Archives of Clinical & Experimental Dermatology

Yumed Text
OPEN ACCESS JOURNALS

Perspective | Vol 8 Iss 1
ISSN: 2583-6374
https://dx.doi.org/10.46527/2583-6374.189

Obesity in Psoriasis: Interlinked Pathophysiology and Therapeutic Perspectives

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Received: February 27, 2026; **Accepted:** March 16, 2026; **Published:** March 26, 2026

Abstract

Background: Psoriasis is a chronic immune-mediated inflammatory disease associated with systemic comorbidities, particularly obesity and cardiovascular disease. Increasing evidence suggests that obesity is not merely a comorbidity but a key contributor to psoriasis pathogenesis, severity, and therapeutic response through shared inflammatory, metabolic, and immunologic mechanisms.

Objective: To review the pathophysiological links between obesity and psoriasis and to evaluate therapeutic strategies targeting obesity, including lifestyle interventions and emerging pharmacologic agents, with emphasis on their implications for disease progression and systemic inflammation.

Results: Obesity contributes to psoriasis through chronic low-grade systemic inflammation mediated by adipokines, including leptin, resistin, and adiponectin, as well as immune cell infiltration in adipose tissue. These mechanisms promote Th1 and Th17 activation, endothelial dysfunction, and increased cardiovascular risk. Excess adiposity is associated with increased psoriasis incidence, greater disease severity, and reduced therapeutic response, particularly to biologic agents. Weight reduction through hypocaloric and Mediterranean diets improves psoriasis severity and reduces inflammatory markers. Pharmacologic agents such as glucagon-like peptide-1 receptor agonists (GLP-1RAs) and the dual GLP-1/GIP agonist tirzepatide demonstrate promising metabolic and anti-inflammatory effects, including reductions in visceral adiposity, inflammatory cytokines, and psoriasis severity in some patients, although responses may vary. Additionally, gut microbiome dysbiosis appears to play a contributory role in systemic inflammation linking obesity and psoriasis, representing a potential therapeutic target.

Citation: Addor FASA. Obesity in Psoriasis: Interlinked Pathophysiology and Therapeutic Perspectives. Arc Clin Exp Dermatol. 2026;8(1):189.

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Conclusion: Obesity plays a central role in psoriasis pathophysiology, influencing disease severity, systemic inflammation, cardiovascular risk, and therapeutic outcomes. Integrated management strategies combining weight reduction, metabolic interventions, and targeted immunomodulatory therapies may improve clinical outcomes. Further studies are needed to clarify the long-term effects of obesity-targeted therapies and microbiome modulation in psoriasis management.

Keywords: ***Psoriasis; Obesity; Glucagon-like peptide-1 receptor agonists; Tirzepatide; Skin microbiome***

1. Introduction

Psoriasis is a chronic multisystemic, autoimmune and inflammatory skin disease, affecting about 0.09%-11.4% of the worldwide population [1].

Psoriasis occurs through the dysregulation of the cytokine network with multiple self-amplifying feeds accelerating pathogenic circuits. The last studies considered psoriasis as a TH17 response disease with the important components of TH1 and TH22 responses and revealed crucial dysregulated components leading to the development of the disease [2].

Psoriatic inflammation can be triggered in predisposed individuals by mechanical stress (Koebner phenomenon), and external factors, like infectious diseases, sun exposure, air pollutants, drugs, or vaccines [3].

The most common clinical presentation is the plaque psoriasis (psoriasis vulgaris) which accounts for more than 80% of cases [4].

Clinically it is characterized by erythematous patches which are covered in thick, silvery-white scales, mainly localized in knees, elbows, sacral region, scalp, and with nail involvement in up to 80% of the patients [5].

The clinical features of psoriasis are heterogeneous, including cutaneous as well as systemic manifestations; psoriatic disease encompasses three primary domains: the skin, joints, and vascular system [6].

Regarding cardiovascular diseases, there is an increased prevalence of hypertension, hyperlipidemia and obesity, characterizing a metabolic syndrome. Therefore, patients with psoriasis may present an adipose tissue dysfunction [7].

It is demonstrated that cardiovascular disease is a crucial comorbidity in patients with psoriatic disease [8].

In 2020, the Brazilian Consensus on Psoriasis emphasized the importance of the weight management, and the recent literature has paid attention to this point because obesity appears to be more than just a comorbidity; Obesity is a factor that exacerbates systemic inflammation and reduces the effectiveness of medications, especially biologics [9].

This review summarizes the events in psoriasis that are related to the occurrence of obesity, and the evidences that could positively influence the progression of psoriasis, improving quality of life and existing cardiovascular comorbidities.

2. Pathophysiological Links

2.1 Psoriasis and cardiovascular disease

Psoriasis and atherosclerosis share overlapping immune pathways that help explain the increased cardiovascular risk observed in psoriatic patients. Psoriasis is driven by Th1 and Th17 activation, with associated pro-inflammatory cytokines such as TNF-α and IL-17; these same mediators contribute to endothelial dysfunction, lipid transport abnormalities, and vascular inflammation [10].

Regulatory T-cell impairment, observed in both psoriasis and acute coronary syndromes, further amplifies chronic systemic inflammation. While IL-12 promotes atherosclerosis progression and IL-17 demonstrates context-dependent pro- and anti-atherogenic effects, elevated Th1 activity is consistently linked to atheroma plaque instability. Together, these convergent immune mechanisms support the concept of psoriasis as a systemic inflammatory disorder with cardiovascular repercussions [11].

Psoriasis confers an elevated cardiovascular risk, driven by the multifaceted interaction of dysregulated inflammatory pathways, immune cell activity, and disturbances in metabolic and vascular homeostasis.

2.2 Adipose tissue disfunction in psoriasis

Adipose tissue dysfunction constitutes a critical systemic link between psoriasis and increased cardiometabolic risk. Psoriatic adipose depots contain expanded populations of immune cells—including T cells, B cells, dendritic cells, neutrophils, mast cells, and adipose-resident macrophages—which promote obesity, insulin resistance, and chronic inflammation [12].

Visceral adiposity is strongly associated with subclinical cardiovascular disease and vascular inflammation in psoriasis and PsA. A distinct macrophage subset contributes to adipokine dysregulation, while perivascular adipose tissue may accelerate atherosclerosis through local secretion of adipokines and chemokines [13].

Elevated leptin levels correlate with both psoriasis severity and subclinical atherosclerosis, whereas resistin and adiponectin further amplify innate immune activation [14].

2.3 Psoriasis and the link with obesity

The prevalence and incidence of psoriasis are elevated in individuals with obesity, and excess adiposity represents a significant predisposing factor for the initiation, progression, and clinical severity of the disease [15].

Obesity, especially the android pattern, promotes the occurrence of psoriasis and worsens its course. On the other hand, psoriasis increases the risk of obesity [16].

According to a systematic review published in 2018, the risk of developing psoriasis increases two to four times with higher body mass index (BMI), waist circumference, and waist-to-hip ratio. BMI is also positively correlated with disease severity among individuals with established psoriasis [17].

Additionally, obesity adversely influences therapeutic responses in psoriasis and is associated with an increased risk of adverse events related to anti-psoriatic pharmacologic agents. A systematic review about obesity and response to anti-tumor necrosis factor alpha (anti-TNF-alpha) reveals that obesity is an under-reported predictor of inferior response to anti-TNF agents in patients with select immune-mediated inflammatory diseases [18].

Given the relationship established between obesity and psoriasis, Nicolau et. Al gathered referral criteria for an endocrinology specialist when attending this group of patients: BMI $\geq$ 35 kg/m², or BMI $\geq$ 27 kg/m² in the presence of obesity-related comorbidities; prior treatment failure, defined as a weight loss of less than 5% after 3 months of structured therapy; suspected syndromic obesity (obesity present since childhood, phenotype etc.); suspected secondary obesity, including endocrine disorders such as Cushing's syndrome, hypothyroidism, and polycystic ovary syndrome; presence of eating disorders, including binge eating disorder, emotional eating, or anxiety-related hyperphagia [19].

Besides, research has found a strong connection between inflammation in fat tissues and cardiovascular diseases in people with psoriasis. Substances released by fat tissue, like leptin, resistin, and adiponectin, can impact inflammation and cardiovascular health. Psoriasis patients often show increased levels of these substances. In this context, the introduction of biological agents has raised the prospect of early systemic intervention to modify the disease course and lower long-term risks. However, evidence supporting this notion is limited, and there are even contrary indications that early systemic treatment might have adverse effects, potentially increasing overall comorbidity [7].

2.4 The role of diet in Psoriasis

As a primary intervention, implementing a hypocaloric diet in overweight or obese patients, is a fundamental strategy recommended by the National Psoriasis Foundation (NPF), to reduce CVD risk. Mediterranean diet was also recommended by the NPF noting that adherence is associated with improved psoriasis skin condition, reduced fat mass, and lower levels of hs-CRP [20].

In a meta-analysis of seven RCTs involving over 900 overweight or obese psoriasis patients, caloric restriction leading to weight loss has shown notable improvement in psoriasis skin severity, including a threefold higher skin clearance rate when combined with psoriasis treatment compared to treatment alone [21].

It is preferable to choose food products with a low glycemic index (whole grain cereals, vegetables and selected fruits); While carbohydrate products with a high glycemic index (e.g., refined sugar, sweets, honey, white bread, white rice, etc.) should be

avoided [22]. Dietary fiber has intestinal and systemic anti-inflammatory effects, with a beneficial effect on intestinal microflora, contributing to weight loss, since fiber helps to promote satiety [23].

3. The Role of Pharmacologic Agents Targeting Obesity and Metabolic Dysregulation in Psoriasis

3.1 Orlistat

Orlistat is a reversible inhibitor of gastric and pancreatic lipases that reduces dietary fat absorption by approximately 30%. Clinical studies have demonstrated that orlistat produces an average weight loss of approximately 4% compared with placebo after one year of treatment and reported a 37% reduction in the progression to type 2 diabetes among patients treated with orlistat, highlighting its potential benefits in metabolic risk reduction [19].

The most common adverse events, occurring in approximately 15%-25% of patients, are diarrhea, steatorrhea, bloating, fecal urgency and oily stools. These symptoms are directly proportional to one's diet, reflecting the drug's mechanism of action in inhibiting fat absorption. Due to its relatively modest weight loss efficacy and the frequency of these adverse effects, long-term treatment adherence is often limited [24].

Studies show that orlistat treatment can have an impact on adipose tissue. They were associated to increased plasma adiponectin levels – an adipokine known to improve insulin sensitivity –, reduced expression of lipogenesis-related genes in epididymal adipose tissue, including fatty acid synthase, sterol regulatory element-binding protein 1c (SREBP-1c), peroxisome proliferator-activated receptor (PPAR), and adipocyte protein 2 [19].

In current literature data, there is no specific link between psoriasis and the use of orlistat. Nonetheless, the weight loss it provides may induce improvements in systemic inflammation and psoriasis severity [19,25].

3.2 Glucagon-like peptide-1 receptor agonists

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) are antidiabetic therapies indicated for individuals with type 2 diabetes mellitus. They provide multiple clinical benefits, including glycemic control, weight loss, with a low risk of hypoglycemia. The most commonly prescribed GLP-1RAs —liraglutide, dulaglutide, semaglutide, and albiglutide—have demonstrated a significant reduction in major cardiovascular events [26].[26]

GLP-1RAs exert their metabolic effects through several mechanisms. The mechanisms include delay of gastric emptying, which slows nutrient absorption and stabilizes glucose levels after meals, and therefore, have an impact on satiety. The suppression of food intake and consequent weight loss provides essential advantages for patients who struggle with obesity or complications from excessive weight [27].

A meta-analysis of randomized controlled trials evaluating exenatide or liraglutide demonstrated a significant decrease in both visceral adipose tissue and subcutaneous adipose tissue. However, the reduction was more pronounced in visceral adipose tissue compared with subcutaneous adipose tissue [28].

It has been demonstrated that, in obese individuals undergoing bariatric surgery, GLP-1 receptor expression is higher in visceral adipose tissue than in subcutaneous adipose tissue, suggesting that visceral fat may be more responsive to GLP-1 receptor agonists than subcutaneous fat [26].

An in vitro study showed that semaglutide reduced adipocyte size in visceral fat adipocytes derived from obese mice. It also decreased the expression of pro-inflammatory genes, including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-6, IL-1β, and monocyte chemoattractant protein-1. In addition, semaglutide reduced the expression of genes associated with endoplasmic reticulum stress and promoted adipocyte browning, as evidenced by increased thermogenesis and enhanced uncoupling protein-1 (UCP-1) activity [29].

The dermatological effects associated with GLP-1 receptor agonists (GLP-1RAs) have recently emerged as an important topic of interest. The most common cutaneous adverse effects described are injection-site reactions, hypersensitivity responses, pruritus, rashes. Rapid weight loss associated with these therapies may also lead to skin laxity, as well as alterations in skin and nail integrity. Regarding immune-driven diseases, evidence suggests that GLP-1RAs may play a part in pro-inflammatory cytokines such as TNF-alpha and IL-17. However, research indicates that they could develop both adverse side effects and possible therapeutic benefits [30].

GLP-1 receptors are expressed on several immune cell populations, including macrophages, invariant natural killer T (iNKT) cells, and intestinal intraepithelial lymphocytes (IELs), where they regulate inflammatory signaling pathways. Exenatide has been shown to increase anti-inflammatory M2 macrophage polarization, while reducing interferon-gamma and IL-4 levels in iNKT cells. Furthermore, GLP-1 receptor activation reduced IL-6 and TNF-α expression in IELs by up to 50%. These findings suggest that GLP-1RAs may provide additional therapeutic benefit in immunomodulated skin diseases, such as psoriasis and hidradenitis suppurativa. However, further clinical studies are required to confirm these effects and to define their therapeutic implications [30].

Clinical studies of patients undergoing liraglutide treatment have demonstrated reductions in systemic inflammatory markers and improvement in psoriasis severity, supporting its potential role as an adjunctive therapy in psoriasis management [31,32].

Emerging research has also explored whether GLP-1 receptor agonists influence cellular stress responses in skin through the regulation of heat shock proteins (HSPs), particularly Hsp70. Hsp70 functions as a stress-inducible molecular chaperone, contributing to the pathogenesis of chronic inflammatory skin diseases, including psoriasis and lupus erythematosus. At present, there is no direct in vivo evidence demonstrating that GLP-1 receptor activation alters Hsp70 expression in human skin. However, experimental studies suggest that GLP-1 signaling may regulate HSP expression in other tissues, such as pancreatic beta-cells and neuronal tissue [30].

Because keratinocytes are a major inducible source of Hsp70 in cutaneous immunity, GLP-1RAs may indirectly influence these pathways through their anti-inflammatory effects and reduction of oxidative stress. Further investigation is still necessary to determine the clinical relevance of these mechanisms in human skin [30].

Treatment with GLP-1 receptor agonists (GLP-1RAs) may be associated with psoriasis flare-ups in a subset of patients, suggesting interindividual variability in immune responses to these agents. This variability highlights the complex immunomodulatory effects of GLP-1RAs and underscores the need to better understand patient-specific factors influencing treatment outcomes. Further clinical studies are necessary to identify patient subgroups that may benefit from GLP-1RAs as a therapeutic option for psoriasis [31,32].

These findings suggest that GLP-1 receptor agonists may have bidirectional effects, potentially improving or exacerbating disease activity depending on individual immune and metabolic profiles. Retrospective studies and pharmacovigilance reports have not demonstrated a significant increase in autoimmune blistering diseases among patients treated with GLP-1 receptor agonists compared with those receiving other antidiabetic therapies, suggesting that these reactions may occur predominantly in susceptible individuals. Further research is needed to clarify these associations and to identify patients who may be predisposed to autoimmune dermatologic responses during GLP-1 receptor agonist treatment [30].

3.3 Tirzepatide

Tirzepatide is a dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. It is used for treating overweight, obesity, and comorbidities related, such as type 2 diabetes [19].

Its mechanism of action partially overlaps with that of GLP-1 receptor agonists, as it promotes earlier onset of satiety and reduces reward-driven (hedonic) food consumption. This effect is further supported by delayed gastric emptying, which prolongs the sensation of fullness after meals. A distinctive aspect of this therapy is its activity on glucose-dependent insulinotropic polypeptide (GIP) receptors, which are highly expressed in adipose tissue. Activation of these receptors enhances adipose tissue performance by increasing its capacity to safely store lipids, thereby improving metabolic efficiency. Furthermore, GIP receptor stimulation contributes to enhanced insulin sensitivity, in part by facilitating greater uptake and handling of circulating free fatty acids within adipocytes [19,33,34].

A recent meta-analysis published in 2026 demonstrated clinical superiority of tirzepatide over semaglutide and placebo in reducing body weight, BMI and waist circumference [33].

General adverse effects are nausea, diarrhea, vomiting, constipation, and decreased appetite. Cutaneous side effects are relatively rare [34].

A retrospective analysis from 2025 indicated that the most reported ones were injection site reactions, hypersensitive reactions, pruritus, hyperhidrosis, alopecia and nail changes. Out of 690 skin reactions from Tirzepatide, only four cases of psoriasis were reported (0.57%). To the present time, these findings support a cutaneous safety profile for the drug [34,35].

Tirzepatide's therapeutic benefits regarding psoriasis are preliminary and based upon studies with GLP-1 receptor agonists – described by a downregulation of TNF-alpha and increased T-reg activity. Further controlled studies are needed to draw more definitive conclusions about Tirzepatide specifically [19,34].

4. Drug Interaction between GLP-1 Receptor Agonists/Tirzepatide and Biologic Psoriasis Agents

GLP-1 receptor agonists do not share metabolic pathways with biologic psoriasis agents, since most biologics are monoclonal antibodies cleared by reticuloendothelial catabolism, not CYP metabolism [36].

Since both drugs are administered subcutaneously, it would be recommended injections on different dates and body sites.

Up to this date, present data have not yet reported interactions caused by the co-administration. However, there is still no studies addressing pharmacokinetic or pharmacodynamic interaction known between GLP-1 receptor agonists and Tirzepatide and biologic psoriasis therapies. Monitoring overlapping immunologic and/or metabolic events is advised.

5. Microbiome Modulation in Psoriasis and Probiotics

The gastrointestinal tract plays a fundamental role in the immune and neuroendocrine, harboring complex microbial communities composed of bacteria, fungi, and parasites [37].

Psoriasis patients exhibit reduced microbiota diversity and compositional changes in key microbial communities compared with healthy controls. Such dysbiosis may influence immune function, exacerbate inflammation, and contribute to disease pathophysiology [37,38].

Evidence indicates that the microbiome regulates immune responses in multiple physiological processes through interactions between innate and adaptive immunity. Several studies have identified gut microbiota dysbiosis as a potential trigger or contributing factor in recurrent psoriasis episodes [37].

Alterations in gut microbiota composition can enhance the release of pro-inflammatory cytokines, including TNF-α and IL-6, which may disseminate through the bloodstream and contribute to the amplification of skin inflammation [39].

Clostridium difficile produces metabolites such as p-cresol and phenol, which are recognized biomarkers of gut dysbiosis. These metabolites may translocate into the bloodstream and accumulate in cutaneous tissues, contributing to decreased skin hydration, impaired barrier function, and altered epidermal differentiation and keratinization [40].

These cytokines may also drive inflammation in extra-cutaneous sites, including the joints, contributing to the systemic immune imbalance associated with psoriatic arthritis [37].[37]

In a study involving *Akkermansia muciniphila*, a bacterium known for its beneficial effects on metabolic health, CRISPR/Cas9 was used to enhance its ability to produce mucin-degrading enzymes. These enzymes improve the bacterium's ability to strengthen the gut barrier and reduce inflammation, making it more effective in treating metabolic disorders like diabetes and obesity [41].

Psoriasis patients exhibit a decrease in the *Lachnospira* and *A. muciniphila* species in gut microbiome. This decrease in *A. muciniphila* was also highlighted by another study that used 16S rDNA sequencing technology to examine microbiota composition in 14 psoriasis patients [42].

Such changes were linked to Short-Chain Fatty Acids metabolism and production in the human colonic microbiota; Butyrate has been implicated in the regulation of various inflammatory factors, including lipopolysaccharides, TNF-α, IL-10, IL-1β [43].

There is limited literature examining the specific relationship among obesity, psoriasis, and gut dysbiosis. Recent research has demonstrated that a high-fat diet (HFD) administered for only one week can induce significant alterations in the fecal metabolome and gut microbiome of rats, with these changes persisting for up to two months. Gut microbiome analyses in HFD-induced obese mice have revealed marked expansion of a distinct evolutionary clade within the Mollicutes class of the Firmicutes phylum. These findings suggest a potential causal link between Mollicutes and psoriasis, highlighting their possible role in disease pathogenesis [44].

A 2021 study analyzing the fecal microbiota of 30 psoriasis patients and 30 healthy individuals revealed significant microbial dysbiosis in the psoriasis group, accompanied by altered cytokine levels. Among the taxa identified, *Megamonas* showed a significantly higher relative abundance in psoriasis patients. This genus has been associated with elevated systemic inflammatory cytokines and has also been found to be increased in metabolic disorders such as obesity [38].

Dietary interventions, such as adopting a Mediterranean diet, is suggested to reduce the progression of psoriasis, regulate the balance of beneficial/harmful bacteria, and increase the diversity of gut microbiota in patients [37].

Yoshida et al. reported that an inulin-enriched high-fiber diet mitigated the severity of imiquimod-induced psoriasis-like dermatitis in mice, leading to reduced epidermal hyperplasia, diminished inflammatory infiltrates—including $Ly6G^+$ neutrophils—and decreased $Ki67^+$ keratinocyte proliferation. At the molecular level, the diet downregulated pro-inflammatory and psoriasis-associated genes (IL-17A, IL-17F, IL-22, IL-1β, TNF-α, CXCL1, CXCL2, and K16) and upregulated regulatory mediators such as TGF-β1 and CDKN1A [45].

Several studies have investigated the effects of Bifidobacterium species on skin disorders. In particular, Bifidobacterium CCFM683 has demonstrated dose-dependent efficacy in attenuating psoriasis through microbiota restoration, modulation of the FXR/NF-κB pathway, suppression of pro-inflammatory cytokines, regulation of keratinocyte function, and maintenance of epidermal barrier homeostasis [37,46].

Furthermore, biological therapies have demonstrated substantial efficacy in improving psoriasis symptoms; however, their effects on regulating the gut microbiota remain an area for further investigation [47].

Taken together, the available evidence supports a complex and bidirectional interplay among psoriasis, gut dysbiosis, and obesity. Psoriasis is consistently associated with reduced microbial diversity and specific compositional shifts that promote systemic inflammation through enhanced production of pro-inflammatory cytokines and microbial metabolites capable of affecting distant organs, including the skin and joints. Obesity—particularly when driven by high-fat dietary patterns—further disrupts gut microbial homeostasis, favoring the expansion of taxa linked to inflammatory and metabolic dysregulation. Conversely, dietary modulation and targeted probiotic interventions have demonstrated the capacity to restore microbial balance and attenuate inflammatory signaling pathways present in psoriasis.

Collectively, these findings reinforce the concept of a gut–skin–metabolic axis in which dysbiosis represents a mechanistic bridge between obesity and psoriasis, highlighting the microbiome as a promising therapeutic target in this systemic inflammatory disease, in which further studies are essential for a better comprehension in obese psoriasis patients.

6. Conclusions

Psoriasis is a complex, systemic, immune-mediated disease in which chronic inflammation extends beyond the skin, involving metabolic, cardiovascular, and immunologic pathways. Accumulating evidence demonstrates a strong bidirectional relationship between psoriasis and obesity, in which excess adiposity contributes to systemic inflammation, adipose tissue dysfunction, and altered adipokine profiles, thereby amplifying disease severity and reducing therapeutic responsiveness.

Pharmacologic treatments aimed at weight reduction, particularly GLP-1 receptor agonists and dual GLP-1/GIP agonists such as tirzepatide, represent promising adjunctive approaches, not only through their effects on weight loss and adipose tissue inflammation but also through direct immunomodulatory mechanisms. Collectively, these findings support the concept that psoriasis management should extend beyond cutaneous symptom control to include comprehensive metabolic assessment and targeted interventions addressing obesity, cardiovascular alterations, nutrition, and gut microbiome health. Effective psoriasis care requires integrated collaboration among dermatologists and other specialists, including endocrinologists, cardiologists, and nutrition professionals.

Future research is essential to clarify these mechanisms and to establish personalized therapeutic strategies that integrate metabolic, immunologic, and microbiome-based approaches to improve long-term outcomes in patients with psoriasis. Further studies of potential drug interactions and safety considerations involving biological therapies and psoriasis systemic drugs - including GLP-1Ras and dual GLP-1/GIP agonists - are warranted to investigate possible synergy and ensure safety within treatment plans.

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