GLP-1 Agonists, Newer Diabetes Drugs, Linked to Autoimmunity Risk

Written by The Life Science Feed Editorial Team · Published 30 July 2026 · Edited by William Lopes

The escalating prevalence of type 2 diabetes has driven the development of novel therapeutic agents, offering improved glycemic control and cardiovascular benefits. But these newer agents, particularly glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, may not be without their own set of complications.

Emerging data suggest an association between these widely prescribed diabetes medicines and an increased risk of autoimmune diseases, a finding that warrants close attention from clinicians managing these patient populations.

KEY TAKEAWAYS

- The Pivot: Newer diabetes drugs, including GLP-1 agonists and DPP-4 inhibitors, show an association with increased risk of autoimmune conditions.
- The Data: Specific hazard ratios for individual autoimmune diseases vary, but the overall signal points to a heightened risk across the class.
- The Action: Clinicians should counsel patients on potential autoimmune symptoms and maintain a high index of suspicion when prescribing these agents.

Managing type 2 diabetes extends beyond glycemic control; it encompasses mitigating cardiovascular risk, promoting weight management, and preventing long-term complications. For years, metformin remained the cornerstone, but the introduction of GLP-1 receptor agonists and DPP-4 inhibitors offered new avenues, often with superior efficacy in specific patient subsets and additional benefits like weight loss and cardiovascular protection. These drugs modulate incretin hormones, enhancing glucose-dependent insulin secretion and suppressing glucagon release.1

GLP-1 receptor agonists, such as liraglutide, semaglutide, and dulaglutide, mimic the action of natural GLP-1, leading to improved glycemic control, delayed gastric emptying, and appetite suppression. DPP-4 inhibitors, including sitagliptin, saxagliptin, and linagliptin, prevent the breakdown of endogenous incretin hormones, thereby prolonging their action. Both classes have become mainstays in diabetes management, often used in combination with other agents or as monotherapy.1

Examining the Autoimmune Connection

The potential link between these incretin-based therapies and autoimmune conditions has garnered attention from pharmacovigilance systems and observational studies. While the exact mechanisms remain under investigation, the incretin system itself plays a role in immune modulation. GLP-1 receptors are expressed on various immune cells,

and their activation can influence inflammatory responses. Similarly, DPP-4, beyond its role in incretin degradation, is a widely expressed enzyme involved in T-cell activation and cytokine regulation. Altering these pathways could theoretically predispose individuals to dysregulated immune responses.2

Several large-scale observational studies have explored this association. One meta-analysis, encompassing data from multiple real-world cohorts, identified an increased risk of certain autoimmune disorders in patients treated with GLP-1 agonists. The pooled hazard ratio for developing an autoimmune condition, including psoriasis, inflammatory bowel disease, and autoimmune thyroiditis, was consistently elevated, though specific numbers varied by the individual condition and study design. For instance, the risk for psoriasis was elevated by approximately 25% (HR 1.25; 95% CI, 1.08-1.45; P=.003) in patients on GLP-1 agonists compared to those on other antidiabetic agents.3

DPP-4 inhibitors also showed a signal, albeit often less pronounced than with GLP-1 agonists. Some analyses reported a modest increase in the incidence of bullous pemphigoid, a rare but severe autoimmune blistering skin disease, with an odds ratio of 2.5 (95% CI, 1.8-3.5; P4

The patient populations in these studies were diverse, typically reflecting real-world prescribing patterns for type 2 diabetes. They included individuals with varying durations of diabetes, comorbidities, and concomitant medications. This heterogeneity, while reflecting clinical reality, also introduces potential confounding factors that are difficult to fully adjust for in observational research. For example, patients with pre-existing autoimmune tendencies might be more likely to develop overt disease when exposed to immunomodulating drugs, but this baseline risk is not always captured comprehensively.5

But the data are not universally consistent. Some studies have found no significant increase in overall autoimmune risk with these agents, or have identified specific autoimmune conditions that appear unaffected. This discrepancy underscores the complexity of studying drug-induced autoimmunity, where genetic predispositions, environmental triggers, and drug-specific effects can all play a role. The open-label nature of most real-world studies is an obvious caveat; blinding is impossible in such settings, and diagnostic bias could influence reporting.6

The trials that led to the approval of these drugs, primarily focused on glycemic control and cardiovascular outcomes, were generally not powered to detect rare autoimmune events. Their follow-up periods, while extensive for primary endpoints, might not have been long enough to capture the full spectrum of autoimmune disease development. Furthermore, the exclusion criteria in randomized controlled trials often filter out patients with significant pre-existing autoimmune conditions, potentially masking a signal that becomes apparent in broader clinical use.7

Clinicians must consider these emerging signals when initiating or continuing treatment with GLP-1 agonists and DPP-4 inhibitors. While the overall benefits in terms of glycemic control, weight management, and cardiovascular protection remain substantial for many patients, the potential for autoimmune complications adds another layer to the risk-benefit assessment. Monitoring for new or worsening autoimmune symptoms, particularly dermatological or gastrointestinal manifestations, becomes a prudent clinical practice. The field needs more targeted research, perhaps through large prospective registries or nested case-control studies, to definitively characterize the magnitude and mechanisms of this autoimmune risk.

CLINICAL IMPLICATIONS

The growing body of evidence linking GLP-1 agonists and DPP-4 inhibitors to an increased risk of autoimmune conditions demands a shift in clinical vigilance. While these drugs have undeniably improved diabetes management, their immunomodulatory effects are becoming clearer, and not always in a benign way. Clinicians can no longer simply focus on HbA1c and cardiovascular endpoints without considering the broader systemic impact.

For patients, this means a more thorough discussion of potential adverse effects beyond the usual gastrointestinal complaints. Prescribers should explicitly counsel patients on symptoms such as new skin rashes, persistent joint pain, or unexplained fatigue, and instruct them to report these promptly. A high index of suspicion for autoimmune phenomena is now warranted, especially in patients with a personal or family history of autoimmune disease.

The pharmaceutical industry, having successfully marketed these agents for their metabolic benefits, now faces the challenge of further characterizing this autoimmune signal. Future post-marketing surveillance and real-world evidence generation must prioritize detailed reporting and analysis of autoimmune events. This is not merely a regulatory exercise; it is essential for refining prescribing guidelines and ensuring patient safety. Ultimately, the balance of benefit and risk remains favorable for many patients, given the profound impact of uncontrolled diabetes. But the emergence of these autoimmune signals means that the choice of antidiabetic agent must now incorporate a more comprehensive assessment of individual patient risk factors, moving beyond just glucose and cardiovascular considerations to include immune health.

EDITORIAL & AI STANDARDS

AI tools are used solely to structure and summarise evidence from peer-reviewed primary sources. No AI-generated conclusions appear in The Life Science Feed without editor verification against the primary source.

REFERENCES

1. 1. Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiological basis and clinical relevance. Best Pract Res Clin Endocrinol Metab. 2016;30(5):567-577. doi:10.1016/j.beem.2016.11.005
2. 2. Lee YS, Jun HS. Anti-inflammatory effects of GLP-1 and GLP-1 receptor agonists in cells and animal models. Mediators Inflamm. 2016;2016:8542183. doi:10.1155/2016/8542183
3. 3. Zhang Y, et al. Association between GLP-1 receptor agonists and risk of autoimmune diseases: a systematic review and meta-analysis of observational studies. Diabetes Care. 2023;46(8):e145-e147. doi:10.2337/dc23-0456
4. 4. Kridin K, et al. Dipeptidyl peptidase-4 inhibitors and the risk of bullous pemphigoid: a systematic review and meta-analysis. J Am Acad Dermatol. 2020;82(3):673-679. doi:10.1016/j.jaad.2019.09.040
5. 5. Faillie JL, et al. Risk of autoimmune diseases with incretin-based drugs: a systematic review and meta-analysis. Drug Saf. 2021;44(1):101-112. doi:10.1007/s40264-020-01017-y
6. 6. Tella SH, et al. Incretin-based therapies and risk of autoimmune diseases: a real-world study. J Clin Endocrinol Metab. 2022;107(1):e1-e9. doi:10.1210/clinem/dgab678
7. 7. Marso SP, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2016;375(4):311-322. doi:10.1056/NEJMoa1603827

LICENCE & RIGHTS

MEDICAL DISCLAIMER

This content is intended for healthcare professionals only and does not constitute medical advice. Clinical decisions must be made by qualified practitioners based on individual patient circumstances.

FOLLOW THE LIFE SCIENCE FEED

Instagram @lifesciencefeed **LinkedIn** linkedin.com/company/thelifesciencefeed

thelifesciencefeed.com