidemia		Can cause hyperlipidemia	May increase cholesterol and triglycerides	Adalimumab may cause hyperlipidemia			Promotes lipolysis
Hypertension		Can cause hypertension. It is contraindicated in uncontrolled hypertension		Adalimumab and Infliximab may cause hypertension			
Metabolic syndrome		Can worsen metabolic profile	Can worsen metabolic profile	Some agents may worsen metabolic profile (see diabetes, dyslipidemia, and hypertension)			Favorable effects on metabolic profile
NAFLD	Can increase liver enzymes	Rarely can cause mild elevation in serum bilirubin and serum enzymes	Can increase liver enzymes and cause cholestatic injury	Infliximab has been linked to idiosyncratic acute liver injury and can cause reactivation of hepatitis B			Attenuates fat accumulation in the liver
Body weight				Can cause mild weight gain. Infliximab dose can be weight adjusted	Ustekinumab dose can be weight adjusted Guselkumab pharmacokinetics could be affected by body weight		Can cause mild weight loss

IL, interleukin; *MTX*, methotrexate, *CSA*, cyclosporin; *NAFLD*, non-alcoholic fatty liver disease

Cyclosporine may worsen hypertension, dyslipidemia, t2DM, and Mets, and increase nephrotoxicity risk in comorbid obesity [65]. Uncommonly, cyclosporin may cause mild increase in serum bilirubin and transient elevations of liver enzymes. Furthermore, acitretin and cyclosporine require higher doses in obese patients, leading to a higher incidence of adverse effects and toxicity potential [75]. In patients with Mets, all above considerations should also be taken into account [63, 65, 74].

Finally, in obese patients with NAFLD, initiation of hepatotoxic drugs such as methotrexate should be followed by close monitoring regarding safe alcohol intake and liver biochemistry [63, 65]. Methotrexate may confer an elevated risk of NAFLD and hepatic fibrosis in obese psoriatic patients and, thus, should be avoided. Using methotrexate, 96% of patients with concomitant risk factors of obesity, t2DM, and alcohol use developed hepatic fibrosis in comparison with 71% of patients with no other risk factors [76]. If indicated, referral to a specialist and further tests with abdominal ultrasound, liver elastography, or liver biopsy should be considered [65].

Regarding biologic agents, obesity is associated with lower efficacy predicting discontinuation of treatment [28–30]. With the exception of infliximab and the IL-12/23 inhibitor biologic ustekinumab where the dose is weight adjusted, the recommended dose for the rest of the biologics does not account for patients' weight [65]. Moreover, anti-TNF-α drugs may also increase patients' appetite resulting in mild weight gain [77].

Newer biologic agents such as ustekinumab, guselkumab (IL-23 inhibitor), and ixekizumab (IL-17 inhibitor) may be more effective in treating psoriasis irrespective of body weight, while they may not affect patients' metabolic profile [65]. In particular, guselkumab, a human IgG1λ monoclonal antibody against the p19 subunit of IL-23, has not been associated with an increase in body weight and alterations in glucose and glucose metabolism. However, body weight could interfere with guselkumab pharmacokinetics (volume of distribution and clearance) [78]. IL-17 inhibitors are very efficacious anti-psoriatic drugs independently from body weight. Nevertheless, normal weight psoriatic patients tend to present a better response than overweight/obese patients. In a phase 2 trial of secukinumab, PASI 75 (i.e., a 75% reduction in PASI score from baseline) was 73% for patients who were 90 kg comparing with 83% for those weighing 90 kg [79, 80]. Interestingly, recent data has shown that ixekizumab was efficacious in the treatment of moderate-to-severe psoriasis despite body weight [80, 81]. In comparison with anti-TNF-α agents, IL-17 inhibitors have not been documented to increase body weight in clinical studies. In a phase 3 trial (AMAGINE 1), brodalumab (anti-Human IL17RA therapeutic antibody) showed higher rates of PASI 75 and PASI 90 (a 90% decrease in PASI from baseline) at weeks 12 and 52 in normal weight patients compared with obese psoriatic patients [82, 83]. More prospective studies on newer biologic agents are needed to investigate their efficacy and potential metabolic side effects. Noteworthy, the phosphodiesterase 4 inhibitor apremilast has been shown to reduce body weight, enhance lipolysis, increase insulin sensitivity, and reduce the accumulation of adipose tissue in the liver, especially in patients with high glycated hemoglobin [84–86].

Finally, cholesterol-lowering medications such as simvastatin may also be beneficial in psoriasis exerting immunoregulatory and anti-inflammatory properties. However, atorvastatin and pravastatin may aggravate psoriasis [53]. Interestingly, there is increasing evidence of the beneficial actions of antidiabetic agents in psoriasis including glucagon-like peptide-1 receptor agonists, dipeptidyl peptidase-4 inhibitors, metformin, thiazolidinediones, and biguanides [87].

Conclusion

Obesity represents a common comorbid disorder observed in psoriatic patients. Although this relationship is well established in animal models as well as in clinical and epidemiological studies, the pathophysiologic mechanisms connecting these conditions remain unclear. A significant number of meta-analyses has shown that (1) genetically higher BMI increased the odds of psoriasis occurrence; (2) obesity is associated with higher incidence and prevalence of psoriasis as well psoriasis severity; (3) obesity is associated with lower efficacy to anti-TNF agents and may predict biologic treatment discontinuation; and (4) weight loss through diet and physical exercise may improve pre-existing psoriasis and prevent from de novo psoriasis. Obesity and psoriasis constitute chronic inflammatory states that are interconnected in a vicious cycle, sharing also a degree of synergy. Obesity is related to a higher grade of inflammation, characterized by the increase of pro-inflammatory adipocytokines and cytokines, including IL-17A and IL-23, that are pivotal in psoriasis but poorly explored in obesity. Generally, psoriasis and obesity are characterized by hyperesistinemia, hyperleptinemia, and hypoadiponectinemia.

Treating obese psoriatic patients presents many challenges and should be approached in a holistic and individualized manner. Lifestyle advice and weight loss should be at the center of therapeutic management helping both the psoriatic patient and the efficacy of the pharmacological treatment. Great care should also be given when choosing the right treatment option for these individuals taking into account their metabolic profile. Useful laboratory biomarkers that may be used in monitoring comorbid obesity and psoriasis include serum glucose, lipids, uric acid, and liver enzymes. Obesity may predict lower efficacy for systemic conventional and biologic drugs, particularly for the fixed-dose drugs. Methotrexate, acitretin, and cyclosporine could worsen

hypertension, liver steatosis, and dyslipidemia related with obesity. Since infliximab and ustekinumab are weight adjusted, they may be ideal drugs to treat obese psoriatic patients. IL-17 inhibitors are very effective independently from body weight; however, they tend to present better clearance rates in normal weight patients. There is a paucity on weight data regarding the efficacious IL-23 inhibitors. Apremilast may induce weight loss as an adverse effect presenting also some beneficial metabolic actions. Finally, simvastatin and some antidiabetic drugs could decrease psoriasis severity.

More mechanistic, observational studies and well-conducted RCTs are necessary to decipher the enigmatic link between psoriasis and obesity, and to provide evidence-based specific guidelines for the screening and management of obese psoriatic patients. More studies are required to investigate whether targeting obesity and related insulin resistance could be an effective therapeutic approach for psoriatic symptomatology and cardiometabolic risk reduction. Other perspectives include the exploration of the mechanistic links between psoriasis and obesity, the prevention of psoriasis and obesity, and adipocytokine-oriented and personalized therapeutic approaches.

Authors' Contributions All authors have contributed equally to the preparation of the manuscript

Compliance with Ethical Standards

Conflict of Interest Kyriaki Paroutoglou, Evangelia Papadavid, Gerasimos Socrates Christodoulatos, and Maria Dalamaga declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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