doi.org/10.58931/cdt.2026.73168

ABOUT THE AUTHOR

Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD

Dr. Jincheng (Jeffery) Shi is a double board-certified dermatologist in Ottawa. He is a graduate of University of British Columbia Medical School and completed his residency at Dalhousie University. He serves as a Clinical Lecturer at University of Ottawa, Division of Dermatology. His practice includes comprehensive (general and pediatric) dermatology with special interests in atopic dermatitis, ethnic dermatology, and "bio-hacking".

Affiliations: Vital Medical Centre, University of Ottawa, Ottawa ON.

Beyond Weight Loss: Practical Considerations for use of Glucagon-like Peptide-1 (GLP-1) and Incretin Therapy in Inflammatory Skin Disease

Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD

Introduction

The use of glucagon-like peptide-1 (GLP-1) based therapies has emerged as a topic in dermatology due to the strong bi-directional association between obesity and immune-mediated inflammatory skin disease. The expanding benefits toward cardiometabolic health with GLP-1 and other incretin therapies supports the existence of a "skin-heart-metabolic" axis, prompting a shift from purely skin-directed therapies to holistic and systemic patient management. Dermatologists should be aware of the mechanisms, clinical evidence, safety profiles, and practical prescribing considerations of existing and novel drugs.

History

Gastric inhibitory peptide (GIP) and GLP-1 were first isolated from gastric porcine extract in the 1970s and 1980s.[1] Early therapeutic use was limited by rapid enzymatic degradation. However, the discovery of exendin-4, an analogue GLP-1 receptor agonist against Gila monster venom, enabled the development of more stable synthetic peptide injectable analogues for clinical use. Successive generations of GLP-1 receptor agonists, including exenatide (2005), liraglutide (2010), dulaglutide (2014), and semaglutide (2017) demonstrated reductions in HbA1c in patients with Type 2 Diabetes Mellitus (T2DM). Although a modest weight loss signal was observed in clinical trials for all agents, efficacy improved substantially for newer formulations. Higher-dose liraglutide was the first GLP-1 receptor agonist approved for chronic weight management in 2014. Subsequent large-scale cardiovascular outcome trials revealed profound cardiovascular and renal protective benefits independent of glycemic control and weight. More recently, semaglutide and tirzepatide achieved mean weight reductions of 15% in the STEP-1 trial[2] and 20-22% in the SURMOUNT-1[3]

trial respectively. These results had demonstrated weight loss typically achieved with surgery, suggesting that obesity was treatable as a chronic metabolic disease rather than a consequence of lifestyle choices. As of 2024, an estimated 12% of American adults had used a GLP-1 medication.

Mechanism of Action

Incretins are gastric signalling peptides that include GLP-1 and GIP among others. GLP-1 receptors are expressed in multiple organs throughout the body, including the skin. In the gastrointestinal (GI) tract, GLP-1 enhances the regulation of insulin secretion, delays gastric emptying, and promotes the reduction of appetite. GIP stimulates glucagon secretion and increases triglyceride storage in adipose tissue. GLP-1 receptors are also expressed on a variety of immune cells, including T cells, B cells, monocytes, neutrophils, eosinophils, and hematopoietic stem cells.[4] GLP-1 receptor agonists have been shown to upregulate anti-inflammatory cytokine interleukin (IL)-10 and downregulate pro-inflammatory cytokines including tumour necrosis factor-alpha (TNF-α), IL-1β, and IL-6.[5] Although mechanisms underlying their effects in skin disease are not fully understood, emerging evidence suggests the involvement of invariant natural killer T cells (iNKT), which shift immune responses toward T-helper (Th)1 or Th17 responses. In two psoriasis patients with T2DM, biopsy-proven plaque iNKT cell burden decreased following GLP-1 therapy.[4] A similar mechanism has been proposed in hidradenitis suppurativa (HS), in which GLP-1 receptor agonists may reduce the Th1/Th17-driven inflammatory cascade and reduce the production of IL-1β and TNF-α, with theoretical downstream effects on neutrophils, macrophages, and plasma cells.[6]

Review of Evidence

Currently, incretin-based therapies are generally accepted as part of adjunct therapeutic ladders for inflammatory skin disease including psoriasis and HS, although they have not yet been included in national-level treatment guidelines. In psoriasis, GLP-1 therapies have been evaluated in case reports, cohorts, and small clinical trials, primarily among patients with concomitant obesity or T2DM. Published case series describe patients aged 48–73 years with mild reductions in Psoriasis Area and Severity Index (PASI) scores ranging between 1.0–30.[6] and Physician Global Assessment (PGA) improvements of up to two points.[7] Cohort studies have demonstrated average reductions in PASI scores of 4.8–15.[7] improving to 2.2–9.2 after 12–18 weeks of treatment.[7] Overall improvement has been highly variable, with response rates ranging from 40–80%. In HS, case series have shown Dermatology Life Quality Index (DLQI) improvements, with scores decreasing from 12.3 to 9.7. However, individual case reports are more variable, showing improvements, including reductions of up to 10–11 points in overall DLQI scores.[7] The current evidence base is limited by small sample sizes, short-term use, typically below 6 months, and a lack of control groups.[8] A recent TriNetX retrospective cohort study of over 22,000 patients with HS has shown that GLP-1 therapy was associated with lower mortality, and reduced systemic complications including infection/sepsis and cardiovascular events.[8] Similarly, a TriNetX analysis of over 540,000 patients with atopic dermatitis had demonstrated similar benefits with lower odds of cardiovascular disease, heart failure, atherosclerosis, and ischemic heart disease.[9] The use of incretin therapies outside dermatologic conditions other than psoriasis and HS is not well-described. Evidence is currently limited to isolated case reports describing Hailey-hailey disease, acanthosis nigricans, and chronic spontaneous urticaria.[10]

Incretin therapy has been studied in combination with established biologic systemic treatment. In the phase IIIb TOGETHER-PsO trial of patients with psoriasis and obesity, 27.1% of participants receiving combination therapy achieved both PASI-100 and 10% or greater weight reduction with ixekizumab plus tirzepatide, compared to 5.8% with ixekizumab alone at 36 weeks.[11] Similarly, in the phase IIIb study TOGETHER-PsA trial, 31.7% of participants with psoriatic arthritis treated with ixekizumab plus tirzepatide achieved both a 50% improvement

in American College of Rheumatology response criteria and 10% or greater weight reduction, compared to 0.8% of patients receiving ixekizumab monotherapy over 36 weeks.[12] These trial results suggest that concomitant use of biologic immunomodulators with incretin therapy can produce synergistic improvements in both skin disease and cardiometabolic health.

Applications in Skin Disease

In Canada, semaglutide (GLP-1 receptor agonist) is currently indicated to improve glycemic control in adults with T2DM as an adjunct to diet and exercise. It can be used in combination with oral metformin or other oral antihyperglycemic medications, or as monotherapy when other treatments are not tolerated or appropriate as standalone therapies. Special authorization and limited use criteria vary by province; however, coverage could require inadequate glycemic control on maximally tolerated doses of metformin/sulfonylurea or intolerance to first-line agents.

Higher-dose formulations were originally indicated for chronic weight management in adults with a body mass index (BMI) of greater than 30 kg/m^2 (class I obesity), or patients with a BMI of 27–30 kg/m^2 with one weight-related comorbidity, including hypertension, T2DM, dyslipidemia, or obstructive sleep apnea. Subsequent indications have been added or are underway for patients with established cardiovascular disease, including prior myocardial infarction, stroke, symptomatic peripheral artery disease, and a BMI greater than 27 kg/m^2, as well as for metabolic dysfunction–associated steatohepatitis. Pediatric use for chronic weight management is also indicated for those aged 12–18 years with a BMI above the 95th percentile for age who have not achieved weight reduction with lifestyle interventions alone. Both injectable and oral formulations are available however, injectable formulations generally produce greater weight loss than their oral counterparts.

Tirzepatide, a dual GLP-1 and GIP receptor agonist, is indicated for the treatment of T2DM and chronic weight management using similar criteria. The same formulation and dosing regimen are used for both clinical indications.

The use of incretin therapies in skin disease remains off-label unless patients meet the criteria for T2DM or chronic weight management **(Table 1)**. In these cases, the primary therapeutic indication is the underlying disease, with any dermatologic improvement considered a secondary benefit. Emerging evidence suggests that these therapies can serve as useful adjuncts for the treatment of psoriasis or HS, potentially enhancing the efficacy of conventional and biologic systemic treatments.[13]

Indications (one of):	Clinical Information Required:
• T2DM with inadequate glycemic control on oral agents • Chronic weight management: BMI >30 kg/m^2 • Chronic weight management: BMI >27 kg/m^2 with one of hypertension, T2DM, dyslipidemia, obstructive sleep apnea • Chronic weight management: BMI >27 kg/m^2 with one of atherosclerotic cardiovascular disease (MI, stroke, symptomatic PAD), metabolic dysfunction–associated steatohepatitis • Pediatric chronic weight management: BMI >95th percentile for age	• T2DM: Hemoglobin A1c • Chronic weight management: height, weight, BMI, comorbidities • Supportive investigations: ambulatory blood pressure, random/fasting blood glucose, hemoglobin A1c, lipid panel, home/overnight sleep study, CT angiogram, coronary CT, liver ultrasound, and growth curves

Table 1. Indications for incretin therapy and clinical criteria necessary to support diagnoses for medication coverage; *courtesy of Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD*

Abbreviation: BMI: Body mass index; **CT:** Computed tomography; **MI:** Myocardial infarction; **PAD:** Peripheral artery disease; **T2DM:** Type 2 diabetes

In the author's opinion, incretin-based therapies may also have theoretical benefits in skin diseases related to friction (folliculitis, intertrigo, hyperhidrosis, lichen simplex chronicus), as well as skin diseases strongly associated with metabolic syndrome (acanthosis nigricans, polyendocrine metabolic ovarian syndrome, hirsutism).

Safety

In addition to known hypersensitivity and pregnancy, there are class-wide contraindications for GLP-1 and related therapies in patients with a personal history of Multiple Endocrine Neoplasia Syndrome Type 2, or a personal/family history of medullary thyroid carcinoma. This precaution is based primarily on findings from rodent studies, in which GLP-1 receptor activation stimulated proliferation of thyroid C-cells. However, human thyroid C-cells are thought to express fewer GLP-1 receptors and exhibit a lower proliferative ability.

GI adverse events were the most commonly reported in phase III clinical trials, including but not limited to nausea, diarrhea, vomiting, constipation,

Prescribing	Counselling	Monitoring
• Standing prescription with dose escalation protocol and refills • Instructions: "Monthly titration schedule, to hold and treat long-term at highest tolerable dose" • Completion of prior authorization paperwork (if applicable) ◦ Wegovy® (semaglutide) FlexTouch® 0.68 mg/mL, inject 0.25 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 1.34 mg/mL, inject 0.5 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 1.34 mg/mL, inject 1 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 2.27 mg/mL, inject 1.7 mg Q1W x 1 mo ◦ Wegovy® (semaglutide) FlexTouch® 2.4 mg/mL, inject 2.4 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 10 mg/2.4 mL, inject 2.5 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 20 mg/2.4 mL, inject 5 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 30 mg/2.4 mL, inject 7.5mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 40 mg/2.4 mL, inject 10mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 50 mg/2.4 mL, inject 12.5 mg Q1W x 1 mo ◦ Zepbound® (tirzepatide) KwikPen® 50 mg/2.4 mL, inject 15 mg Q1W x 1 mo	• Overall goal: balance weight loss with treatment tolerability • Eat and drink slowly • Stop when early satiety is reached • Expect decrease in bowel movement frequency • Increase fluid and fiber consumption if constipation occurs • Consume daily protein >0.8 g per kg of body weight per day • Resistance training 2-3 times per week is suggested • For tirzepatide, use additional contraceptive method in first 4 weeks of treatment for reproductive potential patients	• Body weight to guide medication renewal and dose escalation • Hemoglobin A1c, for medication renewal • Routine parameters for skin disease (e.g. PGA, BSA, PASI, HiSCR, AN count)

Table 2. Overview of prescribing information, key counselling points, and monitoring parameters for incretin treatment; *courtesy of Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD*

Abbreviation: AN count: Abscess and nodule count; **BSA:** Body surface area; **HiSCR:** Hidradenitis suppurativa clinical response; **mo:** month; **PASI:** Psoriasis Area and Severity Index; **PGA:** Physician Global Assessment; **Q1W:** Once weekly

dyspepsia, and abdominal pain. For semaglutide, nausea was the most frequent adverse event, occurring in 44.2% of treated participants. Most events were categorized as mild-moderate, transient, and often resolving after the dose escalation period. Treatment discontinuation due to adverse effects occurred in 4.5% of treated participants.[2] In trials of tirzepatide, although the incidence of nausea was lower, occurring in 33.3% of participants receiving the 10 mg dose, discontinuation due to adverse events occurred in 7.1% of treated participants.

Rare but notable side effects include, gall bladder disease, mood changes, worsening of diabetic retinopathy, non-arteritic anterior ischemic optic neuropathy, and severe lean muscle mass loss. While pancreatitis has been reported, current meta-analyses do not support an increased risk. Relative contraindications for use include older adults, frail individuals, or those planning to become pregnant.

Counselling and Practical Considerations

Semaglutide is available as a prefilled FlexTouch® pen in doses of 0.25, 0.5, 1, 1.7, and 2.4 mg, with needles supplied as part of the device. Tirzepatide is available as a KwikPen® in doses of 2.5, 5, 7.5, 10, 12.5, and 15 mg; needles are not included but are available without a prescription. For chronic weight management, doses are titrated at monthly intervals to the maximally tolerated dose, balancing weight loss with side effects. Although close follow-up is suggested, this may be impractical in dermatology practice. Therefore, a slower titration schedule with reassessment every 3–6 months may be preferable. Select patients may benefit from a "microdosing" strategy, particularly during dose escalation or de-escalation, when transitioning between agents, when experiencing severe GI side effects, or when medication costs are a concern. "Microdosing" refers to a patient-selected dose by counting pen clicks on compatible FlexTouch®/KwikPen® devices rather than delivering the full preset dose. This dosing strategy requires appropriate counselling and access to additional needles. Demonstration devices can be helpful for improving patient understanding and confidence. In the author's experience, prescribing multiple units of each dosage under a standing prescription can facilitate patient-directed dose titration **(Table 2)**. Prior authorization is commonly required by private insurance plans and can typically be completed using forms available through the insurer's website.

Reported dermatologic adverse effects include injection site reactions, altered skin sensation (dysesthesia and hyperesthesia), alopecia, and rare cases of keratinocyte carcinoma and drug hypersensitivity reactions.[14] Rapid weight loss may contribute to increased perceived facial aging through reductions in adipose-derived stem cell and fibroblast activity, as well as interactions with advanced glycation end products.[15]

Patient counselling should focus on setting goals for long-term use and strategies to maximize tolerability to achieve metabolic and cutaneous benefits.[16] Patients should be advised to adopt behavioural eating modifications including eating and drinking slowly and stopping when early satiety cues are reached to avoid acute nausea or vomiting. A decrease in bowel movement frequency is also expected due to slowed GI transit. Transient episodes of constipation can be managed with increased fluid intake and dietary fiber supplementation. Lean muscle mass loss can be minimized by prioritizing daily protein intake and engaging in resistance training. Daily protein intake should exceed 0.8 g/kg of body weight and can be achieved through nutritional supplement drinks/powders or lean meat consumption. Resistance training regimens are ubiquitous and should target major muscle groups and ideally be performed 2–3 times per week. Patients with reproductive potential who are taking oral contraceptives and tirzepatide should be advised to use additional contraceptive methods during the first four weeks of treatment due to reduced absorption of oral contraceptives.[17]

Future Directions

Emerging incretin therapies combine GLP-1 activity with additional mechanisms. In the phase III TRIUMPH-4 trial, patients with obesity and osteoarthritis achieved a mean body mass reduction of 28.7% and experienced improvements

in knee osteoarthritis pain scores (Eli Lilly, unpublished data, December 2025). Favourable changes were also observed in several secondary endpoints, such as reductions in markers of cardiovascular risk including non-high-density lipoprotein cholesterol, triglycerides, high-sensitivity C-reactive protein and systolic blood pressure. GI-related adverse effects (nausea, diarrhea, constipation, vomiting, decreased appetite) remained the most common side effects, although discontinuation rates (12.2–18.2%) were comparable to or lower than those reported with existing agents. Overall, the weight loss signal exceeded that observed in STEP-1[2] (15%) and in SURMOUNT-1[3] (20–22%).

Further studies are needed to investigate the cutaneous benefits of incretin-based therapies, including high quality meta-analyses and randomized double-blind clinical trials. Both translational and clinical research are required to clarify whether clinical improvements in psoriasis and HS are driven primarily by weight loss, drug concentrations, or a combination of these mechanisms.

Correspondence

Jeffery (Jincheng) Shi, MD, FRCPC, DABD, FAAD
Email: jinchengdermatology@gmail.com

Financial Disclosures

J.S.: Advisory boards/Speaker's bureau/ Sponsorship: Abbvie, Arcutis, Celltrion, Incyte, Lilly, Organon, Pfizer, Sanofi-Regeneron, Searchlight, Sun Pharma, UCB.

References

1. Drucker DJ. The GLP-1 journey: from discovery science to therapeutic impact. J Clin Invest. 2024;134(2):e175634. doi:10.1172/JCI175634
2. Wilding JPH, Batterham RL, Calanna S, Davies M, van Gaal LF, Lingvay I, et al. Once-weekly semaglutide in adults with overweight or obesity. N Engl J Med. 2021;384(11):989–1002. doi:10.1056/nejmoa2032183
3. Jastreboff AM, Aronne LJ, Ahmad NN, Wharton S, Connery L, Alves B, et al. Tirzepatide once weekly for the treatment of obesity. N Engl J Med. 2022;387(3):205–216. doi:10.1056/nejmoa2206038
4. Bendotti G, Montefusco L, Lunati ME, Usuelli V, Pastore I, Lazzaroni E, et al. The anti-inflammatory and immunological properties of GLP-1 Receptor Agonists. Pharmacol Res. 2022;182:106320. doi:10.1016/j.phrs.2022.106320.
5. Lu C, Xie T, Guo X, Wu D, Li S, Li X, et al. Glucagon-like peptide-1 receptor agonist exendin-4 mitigates lipopolysaccharide-induced inflammatory responses in RAW264.7 macrophages. Int Immunopharmacol. 2019;77:105969. doi:10.1016/j.intimp.2019.105969
6. Krajewski PK, Złotowska A, Szepietowski JC. The therapeutic potential of GLP-1 receptor agonists in the management of hidradenitis suppurativa: a systematic review of anti-inflammatory and metabolic effects J Clin Med. 2024;13(21):6292. doi:10.3390/jcm13216292
7. Paschou IA, Sali E, Paschou SA, Psaltopoulou T, Nicolaidou E, Stratigos AJ. The effects of GLP-1RA on inflammatory skin diseases: a comprehensive review. Eur Acad Dermatol Venereol. 2025;39(12):2047-2055. doi:10.1111/jdv.20694
8. Sheth S, Merola JF, Weber BN, Prussick R, Yeung J, Liu C, et al. The National Psoriasis Foundation Primer on GLP-1 Receptor Agonists in Psoriasis: a review. JAMA Dermatol. 2026;162(6):619-630. doi:10.1001/jamadermatol.2026.0859
9. Katz A, Nong Y, Ma EJ, Roberts AM, Chou PP, Jeong CY, et al. Effects of GLP-1 receptor agonists on major cardiovascular events among patients with atopic dermatitis: a population-based study. Dermatitis. Published online February 6, 2026. doi:10.1177/17103568251410211
10. Lal K, Herringshaw E. The Use of GLP-1 agonists in the management of cutaneous disease. J Clin Aesthet Dermatol. 2024;17(9):34-37.
11. Lebwohl M, Blauvelt A, Kartman CE, Leatherwood C, Gordon KB, Sattar N, et al. Ixekizumab with or without tirzepatide in adults with psoriasis and overweight or obesity: a phase 3b randomized clinical trial. JAMA Dermatol. Published online May 15, 2026. doi:10.1001/jamadermatol.2026
12. Merola JF, Mease P, Kivitz A, Sattar N, Coates LC, Aletaha D, et al. Ixekizumab with tirzepatide achieved greater disease control than ixekizumab alone in adults with psoriatic arthritis and overweight or obesity: results from a randomized clinical trial. Arthritis Rheumatol. Published online March 28, 2026. doi:10.1002/art.70134
13. Burshtein J, Armstrong A, Chow M, DeBusk L, Brad Glick, Gottlieb AB, et al. The association between obesity and efficacy of psoriasis therapies: an expert consensus panel. J Am Acad Dermatol. 2025;92(4):807–815. doi:10.1016/j.jaad.2024.12.016
14. Tran MM, Mirza FN, Lee AC, Goldbach HS, Libby TJ, Wisco OJ. Dermatologic findings associated with semaglutide use: a scoping review. J Am Acad Dermatol. 2024;91(1):166-168. doi: 10.1016/j.jaad.2024.03.021
15. Paschou IA, Sali E, Paschou SA, Tsamis KI, Peppa M, Psaltopoulou T, et al. GLP-1RA and the possible skin aging. Endocrine. 2025;89(3):680-685. doi:10.1007/s12020-025-04293-w
16. Fitch A, Gigliotti L, Bays HE. Application of nutrition interventions with GLP-1 based therapies: a narrative review of the challenges and solutions. Obes Pillars. 2025;16:100205. doi:10.1016/j.obpill.2025.100205
17. Calvarysky B, Dotan I, Shepshelovich D, Leader A, Cohen TD. Drug-drug interactions between glucagon-like peptide 1 receptor agonists and oral medications: a systematic review. Drug Saf. 2024;47(5):439-451. doi:10.1007/s40264-023-01392-3