

The Emerging Role of Dual GLP-I and GIP Receptor Agonists in Glycemic Management and Cardiovascular Risk Reduction

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Abstract: The incretin pathway is a self-regulating feedback system connecting the gut with the brain, pancreas, and liver. Its predominant action is on the postprandial glucose levels, with extraglycemic effects on fat metabolism and endothelial function. Of the two main incretin hormones released with food ingestion, the actions of glucagon-like peptide-1 (GLP-1) have been exploited for therapeutic benefit. However, little attention has been paid to glucose-dependent insulinotropic polypeptide (GIP) until the recent experimental introduction of dual agonists, or “twincrins”. Interestingly, simultaneous activation of both receptors is not only replicative of normal physiology, it seems to be an innovative way to enhance their mutual salutary actions. In patients with type 2 diabetes, dual agonists can have powerful benefits for glucose control and weight reduction. Additionally, there is mounting evidence of their favorable cardiovascular impact, making them potentially appealing pharmacologic agents of choice in the future. Although we seem to be poised on the horizons of exciting new breakthroughs, much knowledge has yet to be gained before these novel agents are ready for prime time.

Keywords: type 2 diabetes, incretins, glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide

Introduction: The Incretin Effect in Health and Disease

The gastrointestinal system has an intricate pathway of hormones that are released from the gut lining upon ingestion of food and regulate glucose metabolism and appetite. The two predominant hormones that are responsible for postprandial insulin secretion are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). Insulin release is higher after enteral, but not intravenous, glucose administration; however, this phenomenon is blunted in the diabetic state (Figure 1). The beneficial actions based on activation of the “entero-insular axis” are complex and multitargeted, involving the gut, brain, pancreas, and liver.¹ Not well-known until recently, this “incretin effect” is severely reduced in patients with type 2 diabetes (T2DM) and has been therapeutically exploited to develop an entirely new class of antidiabetic drugs.² The administration of GLP-1 agonists (GLP-1As) can sufficiently replace the action of incretins and lower glucose levels. Since their debut, these novel agents have formed an important armamentarium in the management of T2DM. Lately, attention has been directed to GIP and its role in glucose homeostasis, and efforts are underway to develop compounds that mimic GIP actions in addition to those of GLP-1. The interplay between the two types of incretins is being explored so that greater understanding might lead to increased glycemic and nonglycemic (eg, cardiovascular) benefits.

Synergy Between GLP-I and GIP in the Healthy State: The Dual Hypothesis

It is established that both GLP-1 and its agonists augment insulin secretion and attenuate postprandial excursions of glucose. Efforts have focused on GLP-1RAs as a therapeutic option for T2DM since they inhibit appetite and food intake

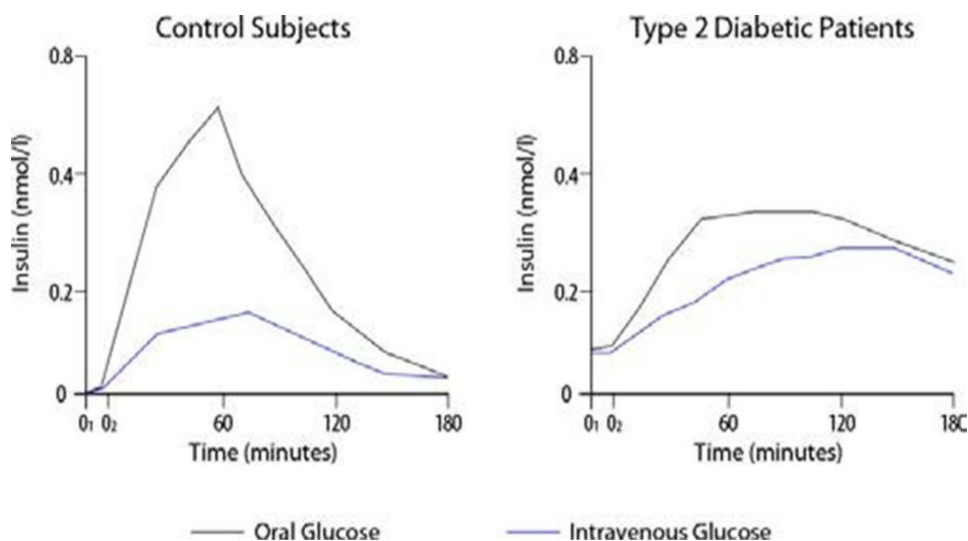


Figure 1 A diagrammatic depiction of the incretin effect. Reprinted from Thompson A, Kanamarlapudi V. Type 2 Diabetes Mellitus and Glucagon Like Peptide-1 Receptor Signalling. *Clin Exp Pharmacol*. 2013;3:4. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.⁶²

and improve glucose regulation. Although the hormones GLP-1 and GIP, as well as their receptors, are closely related, GIP receptor (GIPR) activation seems to be devoid of these actions.³ In fact, the effects of GIPR activation on glycemia and body weight have been controversial. In experimental animal models, GIPR agonists improved glycemia and prevented obesity from high-fat diet.⁴ In the natural, healthy state, Central GIP signals decrease food intake and overcome the weight-promoting effects of physiologic GIP levels in adipose tissues.⁵ As a synergistic action, body weight reduction by GIPR/GLP-1R dual agonists is greater than GLP-1R single agonists alone in overweight and obese persons.⁶ It appears that simultaneous activation of GLP-1R and GIPR might well have greater, multiplicative effect on glucose-lowering abilities than either agent alone. Human studies indicate that the insulinotropic action of GIP is blunted in individuals with severe hyperglycemia, in contrast to the intact action of GLP-1.⁷ Recent data shows that GIP is responsible for a substantial portion of postprandial insulin secretion in T2DM and mild hyperglycemia in early disease.⁸ GIPR deficiency in mice leads to impaired glucose tolerance with reduced β -cell function,⁹ while GIP overexpression results in improved glucose tolerance, enhanced β -cell function, and resistance to high-fat diet-induced obesity.¹⁰ These hormones seem to work in tandem; GLP-1 inhibits glucagon secretion when plasma glucose concentration is high, while GIP acts at lower glucose levels.¹¹ Thus, the latter functions as both an ally and a rival in T2DM, depending upon the glucose status, the stage in the natural history of the disease, and the degree of GIP-1 presence in the system. A comparison of the various actions of these partner hormones in the T2DM patient is shown in Figure 2.

In a paradoxical fashion, postprandial hyperglucagonemia – a common finding in T2DM – contributes to glucose excursions in the fed state.¹² Glucagon's stimulatory effect on endogenous hepatic glucose production is a prime culprit in glucose elevations after meals. Glucagon seems to regulate energy homeostasis and body weight. Both incretin hormones are known to modulate alpha cell glucagon secretion, albeit at different glucose levels and directions. Pharmacological dual incretin receptor agonist therapies utilize effects on glucagon secretion that are of clinical importance in antidiabetic regimens.¹³

“Twincretins”: Dual GLP-1 and GIP Receptor Agonists

Research on incretin-based therapies for T2DM has seen an exponential increase in the past three decades. The development of a variety of GLP-1RAs with beneficial actions on both glycemia and body weight has been the hallmark of pharmacologic progress in this arena. GLP-1RAs have indeed revolutionized the landscape, with the availability of formulations that are conveniently administered in daily or weekly doses.¹⁴ GLP-1RAs work by potentiating glucose-dependent insulin secretion from the β -cells of the pancreas accompanied by a low risk of hypoglycemia. Their desirable

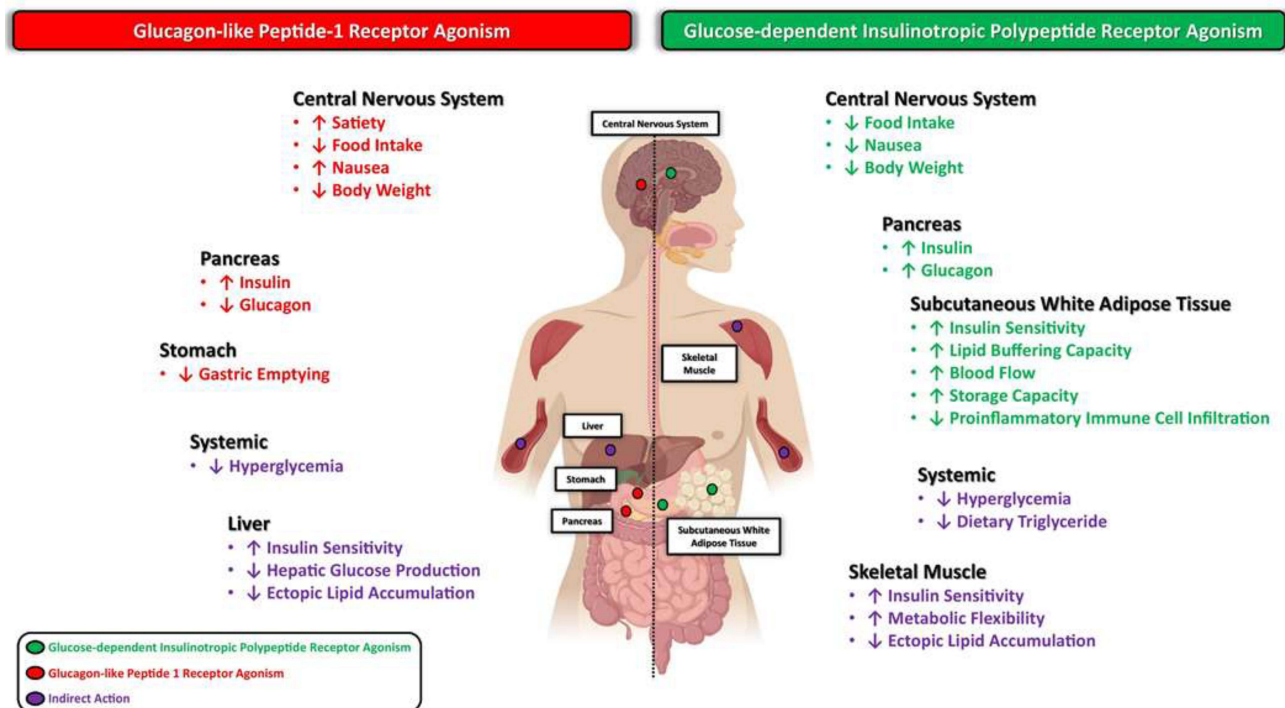


Figure 2 Pleiotropic actions of glucagon-like polypeptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) in type 2 diabetes. Reprinted from Samms RJ, Coghlan MP, Sloop KV. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab.* 2020;31(6):410–421. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.²⁵ intended).

action on body weight stems from central appetite suppression and retardation of gastric emptying;¹⁵ they also reduce body weight by activating GLP-1R in the central nervous system and suppressing appetite. In addition, recent studies indicate that some GLP-1R agonists, such as liraglutide, semaglutide, and dulaglutide, exert cardiovascular and renal benefits, and are endorsed for use in patients with these complications.¹⁶ On the other hand, the investigational use of GIPR agonists (GIPRAs) has not yielded similar advantages, partly because of a lack of understanding of GIP dose-response actions.¹⁷ Indeed, pharmacologic responses to GIPRAs alone in patients with T2DM have been clinically disappointing with respect to improvements in glucose and cardiorenal outcomes.¹⁸

With continued efforts in the development of newer antidiabetic agents, unimolecular GLP-1R/GIPR dual agonists (“twincretins”) can provide added efficacy, especially among obese individuals with T2DM. Recent studies using GLP-1R/GIPR dual agonists, especially the SURPASS clinical trials, have revealed beneficial effects of GIP activation when used in conjunction with GLP-1RAs.^{19,20} Animal studies have borne out the concept of dual-receptor activation.²¹ For example, in diet-induced obese mice, use of a novel GIP analogue enhanced GLP-1RA-induced body weight loss and improved glycemic control secondary to suppression of food intake.²² There was amelioration of glucose and lipid metabolism and improved β -cell mass in obese diabetic (db/db) mice with dual agonist use.

Encouragingly, GLP-1R/GIPR agonists have demonstrated favorable outcomes in T2DM when studied in human clinical trials. The GLP-1R/GIPR dual agonist NNC 0090-2746 (Novo Nordisk) significantly improved hemoglobin A1c (A1c) in T2DM (a reduction of -0.96% vs placebo) over a 12-week period, accompanied by a reduction in body weight.²³ When compared with liraglutide, the same agent reduced A1c by an equivalent amount but led to a significantly greater reduction in weight by NNC 0090-2746 was significantly greater than that of liraglutide (a -1.17% decrease compared to placebo). In another report, a 26-week treatment with the GLP-1R/GIPR dual agonist LY3298176 (Tirzepatide, Eli Lilly), showed significant reduction in A1c in an incremental, dose-dependent manner (4 doses from 1 mg to 15 mg, A1c reduction from -1.06% to -1.94% respectively).²⁴ The comparators were 1.5 mg of the GLP-1R dulaglutide and placebo (A1c reductions of -1.21 and -0.06% respectively). Both reductions in weight and

gastrointestinal side-effects were more frequent in the LY3298176 arm than in the other two groups. These studies clearly showed that the simultaneous activation of GIP and GLP-1 receptors was anti-obesogenic and could be utilized for its therapeutic potential.

The individual actions of GLP-1R and GIPR activation are difficult to separate out; the possibility exists that dual incretin receptor agonists work mainly by potent activation of the GLP-1R.²⁵ However, the specific contribution of the GIPR and GLP-1R to the pharmacological effects of dual incretin receptor agonism are currently undetermined. For instance, unimolecular doses of the dual-receptor agonist tirzepatide has effects that closely resemble dulaglutide, a pure GLP-1RA.²⁶ Experiments in pancreatic islets reveal that β -arrestin limits the insulin response to GLP-1, but not GIP or tirzepatide, suggesting that the biased agonism and imbalance of tirzepatide toward the GIP receptor and its unique GLP-1 receptor signaling properties might be at the basis of its potent action.²⁷ Higher doses of tirzepatide were noted to significantly ameliorate biomarkers related to fatty liver while increasing adiponectin levels in T2DM.²⁸

Glucagon is released from pancreatic α -cells and promotes hepatic glycolysis and gluconeogenesis in the liver to increase plasma glucose levels. Although GIP and its experimental analogs seem to have a glucagon-elevating effect, its end-action on metabolic parameters, especially when GLP-1 is present, is neutral or tilted towards benefit.¹³ Further research is needed to investigate the interconnected pathophysiologic roles of glucagon, GLP-1, and GIP while determining the niche for “twincretin” therapy in T2DM.²⁹

GIP Agonism as a Potential Therapeutic Approach for Atherosclerotic Cardiovascular Disease

The cardioprotective actions of incretin-based agents, particularly the GLP-1RAs, have a bulk of supporting evidence in the form of clinical studies.³⁰ However, the role of GIP in the genesis and progression of cardiovascular disease (CVD) remains to be elucidated. Since pharmacological doses of GIPRAs have been found to exert anti-obesity and anti-inflammatory effects, it is tempting to propose that they could retard the atherosclerotic process and translate into reduction of adverse clinical outcomes.³¹ Since there is significant residual CVD risk in patients with diabetes, even after accounting for traditional risk factors, the development of novel therapeutic avenues is needed to address it.^{32,33} A summary of the cardiovascular properties of GIP is presented in Table 1.

Both GIP and GLP-1 have been reported to exert direct effects on the cardiovascular system in addition to pancreatic beta cells.^{34,35} However, the controversy surrounding the possible benefits of GIPR agonism stems from two main observations: its impaired insulinotropic effects,^{36,37} and the prevention of weight gain by suppression of endogenous GIP-induced adipogenesis,^{38,39} However, these seemingly discouraging observations have been questioned by the finding of the central anorexic effects of GIP,^{40–42} and benefits of the GLP-1R/GIPR dual agonist LY3298176 (tirzepatide) in diabetic and overweight individuals. An intriguing and likely possibility is the potential function of GIP to enhance the actions of GLP-1.^{25,26} GIP is known to bind to the GLP-1R/GIPR heterodimer, a member of the family of G protein-coupled receptors.⁴³ Indeed, this may explain the potent metabolic effects of tirzepatide when pitted against a GLP-1 agonist alone.⁴⁴

The actions of GIP in vascular endothelial cells are notable for enhancing the intracellular calcium levels and nitric oxide without affecting endothelin-1 production.⁴⁵ GIP could exert both anti-atherogenic and pro-atherogenic effects, which may depend on the types of endothelia studied (Figure 3).⁴⁶ GIPR is expressed in monocytes that infiltrate vessel walls and differentiate into macrophages and form cells as a component of the atherosclerosis plaque.^{47–49} Anti-atherogenic effects of GIP in mouse models point to its protective effects at pharmacological concentrations).^{50,51} GIP infusion reduced aortic plaque formation, intra-plaque macrophage accumulation, and foam cell formation in diabetic mice, while its overexpression stabilizes the atherosclerotic plaque in non-diabetic animals.⁵¹ The latter also reduces macrophage accumulation and increases the collagen content of aortic plaques.⁵² The infusion of active GIP tends to suppress injury-induced neointimal hyperplasia and vascular cell proliferation, thus potentially inhibiting restenosis after angioplasty.⁵³ With respect to cardiac remodeling, left ventricular cardiomegaly and interstitial fibrosis was countered in mouse models of inactivated GIPR,⁵⁴ and deleterious effects of GIP were reported in myocardial infarction.⁵⁵ In a broad sense, these findings suggest that effects of GIP on cardiac remodeling may differ based on the ambient pathophysiologic milieu.

Table I Cardiovascular Effects of GIP in Animal Models

Animal Model		GIPR Activation	GIPR Inhibition
Atherosclerosis	ApoE knockout mice	↓Plaque formation ↓Macrophage foam cell formation ↑Plaque stability	
	ApoE knockout mice with diabetes	↓Plaque formation ↓Macrophage foam cell formation	
Restenosis	Femoral artery wire injury (male C57BL/6 mice)	↓Neointimal formation ↑endothelial regeneration	↑Neointimal formation
	Femoral artery wire injury with diabetes (male db/db mice)	↓Neointimal formation	
Cardiac remodeling	Angiotensin II infusion (male C57BL/6-background ApoE knockout mice)	↓Cardiomyocyte enlargement ↓interstitial fibrosis	↓Mortality ↓Scar formation →Left ventricular function
	Coronary artery ligation (male C57BL/6-background mice)	↑Scar formation	
	Transverse aortic constriction (male C57BL/6-background mice)		
	Doxorubicin injection (male C57BL/6-background mice)		↓Cardiac atrophy → Mortality
Inflammation	Standard diet (C57BL/6 and db misty mice)	↓Adipose tissue inflammation ↑Adipose tissue inflammation	
	High fat diet	↓Adipose tissue inflammation ↑Adipose tissue expression and blood levels of adiponectin	↑Blood and adipose tissue levels of IL-6
	Diabetes (male db/db mice)	↑Adipose tissue inflammation	
	Gingivitis (C57BL/6-background mice)		↑Gingival inflammation
	Endotoxemia (C57BL/6 mice)	↓ Blood IL-6 level	

Notes: Arrows: ↑, increase; →, no change; ↓ decrease. Adapted from Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a potential therapeutic target for atherosclerotic cardiovascular disease—a systematic review. *Int J Mol Sci.* 2020;21(4):1509. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.³²

The role of GIP in inflammatory responses has been studied by various investigators (Figure 3).^{50,56,57} It is indicated by its downregulation after being incorporated into macrophages. Anti-inflammatory effects of GIP in immune cells have also been noted.⁵⁸ GIPR has also been shown to be expressed abundantly in differentiated, but not undifferentiated premature adipocytes,^{57,59} thus signifying a role in the regulation of body fat deposition and function. Daily GIP injections led to a decrease in the adipose tissue gene expression levels of pro-inflammatory cytokines, such as IL-1 beta, IL-6, TNF-alpha in wild-type mice,⁶⁰ while blood levels of adiponectin, an anti-inflammatory and insulin-sensitizing adipokine, are enhanced.⁵⁵

To recapitulate, GIP appears to have a dose-related, binary relationship with adipose tissue inflammation. Its anti-atherogenic actions include nitric oxide production, inhibition of cell proliferation in vascular smooth muscle cell proliferation, and suppression of inflammatory responses in monocytes, macrophages, and adipocytes.⁶¹ On the other hand, adipocyte inflammation is increased.⁵⁷ It is important to note that, true to its name “insulinotropic”, GIP exhibits insulin-like lipophilic properties, promoting the deposition, storage capacity, buffering actions, and insulin sensitivity of white adipose tissue.²⁵

Conclusions

Understanding the enteroinsular axis has been the basis of seminal advancements in the therapeutic approach to diabetes management, with translation of research discoveries into effective pharmacologic therapies. Of late, attention has been

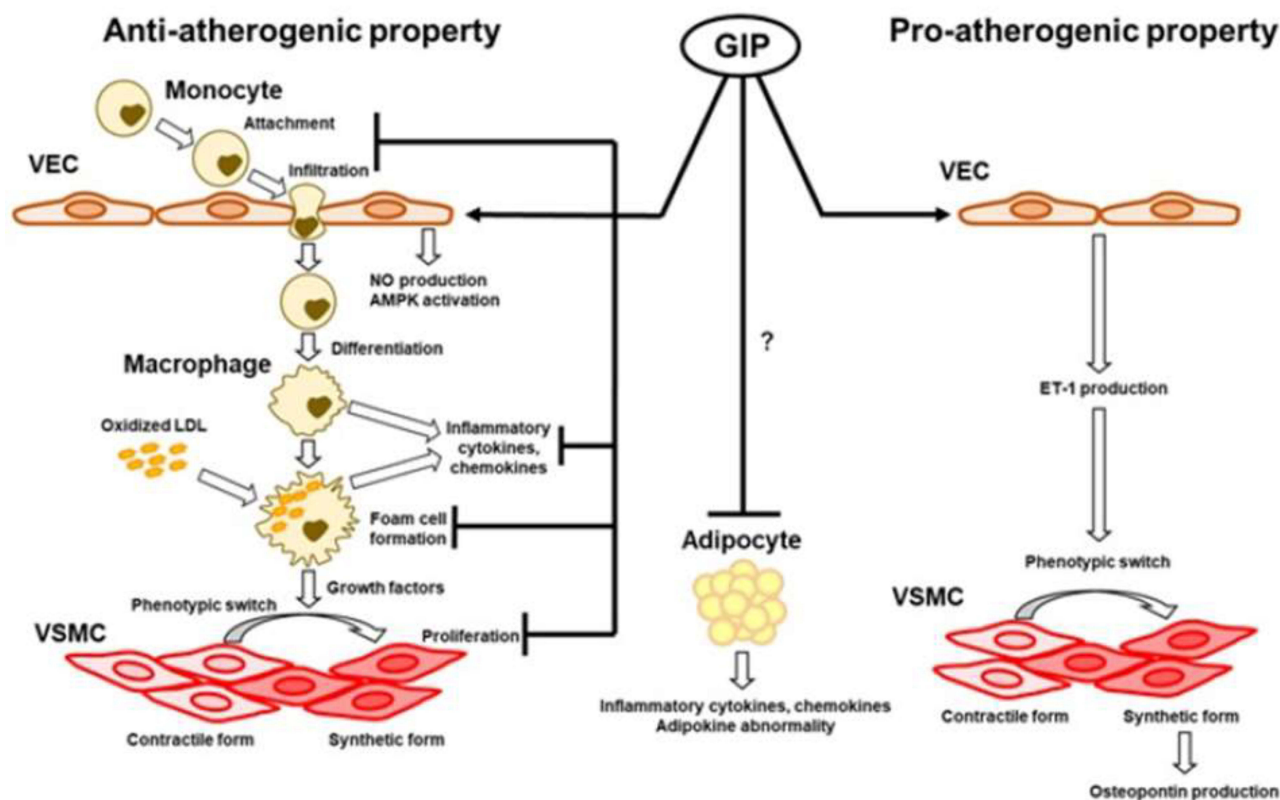


Figure 3 Diagrammatic relationship between GIP and atherosclerosis. Reprinted from Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a potential therapeutic target for atherosclerotic cardiovascular disease—a systematic review. *Int J Mol Sci.* 2020;21(4):1509. Creative Commons license and disclaimer available from: <http://creativecommons.org/licenses/by/4.0/legalcode>.³²

focused on the role that GIP plays in maintaining metabolic homeostasis, most likely in concert with GLP-1. Physiologic replacement of both these incretin agents in the form of dual GLP-1/GIP receptor activating compounds (“twincretins”) has yielded encouraging results vis-à-vis glucose and body weight regulation. There is mounting evidence from animal models and in vitro studies pointing to complex, yet possibly overall cardioprotective, actions of GIP in human health. As a word of caution, these favorable outcomes are preliminary and require confirmation. Side-effects and possible issues with long-term use of these novel agents have yet to be fully evaluated. Nevertheless, the untangling of the incretin system promises to deliver further gains in our efforts to translate future knowledge into therapeutic benefit for patients.

Disclosure

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References

- Campbell JE, Drucker DJ. Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metab.* 2013;17(6):819–837. doi:10.1016/j.cmet.2013.04.008
- Nauck MA, Meier JJ. The incretin effect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. *Lancet Diabetes Endocrinol.* 2016;4(6):525–536. doi:10.1016/S2213-8587(15)00482-9

3. Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. *J Diabetes Investig.* 2010;1(1–2):8–23. doi:10.1111/j.2040-1124.2010.00022.x
4. Hasib A, Ng MT, Khan D, Gault VA, Flatt PR, Irwin N. A novel GLP-1/xenin hybrid peptide improves glucose homeostasis, circulating lipids and restores GIP sensitivity in high fat fed mice. *Peptides.* 2018;100:202–211. doi:10.1016/j.peptides.2017.10.015
5. Grill HJ. A role for GLP-1 in treating hyperphagia and obesity. *Endocrinology.* 2020;161(8):bqaa093. doi:10.1210/endo/bqaa093
6. Williams DM, Nawaz A, Evans M. Drug therapy in obesity: a review of current and emerging treatments. *Diabetes Ther.* 2020;11(6):1199–1216. doi:10.1007/s13300-020-00816-y
7. Elahi D, McAloon-Dyke M, Fukagawa NK, et al. The insulinotropic actions of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (7–37) in normal and diabetic subjects. *Regul Pept.* 1994;51(1):63–74. doi:10.1016/0167-0115(94)90136-8
8. Holst JJ, Rosenkilde MM. Recent advances of GIP and future horizons. *Peptides.* 2020;125:170230. doi:10.1016/j.peptides.2019.170230
9. Yamada Y, Seino Y. Physiology of GIP—a lesson from GIP receptor knockout mice. *Horm Metab Res.* 2004;36(11–12):771–774. doi:10.1055/s-2004-826162
10. Kim SJ, Nian C, Karunakaran S, Clee SM, Isales CM, McIntosh CH. GIP-overexpressing mice demonstrate reduced diet-induced obesity and steatosis, and improved glucose homeostasis. *PLoS One.* 2012;7(7):e40156. doi:10.1371/journal.pone.0040156
11. Holst JJ. The incretin system in healthy humans: the role of GIP and GLP-1. *Metabolism.* 2019;96:46–55. doi:10.1016/j.metabol.2019.04.014
12. Girard J. Glucagon, a key factor in the pathophysiology of type 2 diabetes. *Biochimie.* 2017;143:33–36. doi:10.1016/j.biochi.2017.10.004
13. Mathiesen DS, Bagger JI, Bergmann NC, et al. The effects of dual GLP-1/GIP receptor agonism on glucagon secretion—A review. *Int J Mol Sci.* 2019;20(17):4092. doi:10.3390/ijms20174092
14. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. *Mol Metab.* 2021;46:101102. doi:10.1016/j.molmet.2020.101102
15. Perez-Montes DE, Oca A, Pellitero S, Puig-Domingo M. Obesity and GLP-1. *Minerva Endocrinol.* 2021;46(2):168–176. doi:10.23736/S2724-6507.20.03369-6
16. Verma S, McGuire DK, Bain SC, et al. Effects of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across body mass index categories in type 2 diabetes: results of the LEADER and SUSTAIN 6 trials. *Diabetes Obes Metab.* 2020;22(12):2487–2492. doi:10.1111/dom.14160
17. Bailey CJ. GIP analogues and the treatment of obesity-diabetes. *Peptides.* 2020;125:170202. doi:10.1016/j.peptides.2019.170202
18. Chia CW, Carlson OD, Kim W, et al. Exogenous glucose-dependent insulinotropic polypeptide worsens post prandial hyperglycemia in type 2 diabetes. *Diabetes.* 2009;58(6):1342–1349. doi:10.2337/db08-0958
19. Coskun T, Sloop KW, Loghin C, et al. LY3298176, a novel dual GIP and GLP-1 receptor agonist for the treatment of type 2 diabetes mellitus: from discovery to clinical proof of concept. *Mol Metab.* 2018;18:3–14. doi:10.1016/j.molmet.2018.09.009
20. Min T, Bain SC. The role of tirzepatide, dual GIP and GLP-1 receptor agonist, in the management of type 2 diabetes: the SURPASS Clinical Trials. *Diabetes Ther.* 2021;12(1):143–157. doi:10.1007/s13300-020-00981-0
21. Finan B, Ma T, Ottaway N, et al. Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. *Sci Transl Med.* 2013;5(209):209ra151. doi:10.1126/scitranslmed.3007218
22. Nørregaard PK, Deryabina MA, Tofteng Shelton P, et al. A novel GIP analogue, ZP4165, enhances glucagon-like peptide-1-induced body weight loss and improves glycaemic control in rodents. *Diabetes Obes Metab.* 2018;20(1):60–68. doi:10.1111/dom.13034
23. Frias JP, Bastyr EJ 3rd, Vignati L, et al. The sustained effects of a dual GIP/GLP-1 receptor agonist, NNC0090-2746, in patients with type 2 diabetes. *Cell Metab.* 2017;26(2):343–352.e2. doi:10.1016/j.cmet.2017.07.011
24. Thomas MK, Nikoienjad A, Bray R, et al. Dual GIP and GLP-1 receptor agonist tirzepatide improves beta-cell function and insulin sensitivity in type 2 diabetes. *J Clin Endocrinol Metab.* 2021;106(2):388–396. doi:10.1210/clinem/dgaa863
25. Samms RJ, Coghlan MP, Sloop KW. How may GIP enhance the therapeutic efficacy of GLP-1? *Trends Endocrinol Metab.* 2020;31(6):410–421. doi:10.1016/j.tem.2020.02.006
26. Urva S, Coskun T, Loghin C, et al. The novel dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 (GLP-1) receptor agonist tirzepatide transiently delays gastric emptying similarly to selective long-acting GLP-1 receptor agonists. *Diabetes Obes Metab.* 2020;22(10):1886–1891. doi:10.1111/dom.14110
27. Willard FS, Douros JD, Gabe MB, et al. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. *JCI Insight.* 2020;5(17):e140532. doi:10.1172/jci.insight.140532
28. Hartman ML, Sanyal AJ, Loomba R, et al. Effects of novel dual GIP and GLP-1 receptor agonist tirzepatide on biomarkers of nonalcoholic steatohepatitis in patients with type 2 diabetes. *Diabetes Care.* 2020;43(6):1352–1355. doi:10.2337/dc19-1892
29. Usui R, Yabe D, Seino Y. Twincretin as a potential therapeutic for the management of type 2 diabetes with obesity. *J Diabetes Investig.* 2019;10(4):902–905. doi:10.1111/jdi.13005
30. Andrikou E, Tsioufis C, Andrikou I, Leontsinis I, Tousoulis D, Papanas N. GLP-1 receptor agonists and cardiovascular outcome trials: an update. *Hellenic J Cardiol.* 2019;60(6):347–351. doi:10.1016/j.hjc.2018.11.008
31. Sheahan KH, Wahlberg EA, Gilbert MP. An overview of GLP-1 agonists and recent cardiovascular outcomes trials. *Postgrad Med J.* 2020;96(1133):156–161. doi:10.1136/postgradmedj-2019-137186
32. Mori Y, Matsui T, Hirano T, Yamagishi SI. GIP as a potential therapeutic target for atherosclerotic cardiovascular disease—a systematic review. *Int J Mol Sci.* 2020;21(4):1509. doi:10.3390/ijms21041509
33. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Emerging risk factors collaboration. diabetes mellitus, fasting glucose, and risk of cause-specific death. *N Engl J Med.* 2011;364(9):829–841. Erratum in: *N Engl J Med.* 2011;364(13):1281.
34. Gimeno Orna JA, Ortez Toro JJ, Peteiro Miranda CM. Evaluation and management of residual cardiovascular risk in patients with diabetes. *Endocrinol Diabetes Nutr.* 2020;67(4):279–288. doi:10.1016/j.endinu.2019.05.004
35. Seino Y, Yabe D. Glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1: incretin actions beyond the pancreas. *J Diabet Investig.* 2013;4:108–130.
36. Vilsbøll T, Krarup T, Madsbad S, Holst JJ. Defective amplification of the late phase insulin response to glucose by GIP in obese Type II diabetic patients. *Diabetologia.* 2002;45(8):1111–1119. doi:10.1007/s00125-002-0878-6

37. Vilsbøll T, Knop FK, Krarup T, et al. The pathophysiology of diabetes involves a defective amplification of the late-phase insulin response to glucose by glucose-dependent insulinotropic polypeptide-regardless of etiology and phenotype. *J Clin Endocrinol Metab.* 2003;88(10):4897–4903. doi:10.1210/jc.2003-030738
38. Nasteska D, Harada N, Suzuki K, et al. Chronic reduction of GIP secretion alleviates obesity and insulin resistance under high-fat diet conditions. *Diabetes.* 2014;63(7):2332–2343. doi:10.2337/db13-1563
39. Nakamura T, Tanimoto H, Mizuno Y, et al. Gastric inhibitory polypeptide receptor antagonist, SKL-14959, suppressed body weight gain on diet-induced obesity mice. *Obes Sci Pract.* 2018;4(2):194–203. doi:10.1002/osp4.164
40. NamKoong C, Kim MS, Jang BT, Lee YH, Cho YM, Choi HJ. Central administration of GLP-1 and GIP decreases feeding in mice. *Biochem Biophys Res Commun.* 2017;490(2):247–252. doi:10.1016/j.bbrc.2017.06.031
41. Mroz PA, Finan B, Gelfanov V, et al. Optimized GIP analogs promote body weight lowering in mice through GIPR agonism not antagonism. *Mol Metab.* 2019;20:51–62. doi:10.1016/j.molmet.2018.12.001
42. Adriaenssens AE, Biggs EK, Darwish T, et al. Glucose-dependent insulinotropic polypeptide receptor-expressing cells in the hypothalamus regulate food intake. *Cell Metab.* 2019;30(5):987–996.e6. doi:10.1016/j.cmet.2019.07.013
43. Harikumar KG, Wootten D, Pinon DI, et al. Glucagon-like peptide-1 receptor dimerization differentially regulates agonist signaling but does not affect small molecule allostery. *Proc Natl Acad Sci U S A.* 2012;109(45):18607–18612. doi:10.1073/pnas.1205227109
44. Wilson JM, Lin Y, Luo MJ, et al. The dual glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1 receptor agonist tirzepatide improves cardiovascular risk biomarkers in patients with type 2 diabetes: a post hoc analysis. *Diabetes Obes Metab.* 2022;24(1):148–153. doi:10.1111/dom.14553
45. Farah C, Michel LYM, Balligand JL. Nitric oxide signalling in cardiovascular health and disease. *Nat Rev Cardiol.* 2018;15(5):292–316. doi:10.1038/nrcardio.2017.224
46. Zhong Q, Bollag RJ, Dransfield DT, et al. Glucose-dependent insulinotropic peptide signaling pathways in endothelial cells. *Peptides.* 2000;21(9):1427–1432. doi:10.1016/S0196-9781(00)00287-4
47. Tahara N, Tahara A, Honda A, et al. Molecular imaging of vascular inflammation. *Curr Pharm Des.* 2014;20(14):2439–2447. doi:10.2174/13816128113199990479
48. Chinetti-Gbaguidi G, Colin S, Staels B. Macrophage subsets in atherosclerosis. *Nat Rev Cardiol.* 2015;12(1):10–17. doi:10.1038/nrcardio.2014.173
49. Chistiakov DA, Bobryshev YV, Orekhov AN. Macrophage-mediated cholesterol handling in atherosclerosis. *J Cell Mol Med.* 2016;20(1):17–28. doi:10.1111/jcmm.12689
50. Nagashima M, Watanabe T, Terasaki M, et al. Native incretins prevent the development of atherosclerotic lesions in apolipoprotein E knockout mice. *Diabetologia.* 2011;54(10):2649–2659. doi:10.1007/s00125-011-2241-2
51. Kahles F, Liberman A, Halim C, et al. The incretin hormone GIP is upregulated in patients with atherosclerosis and stabilizes plaques in ApoE^{-/-} mice by blocking monocyte/macrophage activation. *Mol Metab.* 2018;14:150–157. doi:10.1016/j.molmet.2018.05.014
52. Mori Y, Kushima H, Koshibu M, et al. Glucose-dependent insulinotropic polypeptide suppresses peripheral arterial remodeling in male mice. *Endocrinology.* 2018;159(7):2717–2732. doi:10.1210/en.2018-00336
53. Hiromura M, Mori Y, Kohashi K, et al. Suppressive effects of glucose-dependent insulinotropic polypeptide on cardiac hypertrophy and fibrosis in angiotensin II-infused mouse models. *Circ J.* 2016;80(9):1988–1997. doi:10.1253/circj.CJ-16-0152
54. Ussher JR, Campbell JE, Mulvihill EE, et al. Inactivation of the glucose-dependent insulinotropic polypeptide receptor improves outcomes following experimental myocardial infarction. *Cell Metab.* 2018;27(2):450–460.e6. doi:10.1016/j.cmet.2017.11.003
55. Ben-Shlomo S, Zvibel I, Varol C, et al. Role of glucose-dependent insulinotropic polypeptide in adipose tissue inflammation of dipeptidylpeptidase 4-deficient rats. *Obesity.* 2013;21(11):2331–2341. doi:10.1002/oby.20340
56. Varol C, Zvibel I, Spektor L, et al. Long-acting glucose-dependent insulinotropic polypeptide ameliorates obesity-induced adipose tissue inflammation. *J Immunol.* 2014;193(8):4002–4009. doi:10.4049/jimmunol.1401149
57. Chen S, Okahara F, Osaki N, Shimotoyodome A. Increased GIP signaling induces adipose inflammation via a HIF-1 α -dependent pathway and impairs insulin sensitivity in mice. *Am J Physiol Endocrinol Metab.* 2015;308(5):E414–25. doi:10.1152/ajpendo.00418.2014
58. Suzuki Y, Nakamura N, Miyabe M, et al. Anti-inflammatory role of glucose-dependent insulinotropic polypeptide in periodontitis. *J Diabetes Investig.* 2016;7(4):497–505. doi:10.1111/jdi.12450
59. Weaver RE, Donnelly D, Wabitsch M, Grant PJ, Balmforth AJ. Functional expression of glucose-dependent insulinotropic polypeptide receptors is coupled to differentiation in a human adipocyte model. *Int J Obes.* 2008;32(11):1705–1711. doi:10.1038/ijo.2008.148
60. Szalowska E, Meijer K, Kloosterhuis N, Razaee F, Priebe M, Vonk RJ. Sub-chronic administration of stable GIP analog in mice decreases serum LPL activity and body weight. *Peptides.* 2011;32(5):938–945. doi:10.1016/j.peptides.2011.02.011
61. Nogi Y, Nagashima M, Terasaki M, Nohtomi K, Watanabe T, Hirano T. Glucose-dependent insulinotropic polypeptide prevents the progression of macrophage-driven atherosclerosis in diabetic apolipoprotein E-null mice. *PLoS One.* 2012;7(4):e35683. doi:10.1371/journal.pone.0035683
62. Thompson A, Kanamarlapudi V. Type 2 Diabetes Mellitus and Glucagon Like Peptide-1 Receptor Signalling. *Clin Exp Pharmacol.* 2013;3:4.

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