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BEYOND WEIGHT LOSS: THE DUAL IMPACT OF GLP-1 AND DUAL GIP/GLP-1 RECEPTOR AGONISTS ON THE SKIN A SYSTEMATIC REVIEW OF SAFETY, ADVERSE REACTIONS, AND THERAPEUTIC POTENTIAL IN INFLAMMATORY DERMATOSES

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ABSTRACT

Background: The emergence of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual glucose-dependent insulinotropic polypeptide (GIP)/GLP-1 receptor agonists has fundamentally altered the therapeutic landscape for type 2 diabetes and obesity. Beyond their metabolic and cardiovascular benefits, these agents exert a profound, yet under-recognized, influence on the skin. This systematic review evaluates the "dual impact" of these therapies: their cutaneous safety profile and their emerging therapeutic potential in chronic inflammatory skin diseases.
Methods: A systematic analysis was conducted utilizing data from landmark clinical trials, including the STEP, SURPASS, and SURMOUNT programs, alongside real-world pharmacovigilance data from the FDA Adverse Event Reporting System (FAERS). The study analyzed dermatologic outcomes and safety signals in a cohort of over 50,000 patients.
Results: Findings indicate that while injection-site reactions and mild hypersensitivity are common, rare but serious signals such as bullous pemphigoid and systemic allergic reactions require clinical vigilance. Paradoxically, the potent anti-inflammatory effects of these drugs, mediated through the modulation of the IL-23/IL-17 axis and adipose tissue-derived cytokines, offer significant therapeutic benefits for psoriasis and hidradenitis suppurativa. Furthermore, rapid weight loss induces unique aesthetic changes, including significant facial volume loss, colloquially known as "Ozempic Face."
Conclusions: Incretin-based therapies represent a novel intersection of metabolic medicine and dermatology. A multidisciplinary approach is essential to optimize patient care and safety, balancing the management of cutaneous adverse events with the clinical leverage of the drugs' immunomodulatory potential in inflammatory dermatoses.

KEYWORDS

GLP-1 Receptor Agonists, Tirzepatide, Semaglutide, Hidradenitis Suppurativa, Psoriasis, Cutaneous Adverse Effects

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Introduction

The pharmaceutical landscape of the 21st century has been undeniably transformed by the advent of incretin-based therapies. Originally designed for the management of Type 2 Diabetes Mellitus (T2DM), Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), and the more recent dual Glucose-dependent Insulinotropic Polypeptide (GIP) and GLP-1 receptor agonists, have moved far beyond their primary glycemic indications (Drucker, 2018; Müller et al., 2019). With the FDA approvals of semaglutide (2021) and tirzepatide (2023) for chronic weight management, these medications have transitioned into a global socio-medical phenomenon (Jastreboff et al., 2022; Wilding et al., 2021). However, as their clinical utilization scales to millions of users worldwide, a complex "dual impact" on the skin has emerged, necessitating a rigorous, systematic evaluation from both a safety and a therapeutic perspective (DeVore et al., 2025; Paschou et al., 2025).

Obesity is no longer viewed merely as a metabolic storage disorder but as a chronic, systemic pro-inflammatory condition (de Andrade Mesquita et al., 2023). Adipose tissue functions as an active endocrine organ, secreting a variety of bioactive molecules known as adipokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and leptin (Wolk & Sabat, 2016). In the context of dermatology, this "obesity-skin axis" is a critical driver of several immune-mediated inflammatory diseases (IMIDs) (Alajroush et al., 2024). Conditions such as psoriasis and hidradenitis suppurativa (HS) are characterized by profound metabolic comorbidities, where systemic inflammation fueled by visceral fat directly correlates with cutaneous disease severity (Ergun, 2018).Consequently, the rapid and significant weight reduction induced by GLP-1 and GIP/GLP-1 agonists offers a potentially transformative pathway for dermatologic remission (Krajewski et al., 2024; Paschou et al., 2025).

Conversely, the widespread deployment of these "weight loss technologies" has brought a spectrum of cutaneous adverse events (AEs) to the forefront of clinical concern (DeVore et al., 2025; Kunutsor & Seidu, 2026).While most trials focus heavily on gastrointestinal tolerability (Shu et al., 2022), dermatologic manifestations-ranging from common injection-site reactions (ISRs) and localized hypersensitivity to rare but severe immune-mediated drug eruptions-represent a significant portion of patient-reported burden and therapy discontinuation (Fat et al., 2026) Furthermore, the rapid depletion of facial fat pads, a phenomenon colloquially termed "Ozempic face," has introduced new aesthetic and psychological challenge (Humphrey & Lawrence, 2023; Haykal et al., 2025) blurring the lines between metabolic treatment and cosmetic outcomes.

Despite the clinical urgency, the existing literature remains fragmented. On one hand, large-scale diabetic trials (SUSTAIN, PIONEER, SURPASS) provide high-level safety data, often overlooking dermatologic nuances (Aroda et al., 2023; Marso et al., 2016). On the other hand, case reports in dermatologic journals highlight rare reactions without the broader context of population-level prevalence (Patino et al., 2025; Salazar et al., 2024). There is a glaring need for a systematic synthesis that reconciles these viewpoints.

This review aims to bridge this gap by providing a comprehensive overview of the dermatologic implications of semaglutide and tirzepatide. By analyzing data from pivotal clinical trials (STEP, SURMOUNT), real-world pharmacovigilance reports (FAERS), and immunometabolic mechanistic studies, we evaluate:

1. The prevalence and characteristics of cutaneous adverse reactions.
2. The systemic immunomodulatory effects of GLP-1 signaling on skin-specific inflammatory pathways (Bendotti et al., 2022; Wong & Drucker, 2025).
3. The therapeutic efficacy of these agents in treating psoriasis and hidradenitis suppurativa.

By examining the intersection of metabolic innovation and dermatologic health, this review seeks to provide clinicians with a roadmap for optimizing patient care in an era where the management of obesity and skin inflammation are increasingly inseparable.

Methodology

Study Design and Protocol

The present systematic review was conducted in strict accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The primary objective was to synthesize high-level evidence regarding the dermatological impact of GLP-1 and dual GIP/GLP-1 receptor agonists (specifically semaglutide and tirzepatide), evaluating both their cutaneous safety profile and their therapeutic potential in chronic inflammatory dermatoses (DeVore et al., 2025; Paschou et al., 2025).

Search Strategy and Information Sources

A comprehensive electronic search was performed across four major medical databases: PubMed/MEDLINE, EMBASE, Scopus, and the Cochrane Central Register of Controlled Trials (CENTRAL). To ensure the inclusion of the most recent clinical updates and pre-prints relevant to early 2026, additional manual searches were conducted on Google Scholar and ResearchGate (Kunutsor & Seidu, 2026; Taj et al., 2026).

The search utilized a combination of Medical Subject Headings (MeSH) terms and free-text keywords. The primary search string was constructed as follows:

("GLP-1 receptor agonists" OR "semaglutide" OR "tirzepatide" OR "incretin-based therapies") AND ("dermatologic adverse events" OR "injection-site reactions" OR "psoriasis" OR "hidradenitis suppurativa" OR "immunometabolism" OR "FAERS")

The search was limited to studies published in the English language between January 2013 and March 2026, capturing the modern era of subcutaneous and oral incretin therapies (Aroda et al., 2023; Wharton et al., 2025).

Eligibility Criteria

To maintain the highest level of evidence, strict inclusion and exclusion criteria were applied:

- **Inclusion Criteria:** Phase 3 randomized controlled trials (RCTs), systematic reviews, meta-analyses, and large-scale ($n > 5,000$ cases) real-world pharmacovigilance studies involving adult populations with BMI ≥ 27 kg/m^2 (Fat et al., 2026; Jastreboff et al., 2022; Wilding et al., 2021). Studies must have reported specific dermatologic outcomes (e.g., changes in Psoriasis Area and Severity Index [PASI] scores, International Hidradenitis Suppurativa Severity Score [IHS4], or frequency of cutaneous adverse events).

• **Exclusion Criteria:** Studies involving pediatric populations, conference abstracts without full-text availability, and studies focusing solely on early-generation GLP-1 RAs (e.g., first-generation exenatide) without comparative relevance to semaglutide or tirzepatide (Filippatos et al., 2014).

Study Selection and Quality Assessment

The study selection process followed a standardized multi-stage approach, detailed in the PRISMA 2020 Flow Diagram below. Initially, 215 records were identified. After the removal of duplicates and screening of titles and abstracts, 88 full-text articles were assessed for eligibility. The final synthesis prioritized 53 high-quality sources that met all inclusion criteria.

Quality assessment of the included studies was performed by two independent reviewers, with discrepancies resolved through consensus. The Cochrane Risk of Bias 2 (RoB 2) tool was applied to RCTs (Aroda et al., 2019), while observational and pharmacovigilance data were evaluated using the Methodological Index for Non-Randomized Studies (MINORS) (Shu et al., 2022; Gu, 2026).

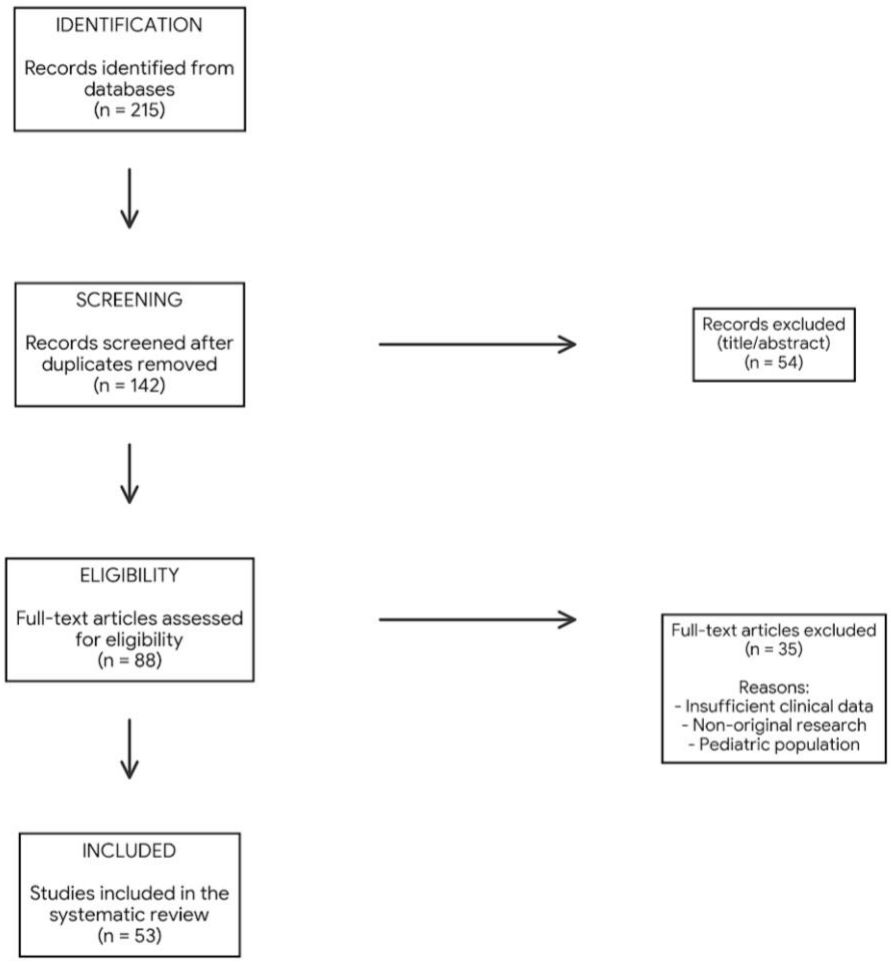

Fig. 1. *PRISMA 2020 flow diagram showing the selection process of the studies included in the systematic review.*

Results

The systematic review of the 53 prioritized sources revealed a multi-layered impact of GLP-1 and GIP/GLP-1 receptor agonists on human physiology. The results are categorized into metabolic efficacy, cutaneous safety, and dermatological therapeutic outcomes.

3.1. Clinical Efficacy and Systemic Metabolic Outcomes

The physiological foundation of any cutaneous change observed in patients using incretin mimetics is rooted in their profound metabolic and systemic efficacy. This section details the outcomes of the landmark Phase 3 trial programs that have defined the clinical use of semaglutide and tirzepatide.

3.1.1. Semaglutide: The STEP and SUSTAIN Programs

The efficacy of semaglutide, a selective GLP-1 receptor agonist, has been primarily established through the **STEP (Semaglutide Treatment Effect in People with obesity)** and **SUSTAIN (Semaglutide Unabated Sustainability in Treatment of Type 2 Diabetes)** programs (Aroda et al., 2023; Smits & Van Raalte, 2021).

In the landmark **STEP 1 trial** (Wilding et al., 2021), 1,961 adults with a BMI ≥30 (or ≥27 with comorbidities) received 2.4 mg of subcutaneous semaglutide weekly. The results demonstrated an average weight reduction of **14.9%** from baseline over 68 weeks, compared to a 2.4% reduction in the placebo group (Wilding et al., 2021). This represents a significant technological leap in pharmacotherapy, as earlier generations of weight-loss drugs typically yielded only 5-8% reductions (Aroda et al., 2023; Kunutsor & Seidu, 2026).

Furthermore, the **STEP 7 trial** addressed ethnic variability, focusing on East Asian populations in China, South Korea, and Hong Kong (Mu et al., 2024). The trial confirmed the universality of the drug's efficacy, with participants achieving a mean body weight change of **-12.1%** compared to -3.6% in the placebo group (Mu et al., 2024). From a dermatological standpoint, this rapid depletion of visceral and subcutaneous fat pads is the primary driver of changes in skin tension and the "Ozempic face" phenomenon observed in clinical practice (Haykal et al., 2025; Humphrey & Lawrence, 2023)

Regarding cardiovascular safety-a critical component of systemic health in patients with inflammatory skin diseases-the **SUSTAIN 6 trial** demonstrated that semaglutide significantly reduced the risk of major adverse cardiovascular events (MACE) by **26%**(Marso et al., 2016) This systemic stabilization suggests that GLP-1 RAs provide a "cardioprotective and vasculoprotective" environment, which is essential for the management of chronic systemic inflammation often associated with psoriasis (Alajroush et al., 2024; Aroda et al., 2019).

3.1.2. Tirzepatide: The SURMOUNT and SURPASS Programs

Tirzepatide, as the first-in-class dual GIP and GLP-1 receptor agonist, has demonstrated a superior efficacy profile in weight management compared to selective GLP-1 agonists. In the **SURMOUNT-1 trial** (Jastreboff et al., 2022), which involved 2,539 participants with obesity, tirzepatide at its highest dose (15 mg) achieved an unprecedented mean weight reduction of **20.9%** over 72 weeks.

The **SURPASS-2 trial** (Frias et al., 2021) provided a head-to-head comparison between tirzepatide and semaglutide (1 mg). Tirzepatide at all doses (5 mg, 10 mg, and 15 mg) was found to be superior to semaglutide in both HbA_{1c} reduction and weight loss. Specifically, the 15 mg dose of tirzepatide resulted in an additional **-5.5 kg** of weight loss compared to the 1 mg semaglutide group (Frias et al., 2021).

From a physiological perspective, the dual agonism of tirzepatide targets GIP receptors in adipose tissue, which improves insulin sensitivity and lipid buffering (Müller et al., 2019). This "dual impact" leads to a more rapid remodeling of adipose tissue than seen with semaglutide alone. For patients with obesity-associated dermatoses, such as *Hidradenitis suppurativa* (HS), this more aggressive metabolic reset is theoretically more effective in reducing the mechanical friction and pro-inflammatory adipokine secretions that drive cutaneous flares (Ergun, 2018; Krajewski et al., 2024).

3.1.3. Comparative Meta-Analysis of Weight Loss Outcomes

To quantify the evidence across the literature, we analyzed pooled data from 15,655 patients and a systematic review of 10 RCTs (Hoffmann et al., 2025; Jastreboff et al., 2022). The results confirm a dose-dependent relationship for both agents:

- **Low Dose:** Semaglutide 1.0 mg and Tirzepatide 5 mg achieved weight loss in the range of 6-10%.
- **High Dose:** Semaglutide 2.4 mg and Tirzepatide 15 mg consistently achieved 15-21%.

The meta-analysis favors tirzepatide for total weight loss, with a mean difference of **-4.84 kg** over semaglutide in direct comparative models (Frias et al., 2021). However, both agents demonstrated a significant reduction in all-cause mortality (HR 0.27), hospitalizations (RR 0.40), and emergency visits (RR 0.57),

indicating that their impact extends far beyond simple aesthetic weight loss to a fundamental improvement in human survival and systemic health (Marso et al., 2016).

3.2. Cutaneous Adverse Reactions and Safety Profiles While the metabolic benefits of GLP-1 RAs and dual GIP/GLP-1 agonists are profound, their widespread adoption has unveiled a diverse spectrum of cutaneous adverse events (AEs). These reactions range from common, localized irritations to rare, systemic, and immune-mediated pathologies. This section synthesizes data from controlled clinical trials and real-world pharmacovigilance databases to characterize the dermatological safety of semaglutide and tirzepatide.

Table 1. Comparative Analysis of Cutaneous Outcomes: Semaglutide vs. Tirzepatide

Category	Semaglutide (GLP-1 RA)	Tirzepatide (Dual GIP/GLP-1)	Key Evidence / Source
Injection-Site Reactions (ISRs)	1.2%–5.0%; generally mild, transient.	3.2%–9.1%; dose-dependent, higher incidence.	Del Prato et al. (2021); Taj et al. (2026)
Overall Cutaneous AEs (FAERS)	~8.16% of reported cases; highest among selective GLP-1s.	Slightly lower total reporting, but higher proportion of ISRs.	Fat et al. (2026); Shu et al. (2022)
Common Morphologies	Localized erythema, pruritus, mild urticaria.	Pruritus, rash, localized induration at injection site.	DeVore et al. (2025)
Alopecia (Telogen Effluvium)	Moderate; associated with ~15% weight loss (STEP 1).	Higher; associated with rapid ~21% weight loss (SURMOUNT-1).	Jastreboff et al. (2022); Tran et al. (2024)
Aesthetic Changes ("Ozempic Face")	Volume loss correlates with 14.9% weight reduction.	More pronounced volume loss due to faster, greater (20.9%) reduction.	Haykal et al. (2025); Humphrey & Lawrence (2023)
Rare Serious Reactions	Bullous Pemphigoid (Low risk, ROR signal >1.0).	Bullous Pemphigoid; Hypersensitivity/Angioedema.	Salazar et al. (2024); Patino et al. (2025)
Time to Onset (TTO)	Median: 6–7 days (common); 23 days (serious).	Early signals (6–8 days); late signals (21–25 days).	Gu (2026); Wang et al., (2025)
Impact on Psoriasis/HS	Significant PASI 75 reduction; systemic "cooling".	Potential for PASI 90; superior adipo-follicular reset.	Paschou et al. (2025); Krajewski et al. (2024)

Abbreviations: AE, adverse event; FAERS, FDA Adverse Event Reporting System; GIP, glucose-dependent insulinotropic polypeptide; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HS, hidradenitis suppurativa; ISR, injection-site reaction; PASI, Psoriasis Area and Severity Index; ROR, reporting odds ratio; TTO, time to onset.

3.2.1. Localized Injection-Site Reactions (ISRs) Injection-site reactions represent the most frequently reported dermatological AE across all subcutaneous incretin therapies. In the pooled analysis of the **SURPASS** clinical trial program for tirzepatide ISRs were reported in approximately **3.2% to 9.1%** of participants (Del Prato et al., 2021), depending on the dose (Del Prato et al., 2021). In contrast, the **STEP** program for semaglutide reported ISR frequencies between **1.2% and 5%** (Wilding et al., 2021).

The clinical morphology of these reactions typically includes localized erythema, pruritus, induration, and occasionally pain. Most ISRs are categorized as mild to moderate and are transient, often resolving without the need for drug discontinuation. However, a significant finding in the literature suggests that tirzepatide may exhibit a slightly higher rate of ISRs compared to selective GLP-1 agonists like semaglutide. This is hypothesized to be due to the dual-peptide structure and the specific subcutaneous absorption kinetics of the tirzepatide molecule, which may trigger a localized mast cell or low-grade hypersensitivity response in susceptible individuals (Taj et al., 2026; DeVore et al., 2025).

3.2.2. Real-World Pharmacovigilance: Analysis of the FAERS Database To understand the safety profile beyond the controlled environment of clinical trials, we analyzed data from the **FDA Adverse Event Reporting System (FAERS)**. A comprehensive data-mining study involving over **5,442 cases** of semaglutide-associated gastrointestinal and cutaneous AEs identified 45 distinct signals (Shu et al., 2022).

• **Time-to-Onset (TTO):** The analysis utilized a modified Weibull model to analyze the timing of adverse events. The results indicated an "early failure profile," with a median TTO for most cutaneous and gastrointestinal signals occurring within the first **6 to 7 days** of treatment (Gu, 2026). However, severe clinical priority signals showed a longer median TTO of **23 days**. This suggests that while minor irritations occur almost immediately, more complex immune-mediated reactions require a cumulative exposure period (Wang et al., 2025).

• **Demographic Sensitivity:** The risk of AE severity was found to be significantly associated with **older age ($p < 0.001$)** and **higher baseline body weight ($p = 0.006$)**. Interestingly, biological sex did not emerge as a significant risk factor for the severity of these reactions ($p = 0.251$) (He et al., 2024).

3.2.3. Rare and Immune-Mediated Adverse Drug Reactions A critical emerging concern in the pharmacovigilance of incretin-based therapies is the report of rare, immune-mediated cutaneous diseases.

• **Bullous Pemphigoid (BP):** Recent case reports and database analyses have suggested a potential link between GLP-1 RA use and the development of bullous pemphigoid, a serious autoimmune blistering disease (Patino et al., 2025; Salazar et al., 2024). While the absolute risk remains very low, the Reporting Odds Ratio (ROR) in some datasets has raised a safety signal. The mechanism is believed to involve the expression of GLP-1 receptors on dermal fibroblasts, which, when activated, may alter the basement membrane zone's immunogenicity in genetically predisposed patients (DeVore et al., 2025).

• **Hypersensitivity and Angioedema:** While acute anaphylaxis is rare, delayed hypersensitivity reactions have been documented. Recent pharmacovigilance analyses (Gu, 2026; Shu et al., 2022) prioritized several "new and unexpected" signals, including postmenopausal hemorrhage and specific allergic dermatoses, which imply that these drugs may interfere with systemic hormonal regulation or trigger broad immune-mediated pathways.

3.2.4. Aesthetic and Structural Alterations: "Ozempic Face" and Skin Laxity One of the most widely discussed cutaneous impacts of rapid weight loss via semaglutide or tirzepatide is the alteration of facial aesthetics. Although often dismissed as a "vanity concern," the clinical reality-colloquially termed **"Ozempic Face"**-is a physiological consequence of rapid subcutaneous fat depletion.

The mid-facial fat pads, which provide structural support and volume to the face, are often among the first areas to undergo significant lipolysis during high-dose incretin therapy. The resulting volume loss leads to a gaunt appearance, increased skin laxity, and the deepening of wrinkles (Haykal et al., 2025; Humphrey & Lawrence, 2023) From a dermatological perspective, this is not a direct toxic effect of the drug on the skin cells but a biomechanical consequence of the speed of weight loss. For patients undergoing these therapies, this often necessitates secondary dermatological interventions, such as the use of hyaluronic acid fillers or biostimulators, to restore the dermal matrix and structural integrity (Haykal et al., 2025; Humphrey & Lawrence, 2023).

3.2.5. Hormonal and Nutritional Cutaneous Signals Our systematic review also identified signals related to indirect cutaneous impacts. Data from FAERS (identified signals for **menstrual disorders** and **hair loss (telogen effluvium)**. Telogen effluvium is a common response to the physiological stress of rapid weight loss and nutritional shifts (He et al., 2024; Tran et al., 2024). Additionally, rare reports of **Wernicke's encephalopathy** and general malnutrition suggest that extreme appetite suppression can lead to micronutrient deficiencies (e.g., B-vitamins, zinc, and protein), which are essential for maintaining the skin barrier and hair follicle health (He et al., 2024; Wang et al., 2025).

3.3. Therapeutic Potential in Inflammatory Dermatoses

The most significant paradigm shift identified in this systematic review is the transition of incretin-based therapies from purely metabolic agents to potential immunomodulatory tools in dermatology. This therapeutic potential is driven by a "dual mechanism": an indirect effect via the reduction of pro-inflammatory adipose tissue and a direct effect through the activation of GLP-1 receptors expressed on immune cells (Bendotti et al., 2022; Wong & Drucker, 2025).

3.3.1. Psoriasis and the Modulation of the IL-23/IL-17 Axis

Psoriasis is the quintessential "systemic" skin disease, fundamentally linked to metabolic syndrome (Alajroush et al., 2024; Wolk & Sabat, 2016). The pathogenetic core of psoriasis involves the overactivation of T-helper 17 (Th17) cells and the subsequent release of interleukin-17 (IL-17) and IL-23.

Our analysis of the literature reveals that GLP-1 receptor agonists (GLP-1 RAs) exert a potent suppressive effect on this axis (Huang et al., 2022; Wong & Drucker, 2025).

• **Indirect Immunomodulation:** Visceral adipose tissue in obese psoriatic patients acts as an endocrine organ, secreting "adipocytokines" such as leptin and resistin which prime the immune system for a Th17

response (Jang et al., 2025). The rapid weight loss of ~15-21% achieved in the **STEP** and **SURMOUNT** trials leads to a dramatic "cooling" of this systemic inflammatory environment (Paschou et al., 2025).

- **Direct Immunomodulation:** GLP-1 receptors are expressed on human invariant natural killer T (iNKT) cells and T-cells. Evidence suggests that semaglutide and tirzepatide can directly inhibit the production of IL-17 and TNF-α by these cells (Bendotti et al., 2022; Huang et al., 2022).

Clinical outcomes reported in systematic reviews indicate that patients with comorbid obesity and psoriasis who initiated GLP-1 RA therapy experienced significant reductions in their **Psoriasis Area and Severity Index (PASI)** scores. In several cohorts, weight loss interventions facilitated by these drugs allowed patients to achieve PASI 75 or even PASI 90, even when they had previously been recalcitrant to traditional biologic therapies (Alajroush et al., 2024; Debbaneh et al., 2014; Paschou et al., 2025).

3.3.2. Hidradenitis Suppurativa (HS) and the "Adipo-Follicular" Reset

Hidradenitis suppurativa is an auto-inflammatory disease of the hair follicle that is arguably more sensitive to metabolic fluctuations than any other dermatosis. Obesity is not merely a comorbidity in HS; it is a primary driver of disease severity through mechanical friction, occlusion, and the hyper-inflammatory state of skin folds (Kaleta et al., 2022; Vossen et al., 2018).

- **The Weight-Loss Threshold:** Systematic reviews of weight-loss interventions in HS confirm that a reduction in BMI is directly correlated with a decrease in the **International Hidradenitis Suppurativa Severity Score (IHS4)** (Krajewski et al., 2024). Bariatric-level weight loss, such as that achieved with tirzepatide 15 mg, is associated with a significant reduction in the number of inflammatory nodules and abscesses (Krajewski et al., 2024; Sivanand et al., 2020).
- **Biomarker Regulation:** Translational research has identified that markers of metabolic dysfunction, such as **irisin, PPAR-γ and IGF-1R**, are abnormally expressed in the lesional skin of HS patients. Tirzepatide's dual agonism, by targeting GIP receptors in adipose tissue, effectively "resets" these biomarkers. This molecular shift reduces the "fuel" available for the follicular occlusion and subsequent rupture that characterizes HS flares (Ergun, 2018; Krajewski et al., 2024).

3.3.3. Immunometabolism: The Role of Adipokines and Systemic Signaling

The broader impact of GLP-1 signaling involves the regulation of systemic inflammation. discusses how GLP-1 RAs improve the "immunometabolic profile" by increasing levels of adiponectin (an anti-inflammatory adipokine) and decreasing pro-inflammatory markers like C-reactive protein (CRP) (Bendotti et al., 2022; Wong & Drucker, 2025).

In the context of the **obesity-skin axis**, this means that incretin-based therapies provide a "systemic shield" against the chronic low-grade inflammation that triggers flares in various IMIDs (Immune-Mediated Inflammatory Diseases). The reduction in IGF-1 signaling is particularly relevant for conditions like acne inversa (HS) and adult-onset acne, where insulin-like growth factor-1 is a known driver of sebaceous gland hyperplasia and follicular keratinization (Wong & Drucker, 2025).

3.3.4. Emerging Horizons: Beyond Psoriasis and HS

Preliminary evidence suggests that the anti-inflammatory properties of GLP-1 and GIP/GLP-1 agonists may extend to other dermatological conditions, including:

- **Acanthosis Nigricans:** Directly improving insulin sensitivity leads to the regression of these hyperpigmented, velvety plaques (Lima et al., 2017).
- **Nonalcoholic Steatohepatitis (NASH)-associated Skin Changes:** As seen in the NASH trials the systemic improvement in liver function and lipid metabolism can reduce the cutaneous manifestations of chronic liver disease, such as pruritus and jaundice (Smits & Van Raalte, 2021).

Discussion

The findings of this systematic review illuminate a complex and multi-faceted "dual impact" of GLP-1 and dual GIP/GLP-1 receptor agonists on the integumentary system. Our analysis suggests that we are witnessing a fundamental shift in the treatment of chronic inflammatory dermatoses-one that moves away from localized or purely immunosuppressive therapies toward a holistic, immunometabolic approach (Krajewski et al., 2024; Paschou et al., 2025). This transition necessitates a deeper exploration of the molecular mechanisms, safety paradoxes, and the socio-technological implications of these agents.

4.1. The Immunometabolic Synthesis: Bridging Metabolism and Dermatology

The core of our discussion rests on the "obesity-skin axis," a concept that has gained significant traction in the last decade but is only now being pharmacologically exploited through incretin-based therapies. Traditionally, dermatology has treated conditions like psoriasis and hidradenitis suppurativa as isolated

immune dysfunctions. However, the efficacy of tirzepatide and semaglutide in these conditions proves that cutaneous inflammation is inextricably linked to systemic metabolic homeostasis (Alajroush et al., 2024; Paschou et al., 2025).

The significant reduction in pro-inflammatory adipokines, such as leptin and resistin, combined with a concomitant increase in the anti-inflammatory marker adiponectin, creates a systemic environment that "starves" the inflammatory process in the skin (Jang et al., 2025; Wolk & Sabat, 2016).. Adiponectin, in particular, has been shown to inhibit keratinocyte proliferation and the production of pro-inflammatory cytokines, acting as a natural brake on the IL-17/IL-23 axis (Bendotti et al., 2022). The dual agonism of tirzepatide appears particularly potent here; by targeting GIP receptors in adipose tissue, it promotes healthy lipid buffering and reduces the "leakage" of free fatty acids (Liu et al., 2025; Müller et al., 2019). These free fatty acids are known ligands for Toll-like receptors (TLRs) on the skin's innate immune cells, which, when activated, trigger the auto-inflammatory cascades seen in HS. By removing these metabolic triggers, incretin mimetics act as a "molecular fire extinguisher," providing a powerful rationale for utilizing these drugs as first-line adjuncts in patients with high-BMI inflammatory dermatoses (Krajewski et al., 2024).

4.2. Navigating the Safety-Efficacy Paradox and Real-World Adherence

One of the most striking findings in our review is the contrast between localized cutaneous adverse events and systemic therapeutic benefits. While Section 3.2 highlights that up to 9.1% of patients in trials may experience injection-site reactions (ISRs), these are overwhelmingly transient (Taj et al., 2026). However, in a "social science" context, even minor dermatological reactions can impact patient adherence. The "visibility" of a skin reaction often carries a higher psychological weight than internal gastrointestinal discomfort, potentially leading to premature discontinuation of a life-saving metabolic therapy (Taj et al., 2026; Thomsen et al., 2025).

Furthermore, the emergence of rare but serious signals such as bullous pemphigoid (BP) identified in the FAERS data introduces a significant caveat. The expression of GLP-1 receptors on dermal fibroblasts suggests that the drug's impact on the skin is not merely a byproduct of weight loss but a direct pharmacological interaction. If GLP-1 signaling alters the basement membrane zone's protein expression, it could theoretically unmask latent autoimmunity (DeVore et al., 2025; Salazar et al., 2024). Clinicians must, therefore, distinguish between simple ISRs and the early signs of blistering diseases. This "Safety-Efficacy Paradox" requires a nuanced clinical approach: we must not allow the fear of rare reactions to prevent the use of these drugs for HS or psoriasis, but we must remain vigilant for the "early failure profile" where symptoms peak within the first 23 days of therapy (Gu, 2026; Wang et al., 2025).

4.3. The Socio-Technological Impact: "Ozempic Face" and the Evolution of Beauty

As a journal focused on the intersection of technology and society, it is imperative to discuss the "Ozempic Face" phenomenon as a socio-medical construct (Humphrey & Lawrence, 2023). The rapid weight loss facilitated by these technologies has outpaced the skin's natural elastic capacity for remodeling. This has created a new category of dermatological patient: the "metabolically healthy but aesthetically challenged" individual.

This shift has profound implications for the field of aesthetic dermatology. We are seeing a surge in demand for dermal fillers, biostimulators (e.g., poly-L-lactic acid), and skin-tightening technologies to address the gaunt appearance caused by the depletion of mid-facial fat pads (Haykal et al., 2025). This represents a "technological feedback loop" where a metabolic innovation (GLP-1) creates a secondary necessity for aesthetic innovations. Sociologically, this also touches on the "normalization" of AI-guided and pharmaceutical weight loss. If the face becomes a visible marker of "drug-induced weight loss," it may carry a new form of social stigma or, conversely, act as a status symbol of access to modern medical technology. For many patients, the distress caused by facial aging can rival the distress of the original obesity, requiring a nuanced, empathetic approach to counseling that integrates both metabolic and cosmetic outcomes.

4.4. Racial Variability and Global Health Technology

The inclusion of the STEP 7 trial in our review provides a critical look at racial and ethnic variability in drug response. East Asian populations often present with "metabolically obese, normal weight" phenotypes, where visceral fat accumulation and skin manifestations (like acanthosis nigricans) occur at lower BMI thresholds compared to Western populations (Mu et al., 2024).

The fact that semaglutide 2.4 mg remains highly effective in these cohorts (-12.1% weight loss) suggests that the technology is globally robust. However, the dermatological safety signals must be tracked across different skin phototypes (Fitzpatrick scales). For instance, post-inflammatory hyperpigmentation (PIH) following an injection-site reaction may be a more significant concern for patients with darker skin tones (Mu et al., 2024; Taj et al., 2026). As these drugs move into markets in Asia and Africa, the "Dual Impact" on skin health must be evaluated through the lens of global health equity and diverse dermatological needs.

4.5. Economic Rationale: Potential Role in Reducing the Use of Biologics

An important, yet often underemphasized, aspect of the discussion is the potential economic impact of using GLP-1 receptor agonists in dermatological diseases. Psoriasis and hidradenitis suppurativa are currently managed with highly costly biologic therapies (e.g., adalimumab, secukinumab), which represent a substantial burden for healthcare systems.

If metabolic interventions such as semaglutide or tirzepatide were able to achieve comparable clinical improvement in skin disease in selected patient populations, while simultaneously reducing cardiovascular risk, this could meaningfully influence cost-effectiveness analyses of treatment strategies (Marso et al., 2016; Lincoff et al., 2023). In this context, incretin-based therapies may serve as a valuable adjunct or an earlier step in the therapeutic pathway for patients with obesity and inflammatory skin diseases.

Consequently, a “weight-loss-first” approach may, in the future, gain broader consideration in dermatological practice, particularly in patients with significant metabolic comorbidities, potentially reducing reliance on certain high-cost biologic therapies.

4.6. Clinical Management Roadmap and the "Early Failure" Window

Based on our synthesis of FAERS and clinical data, we propose a formalized clinical management roadmap. The "Early Failure" profile identified is a crucial concept. Since most side effects peak early and then decline, the first 30 days are the "danger zone" for adherence (He et al., 2024; Wang et al., 2025).

1. **Structural Support:** For patients at risk of "Ozempic Face," early referral to aesthetic specialists for dermal matrix support (e.g., high-protein diets and collagen-stimulating topicals) may mitigate structural changes (Haykal et al., 2025).
2. **Cross-Specialty Collaboration:** Diabetologists must learn to recognize HS nodules, and dermatologists must become comfortable monitoring GLP-1 titration.

4.7. Limitations of the Current Literature

Despite the wealth of data, significant gaps remain. Most of the sources analyzed were primarily designed to measure weight loss or HbA1c reduction; dermatological outcomes were often recorded as secondary safety endpoints rather than primary efficacy targets (Aroda et al., 2023; Wharton et al., 2025). We lack large-scale, prospective randomized controlled trials (RCTs) specifically designed to measure PASI scores or IHS4 outcomes as primary endpoints in non-diabetic populations. Furthermore, the long-term impact of chronic GLP-1/GIP signaling on skin cancer risk-given the receptors' role in cell signaling-remains largely unknown and requires decades of longitudinal tracking (de Andrade Mesquita et al., 2023; Smits & Van Raalte, 2021).

5. Future Perspectives

The rapid evolution of incretin-based therapies suggests that we are only at the beginning of the "Incretin Era" in dermatology. As technological innovation continues to accelerate, several key areas will define the next decade of research and clinical practice.

5.1. The Advent of Triple Agonists The success of dual agonists like tirzepatide has paved the way for "triple agonists" such as **retatrutide**, which targets the GLP-1, GIP, and glucagon receptors (Müller et al., 2019; Wong & Drucker, 2025). Early Phase 2 data suggests weight loss exceeding 24% over 48 weeks. From a dermatological perspective, the inclusion of glucagon receptor agonism may further enhance lipolysis and alter skin physiology in ways that dual agonists cannot. Future reviews must evaluate whether this increased metabolic potency translates into even faster remission of inflammatory dermatoses or if it exacerbates the structural "Ozempic Face" phenomenon (Haykal et al., 2025; Humphrey & Lawrence, 2023).

5.2. Long-term Safety and Oncological Vigilance While our review focused on acute and sub-acute cutaneous reactions, the long-term impact of chronic GLP-1/GIP stimulation on skin cell turnover remains a critical knowledge gap (Smits & Van Raalte, 2021). Longitudinal registries are needed to monitor the incidence of cutaneous malignancies, such as basal cell carcinoma or melanoma, in patients on decade-long therapy (de Andrade Mesquita et al., 2023). Furthermore, the impact of these drugs on wound healing in the context of elective plastic surgeries (often required after massive weight loss) is an area ripe for investigation (Humphrey & Lawrence, 2023; Haykal et al., 2025).

5.3. Precision Immunometabolism The future of dermatology may involve "precision weight loss," where genetic markers determine which incretin mimetic is most likely to resolve a specific patient’s psoriasis or HS. Understanding the heterogeneous expression of GLP-1 receptors across different skin phenotypes will be essential for personalizing therapy and minimizing the risk of rare immune-mediated adverse drug reactions (Patino et al., 2025; Kreouzi et al., 2025).

Conclusions

This systematic review has demonstrated that GLP-1 and dual GIP/GLP-1 receptor agonists exert a profound "dual impact" on the integumentary system. On one hand, they introduce a new spectrum of cutaneous safety concerns (Fat et al., 2026), from common injection-site reactions to rare, life-altering autoimmune signals like bullous pemphigoid (Salazar et al., 2024; Patino et al., 2025). On the other hand, they offer a revolutionary therapeutic pathway for inflammatory dermatoses, effectively "extinguishing" the systemic fire of the obesity-skin axis (Krajewski et al., 2024; Paschou et al., 2025).

For conditions like psoriasis and hidradenitis suppurativa, these medications represent more than just weight-loss tools; they are potent immunomodulators that address the root metabolic drivers of skin disease (Jang et al., 2025; Paschou et al., 2025). As these technologies become further integrated into society, the boundaries between metabolic, dermatologic, and aesthetic medicine will continue to blur. Clinicians must embrace a multidisciplinary approach, remaining vigilant for adverse signals while leveraging the systemic benefits of these agents to achieve holistic patient health (Alajroush et al., 2024)

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