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# Glucose-dependent Insulinotropic Polypeptide in Type 2 Diabetes Mellitus: Advancements in Treatment and Clinical Applications

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## Abstract

Type 2 diabetes mellitus (T2DM) is a major global health challenge, primarily driven by the body's impaired ability to effectively utilize insulin. The incretin hormones glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) play essential roles in regulating glucose metabolism. GIP, an intestinal hormone, exerts a wide range of physiological effects, including the promotion of insulin secretion following meals and the stimulation of glucagon release under euglycemic and hypoglycemic conditions. Moreover, GIP facilitates triacylglycerol absorption in adipose tissue and reduces bone resorption. Numerous GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists have been developed to harness these hormonal benefits for T2DM treatment. Some of these therapies have demonstrated notable success in managing weight and reducing cardiovascular disease risk. A deeper understanding of cellular and molecular pathways underlying these effects holds promise for developing next-generation incretin-based therapies with enhanced efficacy and fewer adverse effects. Although numerous studies have targeted the GLP-1 receptor for T2DM management, the therapeutic potential of the GIP receptor (GIPR) remains under investigation. Despite emerging evidence linking GIP to key mechanisms in T2DM pathophysiology, its full clinical utility has yet to be determined. This article explores GIP's potential as a therapeutic target for T2DM, examining its role in regulating pancreatic α- and β-cell function, adipose tissue dynamics, bone remodeling, lipid metabolism, cardiovascular disease, and kidney disorders. It also evaluates the therapeutic potential of both GIPR agonists and antagonists, illustrating how these approaches may enhance the understanding of GIP's relevance in T2DM management. Additionally, this discussion addresses challenges associated with translating GIP-targeted therapies into clinical practice, offering insights into overcoming existing barriers and advancing more comprehensive treatment options.

**Key Words: Glucose-dependent insulinotropic polypeptide; glucagon-like peptide-1; type 2 diabetes mellitus; β-cell function; weight reduction**

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## 1. Introduction

Incretin hormones are crucial for stimulating insulin secretion after meals, thereby regulating glucose homeostasis. These hormones enhance glucose tolerance by promoting insulin activity, facilitating the clearance of approximately 80% of ingested glucose[1]. The main incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). GLP-1, a 30-amino acid peptide, is synthesized by enteroendocrine L cells in the distal ileum and colon, whereas GIP, a 42-amino acid hormone, is secreted by K cells in the upper intestine, predominantly in the duodenum and jejunum. GIP secretion is stimulated by the consumption of food, especially carbohydrates and fats[2]. The physiological effects of GIP and GLP-1 are transient because of their rapid degradation and inactivation caused by the enzymatic activity of dipeptidyl peptidase 4 (DPP4) and subsequent renal clearance. After food consumption, GLP-1 and GIP are rapidly secreted, with evidence indicating that neural mechanisms affect their release. Both hormones stimulate insulin secretion from pancreatic β cells in a glucose-dependent manner. In addition to its insulinotropic[3] and glucagonotropic[4] functions in the pancreas, GIP has been implicated in lipid metabolism[5] and bone remodeling[6]. Advances in research and development have led to the introduction of incretin-based medications, primarily targeting GLP-1 and GIP pathways. Studies have reported the cardiovascular and renal benefits of specific incretin-based treatments, reinforcing their integral role in modern diabetes management.

The effect of incretin is markedly decreased in individuals with type 2 diabetes mellitus (T2DM) because of a substantial reduction in the sensitivity of β cells to GIP[7] and a decline in GLP-1 secretion following food intake[8,9]. The clinical utility of GIP has been limited by its unfavorable pharmacokinetic properties, the less potent biological effects of native GIP, and primarily, the decreased response of β cells to GIP observed in patients with poorly controlled T2DM[9,10]. However, recent findings challenge this perspective. Emerging evidence indicates that resistance to GIP can be reversed, and its insulinotropic function can be restored through improved glycemic management[11]. Moreover, sulphonylurea treatment, which induces ATP-sensitive potassium ($K_{ATP}$) channel closure, enhances the insulinotropic effect of GIP in these patients[12]. Studies in diabetic animal models have demonstrated that GIP receptor (GIPR) desensitization is attributable to hyperglycemia-induced alterations in $K_{ATP}$ channel activity instead of an inherent genetic defect[11-13]. Decreased GIPR expression may further contribute to this impaired response[14]. Recent advancements in GIPR agonists with improved bioavailability and dual receptor agonists targeting both GLP-1 receptors (GLP-1Rs) and GIPRs have demonstrated superior efficacy in glucose regulation and weight reduction compared with GLP-1R agonists[15,16]. These findings suggest that enhancing GIP signaling, particularly in combination with other glucose-lowering therapies and DPP4-resistant GIP analogs, represents a promising strategy for T2DM treatment[15].

Initially regarded solely as an incretin hormone, GIP has become a potential therapeutic target with broader metabolic implications, prompting extensive research into its diverse physiological effects. Preclinical studies have suggested that both GIPR agonists and antagonists provide comparable metabolic benefits, presenting a paradox regarding which approach may offer superior clinical outcomes[17]. Further investigation is required to determine how these opposing strategies targeting the same receptor will perform in clinical settings. Both approaches may ultimately prove successful[17].

This review explores the therapeutic potential of GIP in the treatment of T2DM. It provides a comprehensive analysis of GIP's role in regulat-

ing pancreatic α- and β-cell function, adipose tissue metabolism, bone remodeling, lipid metabolism, cardiovascular disease, and kidney disorders. Furthermore, this review evaluates the significance of both GIPR agonists and antagonists in advancing the understanding of GIP-mediated pathways in T2DM management. In addition, this review examines the challenges associated with integrating GIP-targeted therapies into clinical practice and proposes strategies to address these barriers.

## 2. GIP and Metabolic Diseases

GIP was initially identified in porcine intestines for its ability to inhibit gastric acid secretion[18], leading to its designation as gastric inhibitory polypeptide. However, subsequent research revealed its insulinotropic properties, prompting the adoption of its current name, GIP[19]. GIP exerts its effects by binding to a specific G-protein-coupled receptor expressed in various tissues, including the pancreas, adipose tissue, bone, heart, and brain[2]. Although the full extent of its physiological functions remains incompletely understood, studies have demonstrated its involvement in bone resorption[20], cell proliferation[21], locomotor activity[22], GLP-1 release[23], and glucocorticoid secretion[24]. These findings indicate the potential therapeutic applications of GIP. In addition, GIP directly benefits pancreatic β cells by promoting cell growth and survival[25,26], stimulating proinsulin gene activity[27], and facilitating stem cell differentiation into insulin-producing cells[28]. In addition to its pancreatic effects, GIP reduces the glucose level by suppressing hepatic glucose production and increasing glucose uptake and fatty acid synthesis[29-31]. The glucose-dependent insulinotropic activity of GLP suggests its potential advantage in T2DM management because it reduces the risk of hypoglycemia associated with other insulin-releasing drugs[3]. The major physiological roles of GIP in T2DM are summarized in Table 1.

Table 1. Major physiological roles of glucose-dependent insulinotropic polypeptide in type 2 diabetes mellitus

| Physiological benefits | Description | Reference(s) |
|---|---|---|
| Insulinotropic effects | • Enhances insulin secretion by binding to pancreatic β-cell receptors, increasing intracellular cAMP levels, activating PKA and EPAC2 pathways, raising calcium ion concentrations, modulating ion channels, and promoting insulin granule release. | 35-41 |
| Protective effects of β cells | • Increases osteopontin transcription, aiding β-cell proliferation and preventing β-cell death by inhibiting nitric oxide synthase activity.<br>• Enhances β-cell survival through activation of the PI3K-PKB/Akt pathway, which influences Forkhead transcription factors and Bax gene transcription.<br>• Enhances β-cell survival through the regulation of ASK1 via Akt pathway activation, which suppresses p38 and JNK activity.<br>• Induces vasoconstriction in islet cells, providing protective benefits during hyperglycemic conditions. | 43<br>44<br>45<br>46 |
| Glucagonotropic effects | • Stimulates glucagon secretion in both euglycemic and hypoglycemic states, affecting both healthy individuals and those with T2DM.<br>• Stimulates pancreatic islet α-cells, increasing glucagon secretion in a dose-dependent manner in vitro.<br>• Stimulates glucagon release only at low glucose levels, demonstrating glucose-dependent GIPR activity in pancreatic islet α-cells. | 4,47<br>47<br>51 |
| Adipose tissue | • Increases triglyceride clearance, reduces triglyceride excursions following an intraduodenal lipid load, and enhances LPL activity, resulting in greater triglyceride synthesis in WAT. | 55 |

| | | |
|---|---|---|
| | • Facilitates circulating triglyceride and free fatty acid removal, along with enhanced triglyceride absorption in adipose tissue, and establishes GIP as a key hormonal regulator of the body's postprandial triglyceride response. | 5,56,57 |
| | • Enhances glucose uptake by increasing insulin sensitivity in adipocytes. | 58 |
| | • Promotes energy storage by driving the expansion of WAT through mechanisms such as adipocyte hypertrophy and preadipocyte differentiation, primarily governed by de novo adipogenesis. | 60 |
| | • Receptor activation may increase the lipid-buffering capacity of WAT, potentially mitigating lipid spillover under conditions of excess energy intake. | 55 |
| | • Prolonged receptor activation increases whole-body insulin sensitivity and reduces liver lipid accumulation in the model of insulin resistance. | 65,66 |
| | • Prevents the accumulation of lipids outside adipose tissue and reduces liver fat buildup. | 69 |
| Bone system | • Reduces both the differentiation and bone resorptive activity of human osteoclasts. | 70 |
| | • Reduces the gene expression of specific osteoclast markers and number of newly formed osteoclasts. | 72 |
| | • Stimulates bone-related parameters, including alkaline phosphatase, P1NP, and cell viability, differ among these cell lines. | 73 |
| | • Reduces apoptosis in both human bone marrow-derived mesenchymal stem cells and osteoblastic Saos-2 cells. | 20,74 |
| | • Improves bone strength in those with prediabetes and prevents the decline in bone strength in those with insulinopenic diabetes and estrogen deficiency. | 75 |
| | • Enhances cortical bone mechanical properties, promotes mineralization, and improves collagen maturity. | 76 |
| | • Lowers CTX level in both healthy individuals and those with T1DM without significantly affecting P1NP. | 75 |
| | • Increases P1NP and osteocalcin levels in young, healthy individuals, suggesting not only inhibition of bone resorption but also support of bone formation. | 79 |
| | • Reduces bone resorption and does so to a greater extent when combined with GLP-1. | 80 |
| Central nervous system | • Reduces energy consumption and provides additional metabolic benefits by acting on brain-centered mechanisms. | 55 |
| | • Elevated level persistently reduces DIO and enhances insulin sensitivity by lowering caloric intake through a direct role in the hypothalamic ventromedial nucleus. | 65 |
| | • Amplification of GLP-1 activity by improving its interaction with anorexigenic neuronal groups in the mediobasal hypothalamus. | 55 |
| | • GIPR-expressing cells in the arcuate nucleus are sensitive to neuropeptides associated with feeding behavior. and activating these GIPR-positive cells can suppress calorie intake. | 55,82 |
| | • GIPR agonists consistently reduce body weight by limiting caloric consumption, potentially through mechanisms involving the recruitment of neuropeptide signaling pathways. | 85,86 |
| Cardiovascular system | • GIPR activation induces the expression of proatherosclerotic factors, such as endothelin-1 and osteopontin, and exerts antiatherosclerotic effects by promoting nitric oxide secretion and inhibiting foam cell formation. | 92 |
| | • Increases the survival rate during experimentally induced ischemia by reducing GIP-mediated hormone-sensitive lipase activation and subsequently reducing intramyocardial triglyceride levels. | 88 |
| | • Receptor activation produces anti-inflammatory benefits, such as reducing inflammation in adipose tissue, lowering blood IL-6 levels, and enhancing both serum adiponectin levels and its expression in adipose tissue. | 93 |

| | | |
|---|---|---|
| | • Reduces various proinflammatory cytokines, including IL-1β, IL-6, and TNF-α, and increases the adiponectin level.<br>• Increases levels of circulating proinflammatory markers, including VCAM-1, MCP-1, IL-6, and IL-1β.<br>• Stimulates lipolysis under conditions characterized by a catabolic nutritional state and low insulin concentrations. | 94<br>92<br>92 |
| Renal system | • Alleviates the impact of diabetic nephropathy by reducing proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α, and increasing adiponectin levels.<br>• Exerts protective effects on renal function indirectly by reducing atherosclerosis through promoting nitric oxide production, enhancing insulin sensitivity in WAT, inhibiting vascular smooth muscle cell proliferation, and reducing inflammatory responses in adipocytes, monocytes, and macrophages.<br>• Exerts protective effects on renal function other indirectly by (a) interacting with brain receptors to curb food intake and supporting weight loss efforts; (b) increasing insulin sensitivity and improving blood flow in subcutaneous WAT, thereby facilitating lipid storage and reducing inflammatory immune cell infiltration; (c) enhancing insulin sensitivity and preventing the accumulation of ectopic lipids in skeletal muscle; and (d) reducing hyperglycemia and dyslipidemia at a systemic level. | 94<br>102<br>93 |

Abbreviations: ASK1, apoptosis signal-regulating kinase 1; cAMP, cyclic adenosine monophosphate; CNS, central nervous system; CTX, C-terminal telopeptide; DIO, diet-induced obesity; EPAC2, exchange protein directed via cAMP2; GIP, glucose-dependent insulinotropic polypeptide; GIPR, GIP receptor; GLP-1, glucagon-like peptide-1; IL, interleukin; LPL, lipoprotein lipase; MCP-1, monocyte chemoattractant protein 1; P1NP, procollagen type 1 N-terminal propeptide; PI3K-PKB, phosphoinositide-3-kinase-protein kinase B; PKA, protein kinase A; T1DM, type 1 diabetes mellitus; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-alpha; VCAM-1, vascular cell adhesion molecule-1; WAT, white adipose tissue.

## 2.1 Effects of GIP on the Pancreas

### 2.1.1 Insulinotropic Effect

For more than 40 years, GIP has been implicated in the development and progression of T2DM[32,33]. Early studies have demonstrated that GIP (1-42) enhances insulin secretion during hyperglycemia in humans[34]. By the 1990s and 2000s, studies have elucidated molecular mechanisms underlying GIP-mediated glucose regulation, revealing its role in insulin secretion through complex signaling pathways[35-37]. GIP exerts its insulinotropic effect by binding to its receptor on pancreatic β cells, initiating a cascade of intracellular signaling events. Receptor activation increases the cyclic adenosine monophosphate (cAMP) level, stimulating protein kinase A (PKA) and triggering the exchange proteins directly activated by cAMP 2 (EPAC2)/cAMP pathway[38]. This signaling cascade enhances insulin release by increasing cytosolic calcium ion levels, modulating ion channel activity, and promoting insulin granule exocytosis. PKA phosphorylates the SUR1 subunit, leading to the closure of $K_{ATP}$ channels and subsequent membrane depolarization[39]. In addition, PKA interacts with phosphoinositide 3-kinase to inhibit potassium channels that suppress insulin secretion, thereby prolonging action potentials. Membrane depolarization facilitates the opening of voltage-gated calcium channels, further increasing intracellular calcium levels. The increased calcium level stimulates additional calcium release from internal stores and promotes insulin granule fusion with the plasma membrane, leading to increased insulin release[38]. This cascade also enhances mitochondrial adenosine triphosphate (ATP) production, reinforcing $K_{ATP}$ channel closure and further depolarization[40]. EPAC2 plays a crucial role in maintaining insulin production by increasing insulin granule density and synthesis[41]. The coordinated actions of PKA and EPAC2 are essential for GIP-induced insulin secretion.

### 2.1.2 Protective Effects of β Cells

Beyond its primary role in stimulating insulin secretion from pancreatic β cells, GIP plays a critical role in protecting pancreatic islet cells by promoting their growth and enhancing their survival[42]. In human islets, GIP upregulates osteopontin transcription, a protein that is often elevated in patients with T2DM and has been implicated in the development of atherosclerotic plaques and diabetes-related complications[43]. Osteopontin supports β-cell proliferation and prevents apoptosis by inhibiting nitric oxide synthase activity. Notably, islets with a weak insulinotropic response to GIP have lower than normal osteopontin levels, indicating a link between GIP-osteopontin dysfunction and T2DM pathogenesis. GIP's regulatory effect on osteopontin expression follows a bell-shaped dose-response curve and is primarily observed under low glucose levels[43].

A key mechanism through which GIP enhances β-cell survival involves the activation of the phosphoinositide-3-kinase/protein kinase B (PI3K-PKB)/Akt signaling pathway, which regulates Forkhead transcription factors and *Bax* gene transcription[44]. The Forkhead box protein O (FOXO) family, which contains phosphorylation sites for PKB, plays a critical role in modulating proapoptotic gene expression. Lower nuclear levels of FOXO proteins, such as FOXO1, suppress the expression of apoptotic genes. Studies on INS-1 cells exposed to glucolipotoxicity have demonstrated an increase in nuclear FOXO1 levels, which facilitates apoptosis by binding to the *Bax* gene promoter. However, GIP treatment enhances PI3K-PKB signaling, leading to increased FOXO1 phosphorylation, decreased binding to apoptotic target elements, and suppression of *Bax* gene expression[44], thereby preventing apoptosis. Beyond its effects on FOXO1 transcriptional activity, PKB/Akt pathway activation also inhibits other apoptotic pathways, including p38 MAPK and Jun N-terminal kinase (JNK)[45]. GIP enhances β-cell survival by modulating apoptosis signal-regulating kinase 1 (ASK1) through Akt pathway activation, which further suppresses p38 MAPK and JNK activity.[45] This mechanism effectively counteracts staurosporine-induced apoptosis in islet cells. The antiapoptotic effects of GIP were abolished by an adenylate cyclase inhibitor, highlighting the critical role of upstream cAMP signaling in preventing mitochondrial apoptosis pathways[45]. Although GIP directly promotes β-cell survival through islet GIPRs, evidence suggests an additional protective mechanism where GIPRs in endothelial blood vessel layers enable GIP to constrict vessels, thereby reducing blood flow to rodent islet cells in vivo. This effect may confer a protective advantage under hyperglycemic conditions by mitigating the excessive islet blood flow observed in diabetes[46].

### 2.1.3 Glucagonotropic Effect

Beyond its insulinotropic effects on β cells, GIP plays a critical role in regulating glucagon secretion by pancreatic α cells. GIP enhances glucagon secretion in a glucose-dependent manner. During hypoglycemia, intravenous administration of GIP activates GIPRs and intracellular signaling pathways, leading to increased glucagon release in humans[47]. By contrast, under hyperglycemic conditions, GIP augments glucose-stimulated insulin secretion without inducing a glucagonotropic response[4]. A human study suggested the existence of a glycemic threshold, ranging from 99 to 108 mg/dL, below which GIP primarily promotes glucagon secretion[4]. By integrating its dual insulinotropic and glucagonotropic functions, GIP contributes to glucose homeostasis, mitigating hyperglycemia following excessive glucose intake and preventing reactive hypoglycemia. This protective mechanism is particularly relevant after lipid-rich meals, where fluctuations in glucose levels can be pronounced. The ability to counteract reactive hypoglycemia is evolutionarily vital given the reliance of central nervous tissue on stable blood glucose levels[48].

The GIPR is present in the 3 primary endocrine cell types of the pancreatic islet: α-cells, β-cells, and δ-cells[49]. Evidence supporting GIPR activation in α-cells stimulating glucagon release remains limited, with some findings from αTC1 cells[47] and rat pancreas models using a GIPR antagonist to demonstrate preventable secretion[50]. This finding indicates that GIP directly affects α-cells, but studies on α-cell GIPR knockouts are lacking. In animal studies, GIP stimulated glucagon only under low glucose conditions, whereas no such effect was observed under high glucose conditions, indicating glucose-dependent GIPR activity in α-cells[51]. These findings suggest that unlike in β-cells, where higher glucose increases insulin secretion through incretin receptors, low glucose enhances the effect of GIP on glucagon in α-cells. Nevertheless, the primary difference is in how GIP affects α-cells and β-cells. In α-cells, GIP more effectively promotes glucagon secretion when glucose levels drop. By contrast, in β-cells, GIP promotes insulin secretion when glucose levels rise. Higher glucose levels boost β-cell activity, whereas lower glucose levels increase α-cell activity. This indicates that the function of GIPR in these cells depends more on the cells' readiness than on glucose levels[52]. The signaling mechanisms of GIPR may exhibit divergent characteristics in α-cells compared with β-cells[52]. This suggests that GIPR action depends more on cell readiness than glucose levels alone, possibly signaling through cAMP/PKA pathways, similar to β-cells[53]. GIPR might strengthen active α-cells at low glucose levels because elevated glucose increases β- and δ-cell activity, suppressing α-cells through interactions, whereas GIP doses promote the release of somatostatin from δ-cells under high glucose levels. Somatostatin inhibits gut GIP secretion and has mixed effects on glucagon secretion. Thus, at high glucose levels, the inhibitory influence of neighboring cells may suppress α-cell GIPR activity, preventing GIP-induced glucagon secretion[52].

## 2.2 Effects of GIP on Adipose Tissue

GIPRs are found in notably high concentrations in adipose tissue[54], suggesting their critical role in regulating energy storage and lipid metabolism. In T2DM, the lipid-buffering capacity of white adipose tissue (WAT) becomes impaired when its storage threshold is exceeded. This dysfunction is characterized by a diminished ability to suppress free fatty acid release in response to insulin, decreased adipose tissue perfusion, and impaired LPL recruitment[55]. Animal studies have indicated that GIP facilitates lipid disposal by enhancing triglyceride clearance, reducing postprandial triglyceride excursions following an intraduodenal lipid load, and increasing both LPL activity and triglyceride synthesis in WAT[55]. In humans, GIP promotes the removal of circulating triglycerides and free fatty acids while enhancing triglyceride absorption in adipose tissue, serving as a key hormonal regulator of postprandial lipid metabolism[5,56,57]. Moreover, studies have revealed that GIP enhances glucose uptake by increasing insulin sensitivity in adipocytes[58]. Similarly, tirzepatide, a dual GIPR and GLP-1R agonist, has been reported to improve insulin sensitivity and facilitate glucose disposal in the WAT of mice lacking *Glp-1r*[59]. These findings further support GIP's direct role in adipose tissue regulation.

GIP promotes energy storage by facilitating the expansion of WAT through adipocyte hypertrophy and preadipocyte differentiation, processes primarily driven by de novo adipogenesis[60]. Although GIPR expression is initially low in preadipocytes, it increases during differentiation and synchronizes with markers essential for adipocyte maturation[61,62]. This expression is regulated by peroxisome proliferator-activated receptor γ (PPARγ), a key modulator of WAT development[63]. PPARγ ligands upregulate GIPR expression, whereas PPARγ knockdown

leads to its reduction[63,64]. In addition, GIP facilitates adipocyte differentiation[61] because the disruption of GIPR expression impairs this process[62]. These findings jointly suggest that GIPR activation enhances the lipid-buffering capacity of WAT, potentially reducing lipid spillover under conditions of excess energy intake[55]. However, further research is required to confirm this hypothesis.

Pharmacological and genetic studies have suggested that sustained GIPR activation enhances whole-body insulin sensitivity and reduces hepatic lipid accumulation in models of insulin resistance[65,66]. These metabolic improvements are closely associated with healthier WAT function, characterized by decreased inflammation, improved lipid-storage gene regulation, increased triglyceride storage capacity, and insulin-sensitizing adipokine secretion[65,66]. Although some of these effects may be attributed to GIP's role as an incretin hormone, its direct actions on adipocytes likely play a major role in enhancing WAT function and insulin sensitivity[55].

In humans, fasting plasma GIP levels are associated with increased visceral fat accumulation instead of subcutaneous fat distribution, independent of insulin levels[67]. Similarly, in the Japanese population, elevated plasma GIP levels were associated with genetic variations that lead to increased visceral obesity and high circulating triglycerides[68]. Another study demonstrated that GIP infusion lowers the level of circulating nonesterified fatty acids while increasing the level of triglycerides, thereby promoting fat storage in adipose tissue. These findings suggest that GIP helps prevent ectopic lipid accumulation and reduce hepatic fat buildup[69]. Additionally, infusion of the GIPR antagonist GIP(3-30)NH2 in humans reduced GIP-induced triglyceride deposition in adipose tissue. This observation further supports GIP's role in regulating adipocyte function and lipid metabolism in humans[57].

## 2.3 Effects of GIP on Bone

GIPR expression has been identified in both human[70] and rodent osteoclasts and osteoblasts[71]. Several studies have demonstrated that GIP modulates bone cell activity and facilitates bone remodeling. A GIP analog was determined to inhibit both the differentiation and bone resorptive activity of human osteoclasts[70]. Furthermore, treatment with a GIP analog reduced the expression of specific osteoclast markers and the formation of new osteoclasts[72], suggesting its direct regulatory effect on human osteoclasts. GIP also exerts anabolic effects on bone, as evidenced by its effect on alkaline phosphatase, procollagen type 1 N-terminal propeptide (P1NP), and cell viability, although these effects differed between cell lines[73]. Furthermore, GIP reduced apoptosis in both human bone marrow-derived mesenchymal stem cells and osteoblastic Saos-2 cells[20,74]. Additional evidence supporting GIP's role in bone metabolism comes from in vivo studies. Administration of a GIP analog not only improved bone strength in prediabetic mice but also prevented the decline in bone strength observed in insulinopenic diabetic and estrogen-deficient rats[75]. Moreover, GIP promotes mineralization, enhances collagen maturity, and is beneficial to the mechanical properties of cortical bone in rat models[76]. These preclinical findings suggest that GIP exerts antiresorptive effects on bone and potentially enhances bone formation, indicating a possible decoupling of bone resorption and formation processes. Further investigation is needed to elucidate mechanisms through which GIP regulates bone cell activity and the interplay between bone formation and resorption.

In humans, endogenous GIP accounts for up to 25% of the reduction in bone resorption following a meal, whereas endogenous GLP-1 exerts no significant effect[77]. GIP infusion reduces the level of C-terminal telopeptide, a marker of bone resorption, in both healthy individuals and those with type

1 diabetes mellitus without substantially affecting P1NP), a bone formation marker[75]. This response is reversed by a selective GIPR antagonist in men[78]. Another study reported that GIP increased P1NP and osteocalcin levels in young, healthy individuals, suggesting that it not only inhibits bone resorption but also promotes bone formation[79]. Moreover, both glucose intake and GIP infusion lower parathyroid hormone (PTH) levels. However, GIP suppresses bone resorption even in individuals with hypoparathyroidism, indicating a PTH-independent mechanism[75]. These findings suggest a rapid effect of GIP on bone remodeling, with the potential to increase bone mass if this effect is sustained over time. Although current evidence supports the immediate antiresorptive and potentially anabolic properties of GIP, its long-term influence on bone remodeling, bone quality, and bone mineral density remains uncertain because clinical trials have yet to provide definitive conclusions[75]. The combined use of GIP and GLP-1 enhanced bone resorption suppression more effectively than the use of either hormone alone[80]. This finding suggests that dual agonists targeting both receptors, which are currently being developed for T2DM, can provide the dual benefit of reducing bone loss and promoting weight loss[75].

## 2.4 Effects of GIP on the Central Nervous System

GIP is increasingly recognized for its broader role in metabolic regulation, extending beyond lipid metabolism in peripheral tissues to affecting key processes in the central nervous system (CNS). A study reported that GIP reduces energy intake and provides additional metabolic benefits by acting through brain-centered mechanisms[55]. GIPR is widely expressed throughout the CNS[81], particularly in regions associated with energy regulation[82]. Although research remains limited, evidence suggests that GIP crosses the blood-brain barrier to access these regulatory sites[81]. In metabolic diseases, GIPR activation has been implicated in promoting weight loss. In transgenic mouse models, persistently elevated GIP levels have been shown to reduce diet-induced obesity and improve insulin sensitivity by lowering caloric intake[65]. This model exhibited increased GIP expression in the hypothalamic ventromedial nucleus, suggesting a direct role in central energy regulation[65]. Consistent with this finding, GIPR is expressed in the hypothalamus of both humans and mice. Studies using GIPR reporter mice have localized GIPR expression to energy-regulating centers, including the arcuate nucleus (ARC), paraventricular nucleus, and dorsomedial hypothalamic nuclei. Within the hypothalamus, GIPR is present in cells that either lack GLP-1R or co-express both receptors in both humans and mice[82]. This distribution raises the possibility of synergistic interactions between GIP and GLP-1, which may occur through the independent activation of their respective receptors on separate cells, coactivation of both receptors on the same cell (generating a distinct signal), or integration of downstream signaling pathways[55]. Further evidence suggests that GIP and GLP-1 activate distinct neuronal populations involved in appetite suppression[83]. GIPR expression in nonneuronal cells of the mediobasal hypothalamus[82], including oligodendrocytes, may enhance GLP-1 activity by facilitating access to anorexigenic neurons in the ARC[84]. This suggests that GIP could potentiate GLP-1-mediated appetite suppression by improving its interaction with these neuronal populations[55]. Notably, GIPR-expressing cells in the ARC possess receptors sensitive to neuropeptides involved in appetite regulation. These neurons are activated by ligands that affect feeding behavior[55], and chemogenetic studies have confirmed that the activation of GIPR-positive cells suppresses caloric intake[82]. Both the central and peripheral administration of GIPR agonists have consistently been reported to reduce body weight by limiting caloric

consumption[85], potentially through mechanisms involving the recruitment of neuropeptide signaling pathways[86]. Beyond the hypothalamus, GIPR is also expressed in brainstem nuclei that mediate food intake in response to gut-derived satiety signals[55,82]. However, whether GIP directly regulates feeding behavior within this region remains unclear.

An important aspect of GIP's therapeutic potential is its ability to mitigate adverse effects commonly associated with GLP-1RA therapy. Nausea, a frequent side effect of GLP-1RAs, often limits their widespread clinical use. GIPR activation may counteract aversive responses triggered by intestinal peptides such as peptide YY and chemotherapy agents, such as cisplatin[87]. This finding supports the potential for combined GIP and GLP-1 therapies not only to enhance weight loss but also to improve treatment tolerability, thereby expanding the clinical applicability of GLP-1RAs[55]. Emerging evidence suggests that GIP promotes weight loss through multiple mechanisms, including the direct inhibition of caloric intake through CNS-mediated pathways, amplification of the anorectic effects of GLP-1, and mitigation of nausea to improve drug adherence. These combined effects indicate the critical role of GIP role in optimizing metabolic therapies and broadening their clinical utility[55].

## 2.5 Effects of GIP on Cardiovascular Disease

Although less extensively studied, GIP may affect the cardiovascular system through its effects on cardiomyocytes[88], endotheliocytes[89], and adipocytes[90]. GIPR is expressed on immune cells circulating in the bloodstream and is distributed throughout the vascular system, including endothelial cells lining blood vessels and cardiac tissues[91]. Given the overlap in intracellular signaling pathways, insights gained from pharmaceutical agents targeting GLP-1 may provide valuable perspectives on the potential vascular effects of GIP. GIPR activation induces the expression of proatherosclerotic factors, such as endothelin-1 and osteopontin, while simultaneously exerting anti-atherosclerotic effects by promoting nitric oxide secretion and inhibiting foam cell formation[92]. However, the importance of these mechanisms remains uncertain. The causal relationship between circulating GIP levels and the expression of endothelin-1 and osteopontin in human cohorts is not well established, raising questions about whether these factors contribute meaningfully to atherosclerosis progression.

In GIPR knockout mice, studies have reported decreased interstitial fibrosis and left ventricular cardiomegaly, despite adverse outcomes following myocardial infarction. Although the survival rate remained unchanged after experimentally induced myocardial infarction, survival markedly improved during experimentally induced ischemia. This cardioprotective response appears to be mediated by decreased GIP-driven activation of hormone-sensitive lipase, leading to lower intramyocardial triglyceride levels[88]. GIPR activation has demonstrated anti-inflammatory benefits, including decreased adipose tissue inflammation, lower circulating interleukin (IL)-6 levels, and increased serum adiponectin levels and adiponectin expression in adipose tissue. By contrast, GIPR inhibition results in elevated IL-6 levels in both blood and adipose tissue as well as increased gingival inflammation[93]. In murine models, daily GIP administration reduces proinflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor-alpha (TNF-α), while simultaneously increasing adiponectin levels, an anti-inflammatory adipokine with insulin-sensitizing properties[94]. Human studies have reported an association of elevated fasting GIP levels with increased circulating proinflammatory markers, including vascular cell adhesion molecule 1, monocyte chemoattractant protein 1, IL-6, and IL-1β. GIPR activation is also associated with increased blood flow

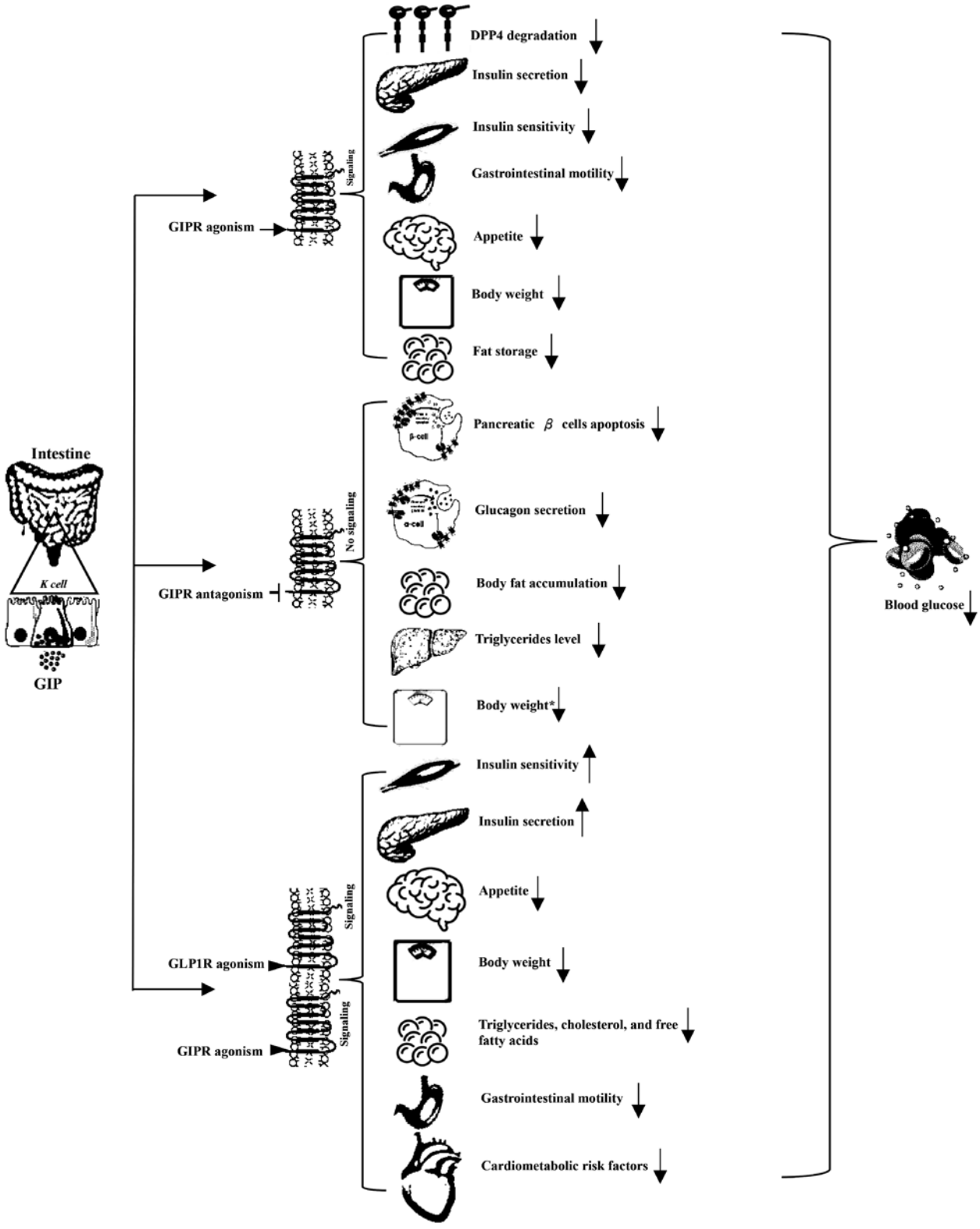


Figure 1. Tissue-specific effects of GIPR agonism and antagonism are presented, highlighting their distinct physiological roles in lowering blood sugar. Furthermore, the interplay between GIPR agonism and GLP-1R agonism is considered, emphasizing potential synergies when these therapeutic approaches are combined.

*Additive weight-loss when combined with a GLP-1R agonist.

in adipose tissue and enhanced lipogenesis. An in vitro study reported that GIP stimulates lipolysis under catabolic nutritional conditions and low insulin concentrations; however, the extent to which these weight-modulating effects observed in animal models translate to humans remains ambiguous[92]. Furthermore, the long-term safety implications of GIPR modulation, whether through agonism or antagonism, have yet to be thoroughly investigated in humans. Given GIP's extensive metabolic effects and its potential involvement in cardiovascular disease (CVD) pathophysiology, further research is essential to determine the clinical relevance of GIPR agonists and antagonists in patients with T2DM and CVD.

## 2.6 Effects of GIP on Renal Disorders

Diabetes increases the risk of kidney disease by disrupting glucose homeostasis and inducing metabolic dysfunction, which progressively impairs renal function. Chronic hyperglycemia contributes to glomerular hyperfiltration, proteinuria, declining filtration rates, and, ultimately, kidney failure. Although GIPR is widely expressed across various tissues, it has not been detected in the kidneys, suggesting that GIP does not exert direct effects on renal function[95]. Inflammation plays a central role in the pathogenesis of diabetic nephropathy, with advanced oxidative protein products implicated in the development of proteinuria, renal cell apoptosis, and subsequent glomerulosclerosis[96]. The influence of GIP on inflammatory processes has been extensively studied[93]. GIPR activation is associated with notable anti-inflammatory effects, including decreased adipose tissue inflammation, lower serum IL-6 levels, elevated adiponectin levels, and enhanced adiponectin expression in adipose tissue. By contrast, GIPR inhibition increases IL-6 levels in both serum and adipose tissue[93]. Elevated IL-6 levels are strongly correlated with the progressive decline in kidney function in patients with diabetes[97]. Adiponectin, known for its anti-inflammatory and insulin-sensitizing properties, plays a crucial role in metabolic regulation and the management of diabetes and other metabolic disorders associated with obesity. Moreover, AdipoRon, an adiponectin receptor agonist, demonstrated significant promise as a therapeutic agent in alleviating the impact of diabetic nephropathy[98].

GIP is associated with the suppression of proinflammatory cytokines, such as IL-6, IL-1β, and TNF-α and concurrently promotes an increase in adiponectin levels[94]. Serum TNF-α levels are inversely correlated with the estimated glomerular filtration rate (eGFR) and positively associated with albuminuria. In addition, TNF-α independently affects all-cause mortality, eGFR decline, and progression to end-stage renal disease[99]. Studies in rat models have demonstrated that TNF-α inhibition can significantly improve diabetic nephropathy[100]. Furthermore, elevated IL-1β levels and polymorphisms in the *IL-1B* gene have been linked to an increased risk of developing and progressing kidney disease in patients with T2DM[101].

GIP provides indirect protective benefits for kidney function by affecting multiple physiological processes. It plays a key role in reducing atherosclerosis by promoting nitric oxide production, enhancing insulin sensitivity in WAT, inhibiting vascular smooth muscle cell proliferation, and suppressing inflammatory responses in adipocytes, monocytes, and macrophages[102]. Furthermore, GIP interacts with central nervous system receptors to regulate food intake, supporting weight loss efforts. In subcutaneous WAT, GIP improves insulin sensitivity and enhances blood flow, facilitating lipid storage and buffering while reducing the infiltration of inflammatory immune cells. In skeletal muscle, it enhances insulin sensitivity and prevents the accumulation of ectopic lipids. On a systemic level, GIP contributes to the reduction of hyperglycemia and dyslipidemia[93].

## 3. GIPR: A Potential Therapeutic Target for T2DM

Although physiological concentrations of GIP or GLP-1 exhibit diminished insulinotropic effects in individuals with T2DM or hyperglycemia models, pharmacological doses of GLP-1 continue to stimulate insulin secretion, whereas equivalent levels of GIP do not [9]. This attenuated incretin effect in T2DM is believed to result from decreased GIPR activity in β-cells. Studies using GIPR and GLP-1R antagonists in healthy individuals have suggested that GIP serves as the primary physiological incretin responsible for insulin secretion[103,104]. This observation corresponds with evidence demonstrating that impaired GIPR activity leads to β-cell dysfunction. Consequently, clinicians and researchers are increasingly interested in GIP's role in normal physiology and its contribution to T2DM pathogenesis[105]. Furthermore, preliminary studies on multireceptor agonists targeting GIPR have demonstrated promising results in reducing body weight in individuals with T2DM[106], suggesting that modulating GIPR activity may unlock mechanisms beyond those mediated by GLP-1R alone. However, whether these mechanisms further enhance β-cell function or involve alternative, non-β-cell processes remains uncertain. GIPR activation also suppresses glucagon secretion, a key regulatory mechanism for controlling blood glucose levels[52]. The dual role of GIPR in stimulating insulin secretion while concurrently inhibiting glucagon release is fundamental to glucose homeostasis[107]. Beyond its pancreatic effects, GIPR affects various metabolic processes in adipose tissue. Its expression in adipocytes has been linked to improved glucose uptake and decreased lipid accumulation [56,108]. Although these mechanisms hold potential for enhancing insulin sensitivity in individuals with T2DM, the therapeutic application of GIPR-based strategies presents challenges, particularly in the need to precisely regulate GIPR activation to prevent excessive insulin secretion.

## 4. Therapeutic Potential for GIPR Agonists and Antagonists in T2DM

GIP plays a crucial role in stimulating insulin secretion from pancreatic β-cells, thereby contributing to blood glucose regulation[109]. This characteristic makes GIP a promising therapeutic target for enhancing insulin release in individuals with T2DM, particularly during the early stages of disease progression when β-cell function is substantially impaired[110]. In T2DM, chronic hyperglycemia and metabolic stress accelerate β-cell dysfunction and apoptosis[111]. As previously discussed, GIP-mediated signaling pathways can mitigate these adverse effects, preserving both β-cell mass and function[45]. In addition to its insulinotropic properties, GIP contributes to glucose homeostasis by inhibiting glucagon release[52]. Through glucagon suppression, GIP helps mitigate postprandial hyperglycemia, a hallmark of T2DM. Furthermore, GIPR activation in adipose tissue can improve insulin sensitivity[58], reduce fat accumulation[69], and promote weight management[106], all of which are critical components of T2DM treatment. Several therapeutic strategies targeting the GIP axis are currently in preclinical and clinical development, including GIP agonists, antagonists, and dual-acting therapies in combination with GLP-1. In addition, DPP4 inhibitors, which are already approved for T2DM treatment due to their ability to increase active GLP-1 levels, also enhance circulating active GIP by preventing its degradation. Given the presence of nutrient-sensing receptors in K cells, direct modulation of GIP secretion may be feasible; however, many of these receptors are also expressed in other enteroendocrine cells, including GLP-1-secreting L cells[112]. An overview of the tissue-specific effects of GIPR agonism and antagonism is provided in Figure 1.

### 4.1 GIPR Agonists

A decreased insulinotropic response to GIP is a hallmark feature of T2DM[113]. The development of GIPR agonists or mimetics holds promise for enhancing insulin secretion while mitigating potential drawbacks, such as promoting weight gain. In preclinical studies, GIPR agonists have demonstrated metabolic benefits. For instance, N-terminally modified analogs, including N-acetyl-GIP and N-pyroglutamyl-GIP, exhibited strong resistance to DPP4 degradation, leading to improved anti-hyperglycemic effects and increased insulin secretion in obese diabetic mice[114]. Long-acting GIPR agonists could lower blood glucose levels and induce modest weight loss in diet-induced obese mice, an effect attributed to decreased food consumption[85]. This weight-reducing effect persisted in GLP-1R-deficient mice but was absent in GIPR-deficient mice, suggesting a direct role of GIPR activation in appetite regulation. In addition, a series of N-terminally modified GIP analogs demonstrated substantial resistance to DPP4 degradation, improved insulin secretion, and enhanced antihyperglycemic effects in diabetic mouse models[115,116]. Beyond its effects on glucose regulation, GIPR activation in adipose tissue may enhance insulin sensitivity, limit fat accumulation, and support weight management, an essential factor in T2DM treatment[117]. However, definitive evidence regarding the efficacy of GIPR agonists in human diabetes management remains limited.

The therapeutic potential of GIP offers several benefits that complement those of GLP-1, making their combined use a promising approach for T2DM management. Both hormones play a critical role in the incretin effect by enhancing insulin secretion in response to meals. Although these hormones act on pancreatic β-cells through distinct mechanisms, their effects appear to be complementary and additive[118]. NNC0090-2746, a dual GIPR and GLP-1R agonist modified with a fatty acid, demonstrated significant improvements in glucose tolerance and weight loss in clinical trials involving patients with T2DM[119]. Moreover, treatment resulted in greater reductions in total cholesterol and leptin levels compared with placebo[119]. Currently, tirzepatide, a dual GIPR and GLP-1R agonist, revealed remarkable clinical efficacy in reducing body weight, improving glucose tolerance, and enhancing insulin sensitivity in individuals with T2DM[106]. Researchers have attributed these effects to the GIPR agonist component, which appears to maintain its activity by stimulating β-cell GIPRs and exerting central effects to reduce food intake[106]. The SURMOUNT-2 trial, a pioneering randomized clinical study, evaluated tirzepatide's efficacy in individuals with obesity and T2DM, focusing primarily on weight reduction instead of glycemic control, as measured by glycated hemoglobin (HbA1c) levels[120]. Results have demonstrated significant and clinically meaningful reductions in body weight, along with notable improvements in HbA1c and other cardiometabolic risk factors. Notably, the magnitude of weight loss achieved with tirzepatide in this trial surpassed that reported for currently approved antiobesity medications for individuals with T2DM, indicating its potential as a highly effective treatment for both obesity and T2DM[120]. Several other clinical trials, collectively known as the SURPASS studies, have recently reviewed tirzepatide's effectiveness compared with various antidiabetic and obesity treatments[121]. Given that dyslipidemia is a risk factor for diabetes progression and incidence[122], tirzepatide's lipid-lowering effects are of particular interest. Tirzepatide consistently reduces the levels of triglycerides, cholesterol, and free fatty acids in affected individuals. Compared with both placebo and dulaglutide, tirzepatide lowered triacylglycerol, diacylglycerol, and phospholipid levels to a greater extent over a 26-week period in patients with T2DM[123]. Lipid species with shorter and more saturated structures are associated with an increased

risk of insulin resistance and T2DM[124]. Following tirzepatide treatment, reductions in triacylglycerols and diacylglycerols primarily involved lipid species with shorter acyl carbon chains and fewer double bonds, whereas changes in unsaturated acyl chains were observed but contributed less significantly to the overall lipid profile shift compared with placebo[123]. These alterations in lipid metabolism were indirectly linked to reductions in body weight and are thought to result from GIPR agonism, which plays a key role in regulating lipid metabolism within adipose tissue[123].

Triagonist peptides, engineered to simultaneously activate the glucagon receptor (GCGR), GLP-1R, and GIPR, have been developed to achieve a precisely balanced stimulation of all 3 pathways. In a phase 2 clinical trial, retatrutide, a single peptide with agonist activity at GIPR, GLP-1R, and GCGR, demonstrated significant improvements in glycemic control and substantial reductions in body weight among individuals with T2DM. Notably, these effects were achieved while maintaining a safety profile comparable to that of GLP-1R agonists and combined GIPR/GLP-1R agonists[125]. Patients treated with retatrutide experienced a weight reduction of 15% or more within 36 weeks, a finding that aligns with the potential for reversing T2DM progression[126,127]. Additionally, retatrutide has been shown to enhance insulin sensitivity, increase adiponectin levels, and promote glucose-dependent insulin secretion, collectively contributing to reductions in fasting insulin and C-peptide concentrations[128]. The peptide is also speculated to enhance energy expenditure and fat oxidation; however, the specific tissues mediating these effects remain unidentified.

Future research should focus on assessing long-term clinical outcomes and evaluating the effects of higher-dose escalations of GLP-1R agonists. Comparative studies examining long-acting GIPR and GLP-1R agonists, as well as co-agonist therapies, will be essential to further advance our understanding of this topic.

### 4.2 GIPR Antagonism

As previously discussed, the effects of GIP are primarily mediated through receptor agonism, which has shown promise in improving insulin sensitivity and supporting weight management[117], offering potential therapeutic benefits for both obesity and diabetes. However, circulating GIP levels are significantly elevated in individuals with obesity and obesity-related T2DM. Studies in obese rodent models have reported a substantial increase in intestinal K-cell mass and elevated circulating GIP concentrations, both in cases of genetic predisposition to obesity and as a consequence of prolonged high-fat, high-calorie diets[129]. These findings suggest that GIPR antagonism may provide an alternative therapeutic approach for managing T2DM. The benefits of GIPR inhibition may be partly attributable to its effects on adipose tissue[130-132]. In murine models, GIPR antagonist treatment for 3 weeks led to improved glucose tolerance and reduced body fat[131]. Additionally, the absence of obesity in GIPR knockout mice further supports the connection between insulin resistance and obesity. Similarly, in mice fed a high-fat diet, lower GIP levels were associated with resistance to weight gain, improved insulin sensitivity, and no adverse effects on bone volume or structural integrity[132].

Inhibiting glucagon secretion has long been a central strategy in the development of anti-diabetic therapies. More recently, GCGR antagonists have demonstrated significant efficacy in controlling hyperglycemia and increasing circulating GLP-1 levels in both diabetic animal models and humans[133]. Similarly, GIPR antagonists show promise in addressing the hyperglucagonemia commonly observed in individuals with T2DM, offering additional therapeutic potential for disease management. These antagonists are particularly valuable

due to their dual benefits: reducing fat accumulation and suppressing glucagon secretion. Given that GIP's insulinotropic effects are diminished in T2DM, GIPR antagonists are unlikely to negatively impact β-cell function, further supporting their potential as a safe and effective therapeutic option.

Until recently, GIPR antagonists were not available for human use, limiting direct investigation into GIP's role in patients with T2DM. At first glance, the therapeutic potential of GIPR antagonism may seem counterintuitive, as blocking this receptor could theoretically reduce pancreatic insulin secretion[57,134]. However, the long-term effects on β-cell function remain uncertain. Although decreased insulin secretion has been observed in both GIPR knockout mice[130] and individuals with GIPR deficiency[135], compensatory mechanisms may counteract this reduction during treatment. One such compensatory mechanism involves increased endogenous GLP-1 secretion, as demonstrated in preclinical studies with diet-induced obese mice[136] and GIPR knockout mice[137]. In the context of T2DM, where the insulinotropic response to GIP is already diminished, GIPR antagonism is unlikely to further impair insulin secretion. This premise is supported by animal studies, which have reported no evidence of glucose intolerance following GIPR antagonist treatment[131,138]. In fact, some studies have indicated improved glucose regulation, potentially due to an upregulation of GIPR expression on β-cells. This observation is consistent with the behavior of G protein-coupled receptors, where antagonists frequently induce receptor surface expression as part of a regulatory adaptation[139,140]. Given that GIPR undergoes internalization and desensitization upon GIP binding, this upregulation serves as a logical compensatory response[115,141,142].

GIPR antagonism has demonstrated significant metabolic benefits in diabetic *db/db* mice, particularly when combined with liraglutide treatment,[143] further reinforcing the potential therapeutic value of integrating GIPR antagonism with GLP-1R agonism. Notably, some researchers suggest that GIPR antagonism may confer protective effects on β-cells by inducing periods of rest, thereby reducing chronic overactivation and mitigating the risk of apoptosis[129]. In support of this hypothesis, *db/db* mice receiving sequential administration of a GIPR antagonist and liraglutide exhibited alternating phases of β-cell rest and activation[143]. This therapeutic approach may represent a novel strategy deserving further investigation. Although earlier studies combining GIPR peptide antagonists with GLP-1R agonists had failed to significantly reduce body weight in diet-induced obese (DIO) rodents or modulate appetite and energy expenditure in obese humans, likely due to differences in animal models, potency, or metabolic degradation—recent findings indicate that a long-acting acylated GIPR antagonist peptide modestly suppressed food intake and reduced body weight in DIO mice. When combined with the GLP-1R agonist semaglutide, this treatment resulted in greater appetite suppression, enhanced weight loss, and a slight improvement in glucose tolerance compared with semaglutide alone[144]. These results align with earlier findings exploring the therapeutic combination of GLP-1R agonism and GIPR antagonism[143]. To date, long-acting acylated GIPR antagonist peptides have not been tested in humans. However, the development of well-characterized, humanized versions could represent a significant breakthrough in this field[129].

Several potential GIPR antagonists have undergone systematic metabolic evaluation, with GIP(3-30)$NH_2$ emerging as the most effective peptide-based antagonist identified for human use. This molecule and its variants have been widely utilized in molecular, cellular, and physiological studies of the GIP system[145]. GIP(3-30)$NH_2$ has been shown to reduce postprandial insulin and glucagon secretion compared with saline infusion in individuals with T2DM and obesity[146], providing direct evi-

dence that endogenous GIP possesses both insulinotropic and glucagonotropic properties. Similarly, the administration of GIP(3-30)$NH_2$ alongside GLP-1 infusion under fasting plasma glucose conditions led to reductions in both insulin and glucagon secretion in patients with T2DM and obesity[147]. The use of GIP(3-30)$NH_2$ has further validated the insulin-stimulating and glucose-lowering effects of endogenous GIP in individuals with T2DM[148]. Notably, approximately 37% of the improvement in β-cell function associated with DPP4 inhibition has been attributed to the action of endogenous GIP[148]. The normalization of plasma glucose levels enhances β-cell responsiveness to endogenous GIP, as demonstrated by comparisons between GIP(3-30)$NH_2$ and saline infusions in patients with T2DM, highlighting GIP's contribution to oral glucose tolerance[149]. Although β-cells are absent in individuals with type 1 diabetes mellitus, administration of GIP(3-30)$NH_2$ following meal consumption and physical activity resulted in an increase in glucose metabolism, suggesting a β-cell-independent role for GIP in glycemic regulation[150]. However, due to its short half-life and the need for intravenous infusion, GIP(3-30)$NH_2$ remains primarily a research tool for investigating the physiological and pathophysiological roles of endogenous GIP. Despite these limitations, studies using this antagonist have underscored GIP's involvement in glucose metabolism across diverse populations, including individuals who are lean or obese and those with or without T2DM[145].

## 5. Current Challenge of GIP in the Treatment of T2DM

Recent studies have revealed intricate interactions among GIP, insulin, and various metabolic factors, providing deeper insights into GIP's role in the pathophysiology of T2DM. However, its clinical implications, particularly concerning glucagon secretion, lipid metabolism, and bone homeostasis, remain a subject of debate in the context of T2DM etiology. Additionally, clinical evidence supporting the efficacy of GIP as a monotherapy for T2DM remains limited. Both GIPR agonists and antagonists offer distinct metabolic benefits, contributing to the management of diabetes-related disorders. Although current research trends favor GIPR agonism over antagonism, concerns persist regarding potential receptor desensitization with prolonged activation, particularly in human models[145]. This issue is especially relevant given tirzepatide's strong bias toward GIPR agonism[106]. Further research is required to elucidate the impact of GIPR agonists and antagonists on specific organs, particularly regarding receptor desensitization. Although substantial evidence suggests that GIPR agonists centrally reduce food intake, findings have remained inconclusive regarding the effects of prolonged exposure on desensitization in appetite-regulatory centers of the brain[145]. Thus, the question of whether GIPR agonists or antagonists will serve as the cornerstone of future T2DM treatment strategies remains unresolved, necessitating further clinical investigation.

GIP's therapeutic potential for T2DM is constrained by its rapid biological degradation and renal clearance. Similar to GLP-1, GIP undergoes enzymatic inactivation by DPP4, which cleaves its N-terminal region, rendering it incapable of stimulating insulin secretion[38]. DPP4-mediated degradation occurs rapidly in circulation, limiting GIP's half-life to approximately 3 to 5 minutes and presenting significant challenges for clinical application. In addition, similar to other peptides, GIP is swiftly cleared from the bloodstream through renal filtration, with an elimination half-life of less than 10 minutes[151]. Due to its peptide-based structure, GIP is most effectively administered via injection; however, advancements in oral delivery systems remain an area of active investigation.

The precise role of GIP in T2DM signal transduction pathways remains incompletely understood,

necessitating further research into its pharmacological interactions when combined with other drugs or receptor targets. Although incretins are well established as key regulators of insulin secretion, their effectiveness in addressing hyperglycemia and dyslipidemia depends on multiple factors, including satiety induction, patient tolerability, and long-term metabolic outcomes in individuals with T2DM. Integrating incretin-based therapies with other pharmacological agents or receptor-specific interventions represents a promising strategy for managing the complex pathophysiology of T2DM and its associated comorbidities. Future research should focus on optimizing these combinatorial approaches to enhance therapeutic efficacy and improve patient outcomes.

## 6. Conclusion

T2DM is a major global health concern, primarily driven by insulin resistance, with the incretin hormones GIP and GLP-1 playing critical regulatory roles. Although numerous studies have focused on GLP-1R as a therapeutic target, the potential of GIPR modulation remains an area of active investigation. Historically, GIP was recognized for its role in glucose regulation and insulin secretion; however, emerging evidence suggests it may also contribute to insulin resistance. Recent studies have revealed a complex interplay between GIP, insulin, and other metabolic factors, indicating the multifaceted role of GIP in T2DM pathophysiology. Therapeutic strategies targeting GIP, including both GIPR agonists and antagonists, hold promise for improving glycemic control and weight management in individuals with T2DM. GIPR agonists enhance insulin secretion, promote bone formation, increase satiety, and slow gastric emptying, whereas GIPR antagonists improve β-cell function, enhance insulin sensitivity, reduce body weight, and regulate lipid metabolism.[129] The clinical success of tirzepatide has renewed interest in GIPR as a therapeutic target for both T2DM and obesity, although concerns remain regarding potential risks associated with prolonged GIPR activation. Evidence suggests that combining GIPR antagonism with GLP-1R activation may offer superior metabolic benefits. Preclinical studies have supported this approach, and the development of AMG133, a conjugated monoclonal antibody therapy that integrates GIPR antagonism with GLP-1R agonism, has progressed to phase 2 clinical trials[112]. The potential of GIP-based therapies in T2DM management represents an exciting avenue for further exploration. A deeper understanding of GIP's molecular mechanisms and signaling pathways could facilitate the development of more targeted and individualized treatment strategies, enhancing therapeutic efficacy while minimizing adverse effects. Evaluating the long-term outcomes of GIP-focused therapies, both as standalone treatments and in combination with GLP-1R-based strategies, is essential to fully establish their benefits in T2DM management. Despite existing challenges, continued research into GIP offers hope for advancing treatment options and improving the quality of life for individuals affected by this widespread metabolic disorder.

### Conflicts of interest

No conflicts of interest associated with this manuscript to declare.

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# 葡萄糖依賴性促胰島素多肽在第二型糖尿病中的角色：治療進展與臨床應用

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## 摘要

第二型糖尿病（Type 2 Diabetes Mellitus, T2DM）是全球一項重大的健康挑戰，其主要由於人體無法有效的利用胰島素。腸促胰素激素，包括葡萄糖依賴性促胰島素多肽（Glucose-Dependent Insulinotropic Polypeptide, GIP）與類升糖素胜肽 -1（Glucagon-Like Peptide-1, GLP-1），在調節葡萄糖代謝中扮演著重要角色。其中，葡萄糖依賴性促胰島素多肽作為一種腸道激素，具有廣泛的生理功能，包括在進餐後促進胰島素分泌，以及在正常血糖和低血糖條件下刺激胰高血糖素釋放。此外，葡萄糖依賴性促胰島素多肽還促進脂肪組織的三酸甘油酯吸收並減少骨質吸收。基於這些激素的生物效應，眾多 GLP-1 受體激動劑及雙效葡萄糖依賴性促胰島素多肽 /GLP-1 受體激動劑已被開發並應用於 T2DM 治療，其中一些療法在控制體重及降低心血管疾病風險方面展現出顯著效果。深入探討這些作用背後的細胞與分子機制，對於研發新一代效果更佳且副作用更少的腸促胰素為基礎之療法具有重要意義。 儘管大量研究將 GLP-1 受體作為 T2DM 管理的核心目標，對於葡萄糖依賴性促胰島素多肽受體（GIP Receptor, GIPR）的治療潛力仍然處於探索階段。儘管有新興證據將葡萄糖依賴性促胰島素多肽與 T2DM 病理生理學中的關鍵機制聯繫起來，但其完整的臨床應用尚待確定。本文旨在探討葡萄糖依賴性促胰島素多肽作為 T2DM 治療標的之可能性，檢視其在在調控胰島 α 細胞與 β 細胞功能、脂肪組織動態、骨重塑、脂質代謝、心血管疾病以及腎功能失調中的角色。同時，本文也評估了 GIPR 激動劑與拮抗劑的治療潛力，探討這些介入方式如何促進對葡萄糖依賴性促胰島素多肽在 T2DM 管理中作用的角色。此外，本文還探討將葡萄糖依賴性促胰島素多肽相關療法轉化為臨床應用所需面對的挑戰，並提出克服這些障礙的可能策略，以推動更全面的治療選項之見解。