Review



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# The Roles of Incretin Hormones GIP and GLP-1 in Metabolic and Cardiovascular Health: A Comprehensive Review

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**Abstract**

The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) play central roles in metabolic and cardiovascular regulation. GLP-1 receptor agonists (GLP-1RAs) are established therapies for type 2 diabetes mellitus (T2DM) and obesity because of their insulinotropic effects, weight reduction, and proven cardiovascular benefit. In contrast, GIP was historically overlooked due to reduced β-cell responsiveness in T2DM. The development of dual GIP/GLP-1 receptor agonists has reshaped this view. Tirzepatide, the first-in-class co-agonist, provides superior glycemic control and weight loss compared with selective GLP-1RAs, demonstrating synergistic actions between the two incretin pathways. This review summarizes key physiology, pathophysiology, and therapeutic evidence in incretin biology. We describe secretion patterns, receptor distributions, and distinct actions of GIP and GLP-1, as well as alterations in incretin signaling in T2DM and obesity. Cardiovascular protective mechanisms are outlined, including improvements in lipid metabolism, reductions in blood pressure, enhanced endothelial nitric oxide activity, suppression of macrophage inflammation, decreased foam-cell formation, and stabilization of atherosclerotic plaques. Emerging directions—such as dual and triple agonists—and unresolved questions regarding long-term vascular effects of GIP and the potential for genotype-guided incretin therapy are also discussed. Collectively, these findings highlight a shift toward integrated incretin-axis modulation for metabolic and cardiovascular disease.

**Keywords:** incretin hormones; GLP-1 receptor agonists; GIP signaling; tirzepatide; dual agonists; insulin secretion; atherosclerosis; cardiovascular protection; metabolic disease; obesity treatment

## 1. Introduction

### *1.1. The Evolving Story of Incretins*

Incretin biology has become increasingly central to modern metabolic therapeutics, reshaping how glucose regulation and obesity are understood and treated. The two primary incretin hormones, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), are secreted from the gut in response to nutrient intake and are central to glucose homeostasis through a phenomenon known as the "incretin effect" [1,2]. For decades, research and drug development overwhelmingly focused on GLP-1. Its ability to stimulate insulin secretion was found to be largely preserved in patients with type 2 diabetes (T2DM), providing a clear rationale for its development as a major therapeutic target [3,4]. This led to a highly successful class of drugs—GLP-1 receptor agonists (GLP-1RAs)—that established a new benchmark for metabolic therapy, creating a high bar for any subsequent innovations [5].

In contrast, GIP was historically relegated to a secondary role, often considered the "neglected incretin" [1]. Its insulin-stimulating action was found to be severely blunted in individuals with T2DM, leading to a widespread consensus that it held little to no therapeutic potential [3]. This view was so entrenched that GIP was largely sidelined in clinical research for years. However, this long-

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held dogma has been dramatically overturned by the development of dual GIP/GLP-1 receptor co-agonists, most notably tirzepatide. Clinical trials have demonstrated that tirzepatide achieves superior reductions in both HbA1c and body weight compared to even the most potent selective GLP-1RAs [6,7]. This remarkable efficacy has not only reignited scientific interest in GIP but has also revealed a more complex, synergistic relationship between these two hormones, prompting a fundamental re-evaluation of their integrated roles in metabolic regulation [1].

This review synthesizes the current understanding of these two pivotal hormones, beginning with their foundational physiology.

### *1.2. Fundamental Physiology of the Incretin System*

A thorough understanding of the fundamental physiology of GIP and GLP-1 is essential to appreciate their roles in health and their therapeutic manipulation in disease. Their distinct origins, receptor distributions, and biological actions form the basis for their individual and combined effects on metabolic and cardiovascular health. This section details these core physiological principles.

## 2. Physiology of GIP and GLP-1

### *2.1. Secretion and Metabolism*

GIP originates from enteroendocrine K-cells predominantly situated in the duodenum and jejunum, whereas GLP-1 is mainly released from L-cells, which become more abundant toward the ileum and colon [8–10]. Their release is triggered primarily by the ingestion and absorption of nutrients, particularly carbohydrates and fats, and to a lesser extent, proteins [1,11]. Following secretion into the bloodstream, both hormones are characterized by extremely short half-lives. Natural GLP-1, for example, has a half-life of only about two minutes [12]. This rapid clearance is due to enzymatic degradation by dipeptidyl peptidase-IV (DPP-IV), an enzyme widely distributed throughout the body that efficiently inactivates both hormones [2,12].

### *2.2. Receptor Distribution*

The biological effects of GIP and GLP-1 are mediated through their specific G protein-coupled receptors, the GIP receptor (GIPR) and GLP-1 receptor (GLP-1R). The widespread distribution of these receptors throughout the body accounts for the pleiotropic effects of these hormones, extending far beyond their primary role in glucose regulation. The table below (Table 1) synthesizes their presence in key tissues relevant to metabolic and cardiovascular health.

**Table 1. Distribution of GLP-1R and GIPR.**

| Tissue/Organ | GLP-1 Receptor (GLP-1R) Presence & Details | GIP Receptor (GIPR) Presence & Details |
|---|---|---|
| Endocrine Pancreas | β-cells: +++ (Abundantly expressed)<br>α-cells: -/+ (Present in a small proportion of α-cells) | β-cells: +++ (Abundantly expressed)<br>α-cells: ++ (Present) |
| Heart | + (Present in all four chambers, particularly the sinoatrial node) | + (Present in all four chambers) |
| Blood Vessels | + (Present, including in endothelial cells) | + (Present in endothelial cells) |
| Adipose Tissue | + (Present, primarily in vascular cells; debated on adipocytes) | ++ (Present, though unclear if on adipocytes or stromal-vascular cells) |
| Bone | -/+ (Absent in cultured osteoblasts but present in bone marrow stromal cells) | ++ (Present in osteoblasts and osteocytes) |
| Brain | ++ (Present in key areas for appetite regulation like the hypothalamus and brainstem) | + (Present in various regions including hippocampus and cortex) |

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This broad receptor distribution is strategically significant. It underlies the capacity of incretin hormones to influence a network of organ systems, including the pancreas, heart, vasculature, and central nervous system. The presence of both GIP and GLP-1 receptors in the heart, blood vessels, and adipose tissue provides a direct anatomical and molecular basis for the cardiovascular benefits observed in clinical trials, suggesting these effects are not solely secondary to metabolic improvements but may also involve direct tissue-level signaling [13].

### *2.3. Core Biological Actions*

While both GIP and GLP-1 share the primary function of stimulating insulin secretion, they possess distinct and sometimes opposing actions, particularly concerning glucagon secretion and gastrointestinal function.

#### 2.3.1. Regulation of Glucose Homeostasis

The defining action of both GIP and GLP-1 is their ability to augment glucose-stimulated insulin secretion from pancreatic β-cells, a process that forms the cornerstone of the incretin effect [14]. However, their influence on the counter-regulatory hormone glucagon differs significantly [1]:

GLP-1 potently suppresses glucagon secretion from pancreatic $\alpha$-cells when glucose levels are elevated, contributing to its glucose-lowering effect [15].

GIP, in contrast, can stimulate glucagon secretion, particularly when glucose levels are low or normal [16,17].

This functional divergence highlights their complementary roles. In healthy individuals, GIP is considered the dominant physiological incretin hormone, contributing more substantially to the total post-meal insulin response than GLP-1 [1,17,18].

#### 2.3.2. Gastrointestinal and Appetite Regulation

GLP-1 and GIP also exert markedly different effects on the gastrointestinal tract and central regulation of appetite.

GLP-1 significantly slows gastric emptying, which retards the delivery of nutrients into circulation and helps blunt postprandial glucose excursions [19,20]. At pharmacological concentrations, it also acts on the central nervous system to reduce appetite, decrease food intake, and promote satiety, which are key mechanisms underlying its efficacy in weight management [5].

GIP has no effect on gastric emptying [21]. While animal studies suggest a potential role for GIP in appetite regulation, this has not been confirmed in human studies, where its effects on food intake remain unsubstantiated [1,22].

Having established their functions in a healthy physiological state, it is crucial to examine how their roles are altered in the context of metabolic disease.

## 3. Pathophysiological Role in Type 2 Diabetes and Obesity

The therapeutic utility of incretin-based drugs stems directly from the altered function and response of the incretin system in metabolic diseases. The key pathophysiological changes observed in T2DM and obesity explain why GLP-1 became a successful drug target while GIP was initially overlooked.

### *3.1. The Diminished Incretin Effect in T2DM: The "GIP Resistance" Phenomenon*

A hallmark of T2DM is a significantly reduced incretin effect, meaning that oral glucose fails to elicit the robust insulin response seen in healthy individuals [23]. While GLP-1 secretion in T2DM is largely preserved or slightly diminished, reports on GIP secretion are inconsistent, with studies showing responses ranging from normal to somewhat increased [1]. The primary driver of this dysfunction is a profound blunting of the insulinotropic action of GIP [1,24]. This phenomenon, often

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referred to as "GIP resistance," means that even high concentrations of GIP fail to effectively stimulate insulin secretion from the diabetic pancreas [3,25].

In stark contrast, the ability of GLP-1 to stimulate insulin secretion is largely preserved in individuals with T2DM [3,4]. This crucial difference provides the foundational rationale for the development of GLP-1RAs as a highly effective therapeutic class; they effectively "replace" the lost incretin effect by activating a signaling pathway that remains functional in the disease state. The precise molecular mechanisms underlying this GIP resistance, and whether this state can be pharmacologically reversed to restore GIP's insulinotropic efficacy, remain areas of intense clinical investigation.

### *3.2. Impact on Adipose Tissue and Lipid Metabolism*

Beyond glucose control, incretin hormones play a role in lipid metabolism and adipose tissue function, where their effects diverge.

GIP has an anabolic role in white adipose tissue. It promotes the clearance of triglycerides from the circulation and their subsequent storage in adipocytes by enhancing the activity of lipoprotein lipase [1,26–29]. This function has fueled a long-standing debate about whether GIP may have a potentially "obesogenic" role by promoting fat deposition [30,31]. Crucially, while GIP's insulinotropic effect is blunted in T2DM, its actions on adipose tissue may be preserved, potentially contributing to altered lipid partitioning and fueling the debate over its role in the pathophysiology of metabolic disease.

GLP-1RAs, conversely, are associated with improvements in the overall lipid profile. Clinical studies have shown that they consistently reduce fasting total cholesterol, triglycerides (TG), and LDL-cholesterol while moderately increasing HDL-cholesterol [32].

These differing roles in metabolic disease set the stage for understanding their equally important and largely beneficial implications for cardiovascular health.

## 4. Cardiovascular Implications and Anti-Atherosclerotic Effects

Beyond their established benefits for glycemic and weight control, a major advantage of incretin-based therapies—particularly GLP-1RAs—is their proven ability to provide cardiovascular protection. The mechanisms responsible for this benefit are multifaceted, involving both indirect improvements in systemic risk factors and direct, vasoprotective effects on the arterial wall, as extensively reviewed by Wang et al. [13].

### *4.1. Clinical Evidence from Cardiovascular Outcome Trials (CVOTs)*

Large-scale, long-term cardiovascular outcome trials (CVOTs) have provided definitive evidence that several GLP-1RAs reduce the risk of major adverse cardiac events (MACE) in patients with T2DM [13]. Across multiple outcome trials, GLP-1RAs consistently lowered major adverse cardiovascular events. Liraglutide improved cardiovascular outcomes in LEADER, semaglutide showed significant stroke and MI reductions in SUSTAIN-6, and dulaglutide demonstrated similar benefits in REWIND.

LEADER Trial: Liraglutide demonstrated a 13% reduction in the risk of MACE (a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) and a significant 22% reduction in cardiovascular death compared to placebo [13,33].

SUSTAIN-6 Trial: Semaglutide led to a 26% risk reduction in the primary composite MACE outcome, driven by a notable decrease in nonfatal stroke and nonfatal myocardial infarction [13,34].

REWIND Trial: Dulaglutide showed a significant reduction in MACE, an effect largely driven by a 24% reduction in nonfatal stroke [13,35].

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*4.2. Indirect Cardioprotective Mechanisms: Modulating Systemic Risk Factors*

A substantial portion of the cardiovascular benefit derived from incretin-based therapies stems from their positive impact on systemic cardiometabolic risk factors.

Improvement in Dyslipidemia: As noted previously, GLP-1RAs and dual GIP/GLP-1RAs effectively improve lipid profiles by reducing levels of triglycerides and LDL-cholesterol while raising HDL-cholesterol, which helps mitigate a key driver of atherosclerosis [13,36]. This improvement extends to postprandial lipemia, where GLP-1RAs have been shown to blunt the rise in triglycerides and atherogenic chylomicron remnants, a key contributor to cardiovascular risk that is often overlooked in fasting lipid panels [37].

Reduction in Hypertension: Clinical trials have consistently shown that GLP-1RAs and the dual agonist tirzepatide significantly reduce systolic blood pressure (SBP) [38,39]. The underlying mechanisms are thought to involve direct renal effects that promote urinary sodium excretion (natriuresis) as well as vasodilation of blood vessels [40–43].

*4.3. Direct Anti-Atherosclerotic Mechanisms*

In addition to improving systemic risk factors, incretins exert direct protective effects on the vasculature that are independent of their metabolic actions. These cellular mechanisms, synthesized from recent reviews [13], directly counteract the key processes involved in the formation and progression of atherosclerotic plaques.

4.3.1. Preserving Endothelial Function

Incretin receptor agonists support vascular health by promoting endothelial nitric oxide synthesis, limiting inflammatory signaling, reducing lipid uptake by macrophages, and curbing maladaptive smooth-muscle proliferation—mechanisms that collectively contribute to plaque stability.

Promoting Vasodilation: They enhance the production of nitric oxide (NO), a potent vasodilator, by activating the enzyme endothelial nitric oxide synthase (eNOS) [44,45].

Reducing Inflammation and Oxidative Stress: They inhibit pro-inflammatory signaling pathways like NF-κB, thereby reducing the expression of adhesion molecules that recruit inflammatory cells to the vessel wall [46,47].

Decreasing Permeability: They strengthen the endothelial barrier, reducing the infiltration of lipoproteins and inflammatory cells, and inhibit endothelial cell apoptosis [48–50].

4.3.2. Modulating Macrophage Activity and Plaque Inflammation

IRAs intervene at critical steps of plaque development by:

Inhibiting Foam Cell Formation: They reduce the formation of macrophage-derived foam cells—a hallmark of early atherosclerotic lesions—by inhibiting the uptake of oxidized LDL (ox-LDL) and up-regulating cholesterol efflux transporters like ABCA1 that remove excess cholesterol from cells [51–54].

Attenuating Plaque Inflammation: They promote the polarization of macrophages toward an anti-inflammatory M2 phenotype, which is associated with tissue repair, rather than the pro-inflammatory M1 phenotype that drives plaque progression [55–57].

4.3.3. Stabilizing Vascular Smooth Muscle Cells (VSMCs)

GLP-1RAs contribute to the stability of advanced atherosclerotic plaques, making them less prone to rupture, by:

Suppressing Abnormal VSMC Behavior: They inhibit the abnormal proliferation, migration, and phenotypic switching of VSMCs from a stable contractile state to an unstable synthetic state [58,59].

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Strengthening the Fibrous Cap: They increase the collagen content within the plaque's protective fibrous cap while reducing the expression of matrix metalloproteinases (MMPs), which are enzymes that degrade the cap and increase rupture risk [60,61].

This deep understanding of incretin biology has paved the way for an evolution in therapeutic strategies, from targeting single receptors to harnessing dual-hormone action.

## 5. The Therapeutic Landscape: From GLP-1RAs to Dual and Triple Agonists

The deepening understanding of incretin pathophysiology has directly fueled an evolution in drug development. This journey has progressed from leveraging the benefits of a single hormone to unlocking the superior potential of co-agonism, fundamentally changing the standards of care for T2DM and obesity.

### *5.1. The Established Role of GLP-1 Receptor Agonists*

For over a decade, GLP-1RAs have become a cornerstone in the management of T2DM and obesity. Their success is built on a solid foundation: a preserved insulinotropic effect in T2DM, robust glucose-lowering efficacy, significant weight reduction benefits, and proven cardiovascular protection in large-scale clinical trials [62–64]. Their established profile has made them a preferred choice for patients with T2DM and co-existing cardiovascular disease or obesity.

### *5.2. The Re-emergence of GIP: Synergies in Dual GIP/GLP-1 Receptor Agonism*

The therapeutic landscape was transformed by the arrival of tirzepatide, the first-in-class dual GIP/GLP-1 receptor agonist. Clinical trial data have shown that tirzepatide achieves unprecedented efficacy, with average HbA1c reductions of approximately 2% and body weight reductions often exceeding 10 kg—results that are superior to those seen with even the most potent selective GLP-1RAs [6,7,36].

These powerful findings have challenged the long-held view that GIP possesses no therapeutic value in T2DM [1]. The superior outcomes strongly suggest an additive or synergistic interaction between GIP and GLP-1 receptor signaling pathways [65,66]. This has sparked a new wave of research aimed at elucidating the precise mechanisms by which GIP agonism, in the context of GLP-1 receptor activation, overcomes the apparent GIP resistance seen in T2DM to produce these enhanced metabolic benefits.

## 6. Conclusions and Future Directions

Insights into incretin physiology have shifted the therapeutic landscape from single-receptor approaches to multi-agonist strategies that integrate metabolic and cardiovascular regulation. While GLP-1 has proven to be a critical pharmacological tool, with its actions on gastric emptying, appetite suppression, and a preserved insulinotropic effect in T2DM forming the basis of a highly successful class of therapeutics, GIP stands as the dominant physiological incretin in healthy individuals. The success of GIP/GLP-1 receptor co-agonists has reconciled this dichotomy, confirming that harnessing the synergy between these two pathways can unlock a new therapeutic frontier with metabolic benefits that surpass what can be achieved by targeting GLP-1 alone.

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## Abbreviations

The following abbreviations are used in this manuscript:

| Abbreviation | Full Term |
|---|---|
| ACAT-1 | Acyl-CoA:cholesterol acyltransferase-1 |
| ApoE−/− | Apolipoprotein E knockout mouse |
| BMI | Body mass index |
| BMSC | Bone marrow stromal cell |
| CVD | Cardiovascular disease |
| CVOT | Cardiovascular outcome trial |
| eNOS | Endothelial nitric oxide synthase |
| GIP | Glucose-dependent insulinotropic polypeptide |
| GIPR | Glucose-dependent insulinotropic polypeptide receptor |
| GLP-1 | Glucagon-like peptide-1 |
| GLP-1RA | GLP-1 receptor agonist |
| HFpEF | Heart failure with preserved ejection fraction |
| IRA | Incretin receptor agonist |
| LDL | Low-density lipoprotein |
| MACE | Major adverse cardiovascular events |
| MMP-9 | Matrix metalloproteinase-9 |
| NO | Nitric oxide |
| NT-proBNP | N-terminal pro–B-type natriuretic peptide |
| ox-LDL | Oxidized low-density lipoprotein |
| PKA | Protein kinase A |
| SBP | Systolic blood pressure |
| T2DM | Type 2 diabetes mellitus |
| TG | Triglycerides |
| TNF-$\alpha$ | Tumor necrosis factor-alpha |
| VLDL | Very low-density lipoprotein |

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