



THE NEW CLASS OF ANTIDIABETIC DRUGS: INCRETIN MIMETICS

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Abstract: Incretin mimetics represent a novel class of antidiabetic drugs that mimic the physiological actions of endogenous incretin hormones, primarily glucagon-like peptide-1 (GLP-1). These agents improve glycemic control through glucose-dependent insulin secretion, suppression of glucagon release, delayed gastric emptying, and appetite reduction. Compared to traditional therapies, incretin mimetics offer enhanced efficacy with a lower risk of hypoglycemia and potential benefits for weight management and cardiovascular protection. This article reviews their pharmacological mechanisms, therapeutic applications, safety profile, and clinical significance in the management of type 2 diabetes mellitus (T2DM).

Keywords: Incretin mimetics, GLP-1 receptor agonists, type 2 diabetes mellitus, semaglutide, liraglutide, glycemic control, pharmacotherapy

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most prevalent chronic metabolic disorders worldwide, affecting over 500 million adults according to the International Diabetes Federation (IDF, 2024). It is characterized by impaired insulin secretion and insulin resistance, leading to persistent hyperglycemia and multiple organ complications including cardiovascular disease, neuropathy, nephropathy, and retinopathy. The increasing global incidence of T2DM is largely associated with sedentary lifestyles, unhealthy dietary habits, obesity, and population aging. In many low- and middle-income countries, diabetes has become a serious public health concern, placing a heavy socioeconomic burden on healthcare systems.

Conventional pharmacotherapy for T2DM includes biguanides (metformin), sulfonylureas, thiazolidinediones, alpha-glucosidase inhibitors, and insulin therapy. Although these agents improve glycemic control, many of them are associated with undesirable side effects such as weight gain, hypoglycemia, fluid retention, or gastrointestinal discomfort. Moreover, these therapies often fail to maintain long-term glycemic stability because they do not address the progressive loss of β -cell function inherent to T2DM pathophysiology.

Recent advances in the understanding of glucose metabolism and gut hormone physiology have led to the discovery of the **incretin effect**, which plays a vital role in postprandial insulin regulation. Incretin hormones—primarily **glucagon-like peptide-1 (GLP-1)** and **glucose-dependent insulinotropic peptide (GIP)**—are secreted by intestinal enteroendocrine cells in response to nutrient ingestion. They potentiate glucose-dependent insulin secretion, inhibit glucagon release, slow gastric emptying, and promote satiety. However, in patients with T2DM, the incretin response is blunted, leading to impaired insulin secretion and unbalanced glucose homeostasis.



To overcome this defect, two major therapeutic strategies have emerged: **incretin enhancers (DPP-4 inhibitors)** and **incretin mimetics (GLP-1 receptor agonists)**. While DPP-4 inhibitors prolong the action of endogenous incretin hormones, incretin mimetics directly stimulate GLP-1 receptors with higher potency and longer duration of action. This class of drugs offers multiple therapeutic benefits, including significant glycemic reduction, body weight loss, and cardioprotective effects, making them superior to many traditional agents.

The first incretin mimetic, **exenatide**, was approved in 2005, marking a milestone in diabetes pharmacotherapy. Since then, several long-acting GLP-1 receptor agonists—such as liraglutide, dulaglutide, and semaglutide—have been developed, providing extended dosing intervals and improved patient adherence. Recent innovations, including **oral semaglutide**, have further enhanced accessibility and convenience for patients who previously relied on injections.

The integration of incretin mimetics into clinical practice has not only improved glycemic outcomes but has also demonstrated cardiovascular and renal benefits, as evidenced by large-scale clinical trials. Consequently, international diabetes management guidelines (ADA, EASD) now recommend GLP-1 receptor agonists as a preferred second-line therapy, particularly for patients with obesity or atherosclerotic cardiovascular disease.

Therefore, this article aims to review the pharmacological mechanisms, therapeutic benefits, and clinical safety profile of incretin mimetics, highlighting their role as a cornerstone in the modern management of type 2 diabetes mellitus. Through an evidence-based analysis of recent studies, this review underscores how incretin-based therapy bridges the gap between effective glycemic control and holistic metabolic health.

Materials and Methods

This review analyzed scientific data published between 2015 and 2025 using databases such as PubMed, Scopus, and ScienceDirect. Search terms included “incretin mimetics,” “GLP-1 receptor agonists,” “type 2 diabetes,” “semaglutide,” “liraglutide,” and “exenatide.”

Peer-reviewed articles, clinical trial reports, and meta-analyses that evaluated the pharmacological mechanisms, therapeutic efficacy, and safety of incretin mimetics were selected. The data were systematically reviewed and synthesized to highlight pharmacological insights, clinical outcomes, and comparative advantages over traditional antidiabetic drugs.

Results

Mechanism of Action

Incretin mimetics stimulate insulin secretion in a glucose-dependent manner and suppress glucagon secretion from pancreatic α -cells. They delay gastric emptying, reduce postprandial glucose levels, and promote satiety through central appetite regulation. As a result, patients experience both improved glycemic control and weight reduction.



GLP-1 receptor agonists bind to receptors on β -cells, activating the cyclic AMP pathway, which enhances insulin biosynthesis and secretion. They also exert cardioprotective effects through improved endothelial function and reduced oxidative stress.

Pharmacological Agents

The main approved incretin mimetics include:

- **Exenatide** – short-acting, derived from Exendin-4 (Byetta, Bydureon).
- **Liraglutide** – long-acting human GLP-1 analog (Victoza, Saxenda).
- **Dulaglutide** – once-weekly GLP-1 RA (Trulicity).
- **Semaglutide** – available as injectable (Ozempic) and oral form (Rybelsus).
- **Lixisenatide** – short-acting daily GLP-1 RA (Lyxumia).

These agents differ in duration of action, molecular structure, and administration frequency, providing flexibility in personalized therapy.

Clinical Efficacy

Randomized controlled trials have demonstrated that incretin mimetics reduce HbA1c levels by approximately 1.0–1.5% and promote weight loss of 2–5 kg. The **LEADER** (liraglutide) and **SUSTAIN-6** (semaglutide) trials confirmed significant reductions in cardiovascular mortality among high-risk T2DM patients. These findings support the dual benefits of incretin-based therapies for glycemic and cardiovascular outcomes.

Safety and Tolerability

The most frequently reported side effects include nausea, vomiting, and diarrhea, especially at the initiation of therapy. These symptoms are typically transient. Long-term studies have not confirmed any significant risk of pancreatitis or thyroid cancer. Overall, incretin mimetics are considered safe, with a favorable benefit-risk ratio.

Discussion

Incretin mimetics have revolutionized diabetes management by providing a multifaceted approach to metabolic regulation. Their glucose-dependent mechanism minimizes hypoglycemia, while additional effects on weight reduction and cardiovascular protection enhance patient outcomes. Unlike older agents, GLP-1 receptor agonists address both the symptoms and underlying pathophysiology of T2DM.

The high cost remains a limitation in low- and middle-income countries, but cost-effectiveness analyses suggest that reduced hospitalizations and complications may offset initial expenses. The availability of oral semaglutide has improved adherence by eliminating the barrier of injection aversion.



Future research is focusing on **dual-agonist molecules** that activate both GLP-1 and glucose-dependent insulintropic peptide (GIP) receptors. These hybrid agents, such as tirzepatide, have shown superior glycemic and weight outcomes in recent studies. Furthermore, ongoing clinical trials are exploring combination therapies with SGLT2 inhibitors to maximize metabolic and cardiovascular benefits.

Conclusion

Incretin mimetics are an innovative class of antidiabetic drugs that combine potent glycemic control with favorable metabolic effects. Their unique ability to improve insulin secretion, suppress glucagon, promote weight loss, and provide cardiovascular benefits positions them as a cornerstone in modern diabetes therapy. As research evolves, next-generation incretin agents promise even greater efficacy and broader clinical applications, marking a new horizon in the treatment of type 2 diabetes mellitus.

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