Incretins and the cardiovascular system: bridging digestion with metabolism

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Lancet Diabetes Endocrinol 2025

Published Online
July 7, 2025
https://doi.org/10.1016/S2213-8587(25)00166-4

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The mechanisms driving the cardiovascular and renal benefits of therapies targeting intestinal hormones in type 2 diabetes are still not fully understood. We propose that incretin hormones—glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP)—act as a critical link connecting digestion, metabolism, and cardiovascular function, supporting physiological adaptations to nutrient intake. Incretin hormones help regulate blood flow and cardiac activity, enhancing nutrient absorption while protecting the heart and vessels. After meals, incretin hormones promote vasodilation—especially in the splanchnic and peripheral circulations—via nitric oxide, improving endothelial function, vascular flexibility, and blood pressure control, which supports tissue perfusion and meets the body's increased metabolic demands. GLP-1 also has mild inotropic effects, promoting efficient circulation without straining the heart. At the same time, vasodilation boosts glucose and lipid uptake, linking digestion directly to energy metabolism. These mechanisms lower vascular resistance, reduce cardiac workload, and improve myocardial glucose use, which becomes especially valuable during ischaemic events. Incretins also have anti-inflammatory and antioxidant effects, which help prevent endothelial dysfunction and arterial stiffening, reducing the risk of atherosclerosis. Clinically, GLP-1 receptor agonists and dual GLP-1 and GIP receptor agonists leverage these effects to improve cardiovascular and possibly renal outcomes in people with type 2 diabetes or obesity. By linking digestion, metabolism, and cardiovascular health, incretin-based therapies do more than just regulate blood sugar; they help reduce morbidity and mortality and are becoming a core component of modern diabetes care.

Introduction

What makes intestinal hormones uniquely effective in providing cardiovascular protection? The introduction of glucagon-like peptide-1 (GLP-1) receptor agonists has reshaped cardiovascular and kidney health trajectories in people living with type 2 diabetes. These agents reduce the risk of major adverse cardiovascular events (MACE) and provide considerable kidney protection. According to the most recent meta-analysis, GLP-1 receptor agonists reduce composite kidney outcomes by 18%, cutting kidney failure risk by 16%, lowering MACE by 13%, and decreasing all-cause mortality by 12%.[1] The positive effects of GLP-1 receptor agonists have been consistently replicated in real-world studies.[2,3] The European Society of Cardiology guidelines on managing cardiovascular disease in diabetes usher in a bold new direction, emphasising glucose-lowering agents with proven cardiovascular benefits.[4] The physiological roles of endogenously secreted incretins (ie, GLP-1 and glucose-dependent insulinotropic peptide [GIP]), including vasodilation and mild inotropic effects, link digestion to metabolism by enhancing nutrient absorption, delivery, and use. These mechanisms seamlessly contribute to cardiovascular protection when applied therapeutically (ie, using GLP-1 receptor and GIP receptor agonists). While dipeptidyl peptidase-4 (DPP-4) inhibitors are sometimes referred to as incretin-based therapies given that they increase the levels of endogenous GLP-1 and GIP, cardiovascular outcome trials have consistently shown their non-inferiority to placebo with regards to hard cardiorenal endpoints.[5] The scope of this Review is to examine how incretin-based therapies—by bridging digestion—protect the cardiovascular system, especially in people living with type 2 diabetes. For the various sections of this Review, table 1 summarises what was previously known or accepted, what new ideas and concepts we bring forward, what the clinical implications are, and what further research should be performed.

Cardiovascular adaptations to nutrient ingestion and the roles of intestinal hormones

Nutrient ingestion elicits a series of cardiovascular adaptations to facilitate efficient digestion and absorption. Postprandial blood flow to the gastrointestinal tract increases (known as postprandial hyperaemia), which is mediated by the release of vasodilatory substances, such as nitric oxide and adenosine. This redistribution of blood flow is accompanied by a transient rise in cardiac output and heart rate to maintain systemic blood pressure.[6] Nutrient-induced activation of the sympathetic nervous system contributes to these haemodynamic changes. The ingestion of specific macronutrients (particularly fatty acids and carbohydrates) can influence these responses, with high-fat meals leading to more pronounced postprandial lipaemia and endothelial activation. Understanding these physiological responses is crucial, as altered postprandial responses lead to impairments in vascular function that are associated with an increased risk of cardiovascular disease.[7]

Gastrointestinal hormones play a pivotal role in modulating cardiovascular adaptations to nutrient ingestion. Upon food intake, enteroendocrine cells dispersed throughout the gastrointestinal tract secrete various hormones in response to luminal nutrient content. Among these, GLP-1 and GIP exert considerable effects on cardiovascular function. Incretin hormones, released postprandially, enhance insulin secretion in a glucose-dependent manner. Of note, incretin secretion

	Previously known or accepted	New ideas and concepts	Clinical implications	Future research
Cardiovascular adaptations to nutrient ingestion and roles of intestinal hormones	Nutrient ingestion elicits cardiovascular adaptations to facilitate efficient digestion and nutrient absorption	Gastrointestinal hormones modulate the cardiovascular system in the postprandial phase	Reduced incretin effect is associated with poor cardiovascular response in the postprandial phase	Clarify to what extent the effects of incretins on the digestive system can contribute to organ protection
Incretins and the regulation of food intake and nutrient disposal	GLP-1 and GIP stimulate insulin secretion wheras only GLP-1 inhibits glucagon secretion; both are rapidly degraded by dipeptidyl peptidase-4	GLP-1 and GIP prepare the organism for nutrient delivery and oxidation, GLP-1 and GIP control food intake and affect amino acid metabolism	Single and dual agonism on GLP-1 and GIP receptor agonists produce considerable improvement on systemic circulation indirectly by improving weight and glucose metabolism, but also by directly affecting intracellular pathways	Improve our knowledge on the role of GIP alone in affecting food intake, eating behaviour, and weight regulation
Incretin effects on the cardiovascular system	GLP-1 and GIP activate intracellular pathways associated with anti-atherosclerotic effects	The ability of GLP-1 and GIP to control the cardiovascular system is linked to their role in digestion, nutrient delivery, and metabolic regulation	The long-term activation of both GLP-1 and GIP receptors offer considerable cardiovascular protection	Clarify the role of incretin receptor activation on the trajectory of atherosclerois in humans; the beneficial effect of incretin on endothelial cells might be expanded to microvascular complications of diabetes
Incretins increase perfusion in the brain	GLP-1 and GIP considerably enhance cerebral blood flow in the postprandial phase	Incretin-based drugs increase blood flow, ameliorate the blood –brain barrier, and positively affect brain function	Incretin not only improves the metabolic milieu, but also offers neuroprotection and slows cognitive decline	Improve the knowledge on the role of incretin-based drugs on the biology of neurotrophic factors
Incretins increase perfusion in skeletal muscle	GLP-1 increases blood flow	GIP might counter GLP-1-mediated increases in blood flow to ensure splanchnic perfusion; the GLP-1-mediated blood flow might improve metabolic control and comorbid conditions, such as heart failure	Incretin-based therapy improves glucose metabolism, and, indirectly, muscle metabolism by affecting blood flow	Clarify the role of GIP in skeletal muscle microvascular circulation
Incretins increase perfusion in the kidney	GLP-1 increases acute renal plasma flow but the chronic effects are uncertain	Renal perfusion is essential to dispose of toxins	Incretin-based drugs ameliorate renal endpoints and might reduce cardiovascular adverse events by improving renal haemodynamics	Elucidate the role of GIP in renal physiology in the light of the effects of tirzepatide
Incretins increase perfusion in the heart	Native GLP-1 and GLP-1 based therapies increase coronary blood flow	Coronary blood flow is essential in the postprandial phase and can, in part, explain the ability of incretins to reduce cardiovascular risk	Incretin-based therapies, beyond their anti-atherosclerotic effects, improve myocardial perfusion	The role of GIP on coronary blood flow is still debatable
Incretins increase perfusion in adipose tissue	GIP, in combination with hyperinsulinaemia, increases blood flow and modulates lipolysis	The effect of GIP on adipose tissue blood flow favour the effect of insulin, promoted the exchange of metabolites, and reduces inflammation	GIP-based receptor agonists could counteract some features of the metabolic syndrome	The cross-talk between GIP and insulin pathways within adipocytes from different area (ie, subcutaneous or visceral), should be better defined
Incretins directly affect substrate oxidation	GLP-1 increases energy expenditure whereas GIP and dual GLP-1 and GIP receptor agonists increase fat oxidation	Incretin hormones create the permissive cardiovascular conditions for nutrient use	Incretin-based therapies facilitate nutrient use, reduce fat mass, and might spare lean body mass loss	The relationship between enhanced blood flow and substrate oxidation is poorly studied

GIP=glucose-dependent insulinotropic peptide. GLP-1=glucagon-like peptide-1.

Table 1: **Summary of the major roles of incretins**

can also be affected by the gut microbiota via a diverse array of bioactive metabolites, such as short chain fatty acids.[8] Evidence also indicates that the incretins themselves—whether naturally secreted or pharmacologically mimicked—modulate microbiota composition by promoting a beneficial microbial population.[9] Therefore, natural incretins and incretin-based drugs might indirectly and positively support cardiovascular health, not only by controlling intermediary metabolism, but also by improving the intestinal microbial ecosystem.

A substantial body of evidence shows that GLP-1 and GIP directly influence cardiovascular physiology. Preclinical and clinical studies show that naturally secreted GLP-1 improves endothelial function, promotes vasodilation, and exerts cardioprotective effects, potentially via nitric oxide-mediated pathways. Similarly, experimental studies showed that GIP receptors are expressed in cardiovascular tissues, and naturally secreted GIP modulates heart rate and myocardial contractility.[10] Other gastrointestinal hormones might cooperate with incretins to achieve the necessary cardiovascular adaptations to food intake, and they are also being explored as targets for cardiometabolic diseases. For example, cholecystokinin, released primarily in response to dietary fat and proteins, facilitates digestion by stimulating pancreatic enzyme secretion and gallbladder contraction in humans, but also interacts with the autonomic nervous system, modulating heart rate, blood pressure, and splanchnic perfusion.[11] Oxyntomodulin is a gut-derived hormone that activates both GLP-1 and glucagon receptors, reducing appetite and increasing energy expenditure. To circumvent the rapid degradation

of naturally-secreted incretins by DPP-4, pharmacologically-mimicked analogues engineered to resist degradation and with a much longer half-life are available, with a greater potential to slow gastric emptying (short-acting receptor agonists), aid weight loss, and improve metabolic parameters (long-acting receptor agonists) in people with type 2 diabetes.[12] Even leptin, primarily known for its role in suppressing appetite, has historically well-known vasodilatory effects in humans[13] that can be easily linked to the integrated control of abdominal blood flow in the fed condition.

The coordinated action of these gastrointestinal secreted hormones ensures that, following nutrient ingestion, there is an appropriate cardiovascular response to meet the metabolic demands of digestion and nutrient disposal. This response includes adjustments in cardiac output, regional blood flow distribution, and vascular tone, thereby maintaining haemodynamic stability during the postprandial period (figure 1).

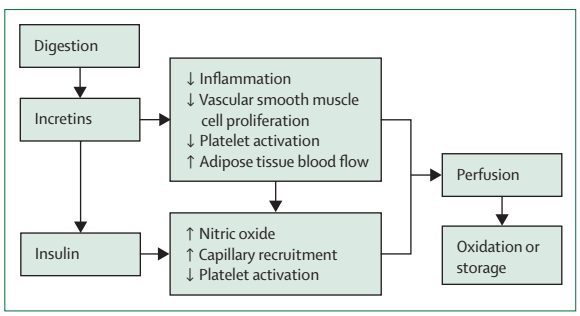

Figure 1: **General schematic representation of the role of incretins in the disposal and use of nutrients**

Incretins and the regulation of food intake and nutrient disposal

GLP-1 and GIP are released in response to nutrient delivery to the gut, playing essential roles in digestion, glucose metabolism, and maintaining energy balance (figure 2). GLP-1, secreted after meals, originates primarily from L cells of the distal small bowel and colon. Most GLP-1 (about 90%) is quickly degraded by DPP-4 before it can enter systemic circulation.[10] GIP is released more proximally by K cells located in the duodenum and proximal jejunum, and is rapidly metabolised, but has a different degradation profile to GLP-1.[14,15] GLP-1 and GIP act on pancreatic β cells via their receptors, promoting glucose-dependent insulin secretion and β-cell trophism. GLP-1 also inhibits glucagon secretion, an effect contributing to glucoregulation.[16] Both hormones facilitate the rapid disposal of ingested nutrients via insulin secretion. GLP-1 also slows gastric emptying, which reduces postprandial glucose rise.[17] GLP-1 promotes satiety and weight loss, while GIP promotes energy storage and lipid metabolism.

The presence of specific, high affinity receptors for both GLP-1 and GIP was shown in the brain.[18,19] Upon receptor stimulation, GLP-1 and GIP can affect food intake and bodyweight, as shown in studies of CNS administration in mice.[20] GLP-1 is involved in appetite regulation, while GIP has a more complex and less direct role, acting on different neuronal areas. GLP-1 reduces appetite and energy intake, but whether GIP alone can affect eating behaviour is controversial. However, pharmaceutical development suggests that, when combined, GLP-1 and GIP display synergistic actions on appetite regulation.[20] When used therapeutically, GLP-1 receptor agonists induce weight loss and satiety.[21,22]

Although the administration of GIP alone does not appear to affect human appetite or energy intake, recent mouse studies indicate that GIP can influence

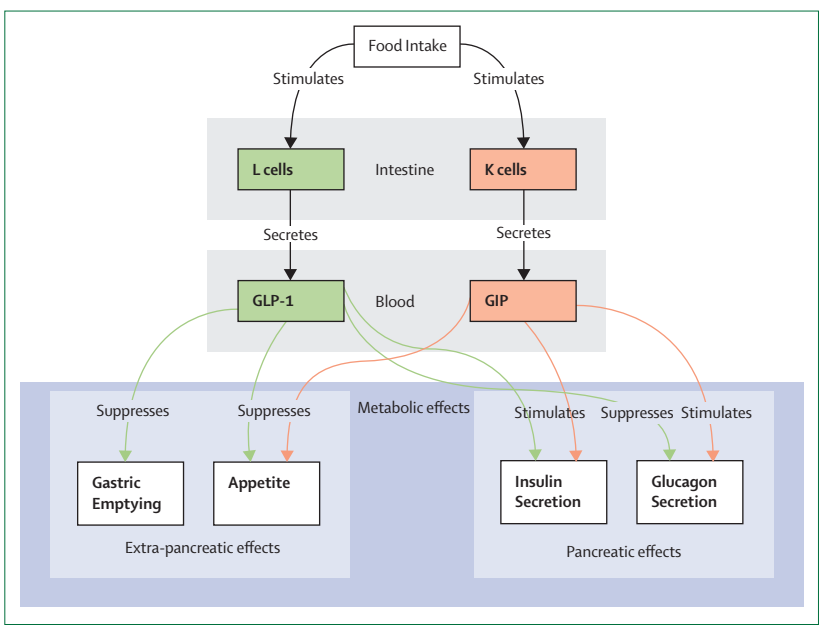

Figure 2: **Main effects of secreted incretin hormones after food ingestion**
GIP=glucose-dependent insulinotropic peptide. GLP-1=glucagon-like peptide-1.

bodyweight and food intake via GIP receptors in the CNS.[21] For instance, when fed a high-fat diet, CNS-specific GIP receptor knockout mice had lower bodyweight, reduced fat accumulation, and improved glucose metabolism.[23] Studies have investigated the effects of co-agonism targeting both GLP-1 receptor and GIP receptor, which can be relevant to understanding the physiological interplay of the co-secreted hormones. One study found that GLP-1 receptor and GIP receptor co-agonism decreases bodyweight and food intake via GIPR signalling in inhibitory γ-aminobutyric acid (GABA)-ergic neurons in mice.[24] Additionally, GLP-1 and GIP dual-agonists have shown superior efficacy for reducing bodyweight compared with GLP-1 alone, with these effects being mediated through CNS GIP receptor signalling in mice.[25] Letting aside controversy on whether GIP per se directly regulates bodyweight, the coordinated activity of GLP-1 and GIP on appetite and energy intake can be viewed as a part of their ability to bridge digestion with metabolism. While the insulinotropic and

glucagon-modulating effects of endogenous incretins are well established, their role in linking digestion to metabolism can be equally crucial. Table 2 illustrates how incretin-driven effects on digestion might contribute to long-term organ protection, particularly in metabolic and cardiovascular contexts.

Incretin effects on the cardiovascular system

Incretin hormones have been widely studied for their ability to protect vascular function in preclinical models and in humans.[26] From a molecular perspective, GLP-1 receptor agonists, such as exenatide, stimulate endothelial nitric oxide production via endothelial nitric oxide synthase (eNOS) phosphorylation, mediated through AMP-activated protein kinase and phosphatidylinositol 3-kinase (PI3K) and Akt pathways in human coronary arteries.[27] Liraglutide reduced inflammatory markers, such as intercellular adhesion molecule-1 and vascular cell adhesion molecule-1, improving endothelial function in a murine model,[28] and enhancing endothelial health by inducing eNOS phosphorylation and suppression of adhesion molecule expression via NF-κB inhibition in mice.[29] GLP-1 receptor agonists exhibit anti-inflammatory and anti-atherogenic effects in endothelial cells, smooth muscle cells, and macrophages, possibly contributing to cardiovascular protection. In mice, GLP-1 suppresses foam cell formation by downregulating CD36 and ACAT-1 in macrophages.[30] GLP-1 receptor agonists also protect endothelial cells from apoptosis induced by advanced glycation end products (AGEs) by increasing the Bcl-2 to Bax ratio, reducing caspase activities, and modulating matrix metalloproteinase expression in mice.[31] GLP-1 receptor agonists affect atherosclerotic lesions by inhibiting plaque progression and promoting stabilisation by reducing macrophage infiltration and calcium deposition in plaques, in mouse models.[32]

GIP has various effects on endothelial cells that are crucial for vascular function. GIP receptors are expressed in multiple endothelial cell types and their splice variants differ depending on the cell type. This diversity in receptor expression leads to cell type-dependent activation of secondary messengers, such as calcium and cAMP, in immortalised human endothelial cells.[33,34] GIP can stimulate different pathways leading to the production of endothelin-1 (ET-1) and nitric oxide, which have opposing effects on vascular tone. For instance, GIP induces ET-1 secretion in hepatic artery endothelial cells but stimulates nitric oxide production in portal vein endothelial cells, highlighting the differential effects of GIP on various vascular beds. GIP can promote endothelial cell proliferation, as evidenced by increased thymidine incorporation. ET-1 mediates this proliferative response in specific endothelial cell types, such as human umbilical vein endothelial cells (HUVECs), but not in others, indicating a role for GIP in endothelial cell growth and repair.[34] The internalisation of GIP receptors and their continued signalling suggests a sustained activation of cAMP and protein kinase A, which might contribute to prolonged cellular responses on the early endosome from endothelial cells.[35] The effect of GIP is particularly evident in the small intestine and the portal system. When GIP is secreted in response to meal ingestion, increased blood flow in some vascular beds and decreased blood flow in others might benefit digestion and nutrient absorption.[33] GIP has been shown to suppress neointimal hyperplasia and facilitate endothelial regeneration in mouse models of peripheral artery disease. This effect is mediated by nitric oxide production and involves a calcium-mediated GIP receptor signalling pathway.[36] GIP can also block AGE signalling pathways in HUVECs by inhibiting AGE-induced reactive oxygen species generation.[37] Overall,

	Role in digestion	Role in organ protection	Clinical result
GLP-1 mediated vasodilation	Direct blood flow to the digestive tract	Reduce blood pressure and cardiac afterload	Anti-hypertensive effect; reduced MACE rates
Stimulation of nitric oxide	Improvement in endothelial response	Reduced atherogenesis	Reduced MACE rates
Anti-inflammatory effect of GLP-1	Prevents the metabolic toxic effects of nutritients	Reduced vascular inflammation in atherogenesis	Reduced MACE rates
GIP-mediated peripheral vasoconstriction	Avoids diverting blood flow from splanchnic circulation	Prevents excess hypotension	Self-limiting blood pressure control (no hypotension)
Increase in heart rate and inotropic effects	Sustains blood flow increase that is required for the postprandial state	Improves cardiac contractility	Reduction in adverse cardiac events
Myocardial perfusion	Instrumental to sustain postprandial blood flow	Improves myocardial flow reserve to reduce ischaemia	Reduction in adverse cardiac events
Cerebral vasodilation	Delivery of hormones and metabolites to food intake-regulating areas	Brain circulatory plasticity and metabolic coupling	Reduced stroke rates; neuroprotection
Muscle vasodilation	Couples nutrient absorption with peripheral disposal	Improved metabolic status and insulin sensitivity	Better metabolic status
Adipose tissue perfusion	Effective delivery of fatty acids to the adipose tissue for storage	Reduced lipotoxicity and ectopic fatty acid deposition	Better metabolic status
Kidney perfusion	Handling of sodium loads; elimination of toxins	Improves renal function	Reduced adverse renal outcomes

GIP=glucose-dependent insulinotropic peptide. GLP-1=glucagon-like peptide-1. MACE=major adverse cardiovascular events.

Table 2: **Possible effects of incretins on digestion that are instrumental to organ protection**

incretins and their mimetics protect endothelial function, potentially suppress plaque progression, modulate various inflammatory and oxidative pathways, and stimulate endothelial cell proliferation and nitric oxide production, crucial for vasodilation and vascular health. Considering this extensive body of evidence, a crucial gap in current knowledge pertains to insufficient robust data supporting the extension of the protective effects of incretins on microvascular complications of diabetes, such as retinopathy and neuropathy.

Incretins increase perfusion in different organs

Physiological adaptations to nutrient ingestion include changes in blood flow, increased heart rate, and metabolic responses. These are crucial for maintaining postprandial cardiovascular homoeostasis and are influenced by the meal composition.[38] The protective effect of incretins on the cardiovascular system is better appreciated considering their role in coupling perfusion and metabolism, similar to what was observed for insulin, which increases perfusion to maximise peripheral glucose disposal.[39] The coupling of perfusion with substrate oxidation is crucial to understanding metabolic processes in various biological systems (figure 3).

Brain

Both GLP-1 and GIP receptors are expressed in various regions of the brain, and play important roles in appetite regulation, neuroprotection, and cognitive function.[40] These receptors are involved in glucose sensing and metabolism, indicating that endogenous incretins can directly influence brain glucose uptake and use.[41,42] In rodent models, GLP-1 receptor activation dilates cerebral arterioles and improves functional capillary density, enhancing cerebral blood flow, and supporting neuroprotection. In both preclinical and clinical studies, during the postprandial phase, peak GLP-1 levels correlate with increased cerebral blood flow in areas linked to satiation and food regulation, as shown in PET studies. This fine regulation of postprandial cerebral perfusion allows key brain regions to sense peripheral signals, including hormones and metabolites.[43] GLP-1 reduces glucose metabolism in specific human brain areas by modulating glucose transport and phosphorylation, key processes for glucose sensing and homoeostasis.[44,45] This transport is facilitated by brain endothelial cells and is crucial to GLP-1's neuroprotective and metabolic effects. The use of GLP-1 analogues in type 2 diabetes can also increase blood–brain glucose transfer capacity, restoring glucose transport at the blood–brain barrier to levels seen in healthy individuals.[44] GLP-1 increases glucose clearance and reduces brain glucose levels by activating hexokinase, which can be protective in stroke and Alzheimer's disease.[46,47] When coupled to the ability of incretins to modulate glucose metabolism and oxidative stress, these metabolic effects can explain the potent effect of GLP-1 against neurodegeneration.[48,49]

GLP-1 and GIP reduce oxidative stress and inflammation, partly by regulating microglial activity. Both promote expression of neurotrophic factors, such as brain-derived neurotrophic factor, glial cell-line derived neurotrophic factor, and nerve growth factor, indicating their role in supporting brain metabolism.[50] In mice and in vitro, GIP maintains neuronal health by enhancing glucose uptake and reducing oxidative stress. GIP's neuroprotective action could rely on preventing ferroptosis via the Epac and Rap1 signalling pathway, which helps preserve neuronal integrity and counteracts age-related brain damage.[51] In summary, incretin hormones, such as GLP-1 and GIP, modulate brain perfusion, glucose metabolism, and oxidative balance

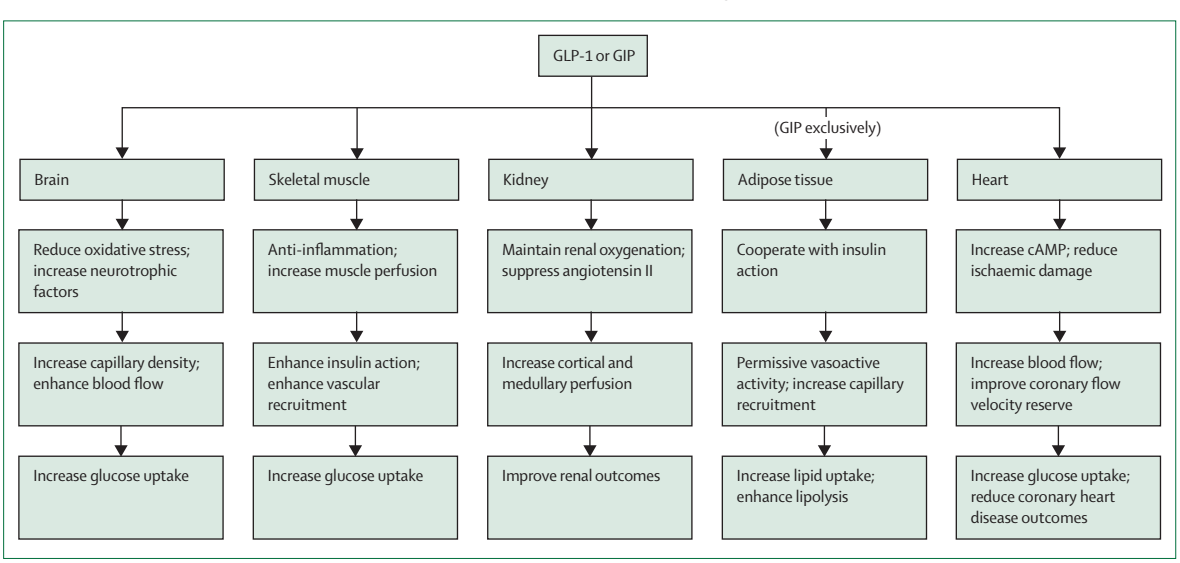

***Figure 3*: Role of incretins in the perfusion and metabolism in various organs and tissues**
GIP=glucose-dependent insulinotropic peptide. GLP-1=glucagon-like peptide-1.

with diverse mechanisms, contributing to their potential function in preventing or treating neurodegenerative diseases.[52]

Skeletal muscle

In humans, exogenous infusion of native GLP-1 can considerably increase skeletal muscle microvascular blood flow, enhancing whole-body glucose uptake in the fed state, which potentially explains the therapeutic role for GLP-1 receptor agonists in improving glycaemic control.[53] GLP-1 recruits skeletal muscle microvasculature in healthy people at physiological concentrations. This recruitment is associated with improved postprandial glycaemic control and tissue function, indicating beneficial vascular actions of GLP-1 beyond its direct glycaemic effects, in healthy people.[54] This effect has been confirmed by studies showing that GLP-1 infusion potently recruited muscle microvasculature in the presence of either acute or chronic insulin resistance by increasing muscle microvascular blood flow.[55] In people with obesity and microvascular insulin resistance, GLP-1 maintains its vasodilatory effects, increasing microvascular blood volume in both skeletal and cardiac muscles. When infused alongside GLP-1, GIP can reduce the muscle microvascular perfusion effects induced by GLP-1. This interaction suggests that GIP can modulate the vascular actions of GLP-1 via specific signalling pathways—eg, balancing ET-1 and nitric oxide.[56] GLP-1 improves muscle microvascular perfusion in rats fed a standard diet or a high-fat diet.[56] Notably, GLP-1 is efficacious in improving perfusion even in rats fed a high-fat diet, which typically exhibit increased visceral adiposity and higher fasting levels of insulin and incretin hormones. In isolated soleus muscle strips, GIP increases glucose uptake by the muscle independently of blood flow.[57] However, data obtained from humans (following an oral glucose tolerance test) suggest that GIP is involved in the impaired microvascular response to glucose challenge.[58] By contrast, preliminary data, also in humans, suggest that GIP administration leads to a considerable increase in microvascular perfusion.[59] The counterbalancing effect of GIP might be seen as functional in redirecting blood flow preferentially to the splanchnic circulation during digestion without diverting it to the periphery, but further studies are needed to reconcile the role of GIP in skeletal muscle perfusion.

Kidney

Activation of GLP-1 receptors—present in large and medium sized renal arteries but not in the tubules or glomeruli—appears to increase medullary and cortical perfusion in the human kidney. The acutely increased renal plasma flow and glomerular filtration rate observed in rodents that received pharmacological doses of GLP-1 suggests a direct effect of GLP-1 receptor activation on the renal vasculature.[60] In healthy men, acute infusion of physiological levels of GLP-1 did not increase renal plasma flow but significantly decreased plasma levels of renin.[61] However, in another study involving healthy male participants, GLP-1 infusion significantly increased medullary perfusion by 32% and cortical perfusion by 13% compared with placebo.[62] The effect of GLP-1 was observed in humans without significant changes in renal arterial blood flow, suggesting that GLP-1 redistributes regional perfusion independently of overall blood flow changes. Notably, GLP-1 preserves renal oxygenation during sodium loading, crucial for preventing renal hypoperfusion and ischaemia, and possibly mediated by its ability to suppress angiotensin-II.[63] In people with overweight, acute infusion of the GLP-1 receptor agonists exenatide increased renal plasma flow,[64] but in another study performed in patients with type 2 diabetes, renal haemodynamics were not affected.[65] As a clinical readout of this physiological function, it is noteworthy that therapy with GLP-1 receptor agonists is associated with improved renal outcomes in participants with type 2 diabetes.[66] A dedicated trial with semaglutide, the Evaluate Renal Function with Semaglutide Once Weekly (FLOW) trial, has shown a significant 24% relative risk reduction of the composite kidney outcome in patients with albuminuric diabetic kidney disease.[67] This trial, along with a recent meta-analysis, provide substantial insight into kidney-related benefits of GLP-1 receptor agonists.[68]

Expression of GIP receptors in the kidney is not well reported[18] and its direct action on this organ is still unclear. Nonetheless, the dual GIP and GLP-1 receptor agonist tirzepatide is associated with improved kidney outcomes, including albuminuria, in adults with type 2 diabetes at increased cardiovascular risk,[69,70] although it should be mentioned that whether GIP receptors play a key role in the effects of tirzepatide in humans is debated.[71]

Heart

During the postprandial phase, an increase in intramyocardial blood flow occurs to meet the heightened metabolic demands associated with nutrient absorption and systemic haemodynamic adjustments. In humans, naturally secreted GLP-1 induces coronary artery vasodilation via mechanisms primarily mediated by nitric oxide-dependent interactions between endothelial and smooth muscle cells.[72]

In coronary arterial smooth muscle cells, GLP-1 enhances ATP-sensitive potassium channel currents, leading to vasodilation.[73] Receptor-dependent and receptor-independent pathways have been implicated. The GLP-1 receptor-dependent pathway involves cAMP and cGMP secondary messengers and increases coronary blood flow.[74] The GLP-1 receptor-independent pathway implicates the cleavage metabolite GLP-1(9-36) to induce vasodilation with cGMP and eNOS. Along with the effect on blood flow, GLP-1 and its metabolites protect against ischaemic cardiac injury by modulating mitochondrial function, shifting substrate use towards glycolysis and

glucose oxidation, and increasing cAMP levels.[75–77] Experimental studies show that chronic liraglutide therapy in Zucker rats with obesity enhances vasodilation in both coronary macrocirculation and microcirculation by reducing myocardial inflammation.[78] Complementing these findings, a study by Stone and colleagues using a porcine model of coronary artery disease showed that semaglutide improved myocardial perfusion, cardiac function, and reduced fibrosis and apoptosis, effects mediated via the AMP-activated protein kinase–eNOS pathway and observable even under cardiac stress.[79]

In people with type 2 diabetes, exenatide increases myocardial blood flow and coronary flow reserve,[80] which can contribute to reducing myocardial infarct size, as shown in patients with ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention.[81–83] In patients with STEMI, liraglutide was associated with a lower prevalence of the no-reflow process after percutaneous coronary intervention.[84] In patients with type 2 diabetes and no history of coronary artery disease, 10 weeks of liraglutide therapy had no significant effect on coronary and peripheral microvascular function.[85] In patients with stable coronary heart disease, liraglutide did not affect myocardial glucose uptake and myocardial blood flow reserve after 24 weeks of treatment.[86] Similar neutral findings were observed in women with overweight.[87] At variance, for participants with type 2 diabetes without cardiovascular disease randomly assigned to pioglitazone or liraglutide, improved myocardial perfusion, energetics, and 6-min walk distance was observed in the liraglutide group.[88] Studies specifically examining the effects of GIP on coronary blood flow are scarce. Based on correlative data, an effect opposite to that of GLP-1 has been hypothesised,[58] recalling what has been observed in the regulation of skeletal muscle microcirculatory flow and might be instrumental to maintain splanchnic blood flow.

Adipose tissue

Although GLP-1 receptors do not appear to be expressed in the adipose tissue, GIP receptors are abundantly present. GIP considerably affects blood flow in adipose tissue, particularly in lean individuals. GIP, in combination with insulin, increases blood flow and triglyceride clearance in subcutaneous abdominal adipose tissue by recruiting capillaries, which enhances lipid uptake and metabolism.[89] This GIP-mediated effect is reduced in people with obesity,[90] a condition reversed by weight loss. GIP infusion, especially when combined with hyper-insulinaemic conditions, significantly increases blood flow in subcutaneous abdominal adipose tissue. This effect is observed as a four-fold increase in blood flow during GIP infusion compared with control conditions.[91] Increased blood flow is associated with capillary recruitment, which enhances the interaction of circulating lipoproteins with lipoprotein lipase, promoting lipid uptake in adipose tissue.[92] Insulin plays a permissive role in the vasoactive effects of GIP and is necessary for GIP to effectively increase blood flow and triglyceride clearance in adipose tissue.

The effect of GIP on adipose tissue blood flow can have consequences. Blood flow in adipose tissue is crucial for exchanging metabolites and hormones. Conversely, disruptions of the blood flow within adipose tissue can negatively affect metabolic processes and contribute to conditions such as the metabolic syndrome.[93] With obesity, adipose tissue often exhibits reduced blood flow due to increased peripheral insulin resistance and vasoconstriction, exacerbating dysmetabolism and inflammation.[94] This reduced flow limits substrate access, leading to local acidosis and oxidative stress, further promoting inflammation. Restricting blood flow in adipose tissue can compromise glucose uptake and promote lipolysis versus lipo-synthesis.[95,96] In addition, reduced blood flow leads to adipose tissue inflammation, which triggers macrophage infiltration and adipose inflammation, promoting metabolic complications.[97] Therefore, in adipose tissue, a cooperation between GIP and insulin is instrumental in determining the metabolic responses in both postprandial and post-absorptive states.[98,99] As a result, GIP-based therapies can support healthier adipose tissue function, a critical factor in combating insulin resistance and preventing fatty acid spillover and ectopic fat accumulation

Incretins and direct substrate oxidation

Increased tissue perfusion can enhance substrate oxidation by the particular tissue, but the net effect depends on specific conditions, such as substrate type, physiological state, and additional factors, such as temperature and incretin activity.[100] By modulating perfusion in various organs, incretin hormones establish the essential condition for substrate delivery and oxidation, but whether they also promote metabolic use of nutrients is debated. In humans, it is difficult to assess the direct effect of GLP-1 on substrate oxidation because of the interfering effect of slowed gastric emptying and the consequent delayed substrate absorption.[101,102] Notably, GIP plays a crucial role in switching from fat oxidation to fat accumulation under enhanced insulin action.[15,103] Higher fasting plasma GLP-1 concentrations are associated with greater rates of energy expenditure and fat oxidation independent of age, sex, and body composition.[104] In an ischaemia or reperfusion injury model, GLP-1 provides a compensatory substrate switch to anaerobic glycolysis in the ischaemic area to overcome the energetic deficit in this region in the face of reduced tissue oxygenation.[105] Fasting levels of GIP are positively associated with the fasting respiratory quotient, whereas GLP-1 showed no significant association.[106] Also, GLP-1-based therapies have the potential to positively affect substrate oxidation by decreasing the levels of reactive oxygen and nitrogen species,[107] or by modulating energy metabolism.[108] A recent paper shows in a mouse model

that the dual GLP-1 receptor and GIP receptor agonist tirzepatide increases fat oxidation; a similar effect is seen in individuals with obesity randomly assigned to receive tirzepatide.[109] While fat use increased, glucose and protein oxidation decreased. This shift might help preserve lean mass while promoting fat loss, according to the authors. Of note, specific amino acids, such as branched chain amino acids (BCAA), methionine, tryptophan and its metabolites, and glutamate can also positively influence obesity and its complications.[110] Recent findings in mice have shown that tirzepatide significantly reduces circulating levels of BCAAs and their corresponding keto acids, both of which are linked to insulin resistance in humans.[111] This effect could also have cardiovascular implications, as shown by Mengya Chen and colleagues where tirzepatide enhances BCAA catabolism, reduces BCAA accumulation, and suppresses mTOR signalling. These molecular changes collectively contributed to improved cardiac function and favourable post-myocardial infarction remodelling.[112]

Incretin replacement in type 2 diabetes

Understanding the therapeutic implications of incretin replacement in type 2 diabetes is crucial to translate the physiological role of GLP-1 and GIP in coupling nutrients delivery with cardiovascular adaptations. The incretin effect is significantly reduced in people with type 2 diabetes:[113] GLP-1 production is reduced although its ability to induce insulin secretion is largely preserved, while the insulinotropic effect of GIP is predominantly reduced rather than the incretin effect as a whole.[114] This effect is further complicated by alterations in DPP-4 activity, which tends to be enhanced locally and systemically in type 2 diabetes.[115] Therefore, restoring incretin physiology in type 2 diabetes can be particularly challenging. GLP-1 based therapies have been successful in improving glucose and weight management, although not all attempts have resulted in the same degree of cardiovascular and renal protection. Whether this variability is due to the blood concentrations achieved with the diverse GLP-1 receptor agonists formulations, the specific molecular structure (eg, human-based or exendin-based),[116] or their peak or duration of action remains unclear. Cardiovascular outcome trials do not help in dissecting these points. The short-acting GLP-1 receptor agonist lixisenatide did not exert cardiovascular protection in patients with type 2 diabetes after an acute coronary syndrome,[117] while the daily use of GLP-1 receptor agonist liraglutide exerted significant protection against MACE in type 2 diabetes and stable cardiovascular disease.[118] Lixisenatide and liraglutide are very different in their effects on the GLP-1 receptor: lixisenatide is a short-acting GLP-1 that causes intermittent activation of the GLP-1 receptor; conversely, liraglutide, results in continuous activation of the GLP-1 receptor and can be considered a long-acting GLP-1 receptor agonist. A similar degree of protection was achieved with the long-acting weekly GLP-1 receptor agonists dulaglutide and semaglutide,[119] whereas the GLP-1 receptor agonist with longest duration of action (exenatide once weekly) failed to achieve a significant reduction in MACE rates versus placebo.[120]

In the trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) trial, there was no clear dose-dependency in the cardiovascular benefit exerted by weekly semaglutide at either 0·5 mg or 1·0 mg.[119] Two major trials have evaluated the cardiovascular effects of an oral GLP-1 receptor agonist. In the small Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes (PIONEER-6), oral semaglutide at 14 mg—achieving plasma levels similar to 0·5 mg of weekly subcutaneous semaglutide—was noninferior to placebo on MACE rates.[121] In contrast, in the more recent large and longer Semaglutide Cardiovascular Outcomes (SOUL) trial, oral semaglutide at 14 mg allowed a significant 14% reduction in MACE compared with placebo.[122] It could be argued that the cardiovascular effects might be specific for human-based (liraglutide, dulaglutide, and semaglutide) versus exendin-based (lixisentide and exenatide) GLP-1 receptor agonists, although the positive results of the Effect of Efpeglenatide on Cardiovascular Outcomes (AMPLITUDE-O) trial with exendin-based efpeglenatide do not support this hypothesis.[123] It should be noted that therapies currently available do not simulate the physiological release of incretins in the portal circulation. Even oral semaglutide that is absorbed in the stomach, reaches the systemic circulation far more readily than when portally administered.[124] Therapy with DPP-4 inhibitors, which should rescue endogenous GLP-1 levels within the physiological range,[125] have a modest effect on glycaemia, no significant weight lowering capacity, and provide no evidence of cardio–renal protection.[126] Rather, providing supraphysiological activation of the GLP-1 receptor appears to be needed to achieve clinically-relevant benefits on disease control and organ protection. Whether cardiovascular outcomes have to do with achieving a certain threshold of GLP-1 receptor activation in the splanchnic district is a fascinating hypothesis that deserves attention.

Evolutionary outlook and conclusion

The evolutionary significance of incretin hormones lies in their conserved genetic structure and adaptation to species-specific functions in time. Incretin hormones are encoded by the proglucagon and GIP genes, which are single-copy genes in mammals with conserved exon–intron structures. The genes for GLP-1 and GIP are present in diverse vertebrate species, indicating that their origin predates the earliest vertebrate divergences.[127] The expression and projections of GLP-1-producing neurons are highly conserved between rodent and primate brains,

 Published online July 7, 2025 https://doi.org/10.1016/S2213-8587(25)00166-4

suggesting a fundamental role in brain function across these species.[128] In nonhuman primates, GLP-1 receptors are localised to cell bodies and fibre terminals in specific brain regions. The highest accumulation of GLP-1 receptors is found in the hypothalamic and brainstem regions, which are crucial for regulating feeding behaviour. In *Drosophila melanogaster*, the midgut-derived hormone neuropeptide F (NPF) acts as an incretin-like hormone.[129,130] NPF regulates lipid metabolism by suppressing glucagon-like hormone production and enhancing insulin-like peptide secretion. Loss of NPF function leads to metabolic dysfunctions, such as lipodystrophy, hyperphagia, and hypoglycaemia, indicating NPF's crucial role in sugar-dependent metabolism.[130] Exendin-4, a peptide found in the saliva of the Gila monster, plays a major role in the lizard's biology. This peptide is essential in the response to mechanical stimulation, such as biting, rather than food detection by smell or taste.[131] Exendin-4 might enhance the metabolic response to large meals by potentiating insulin secretion and other extra-pancreatic actions, aiding in nutrient storage.[132,133] Bednarova and colleagues have illustrated the role of glucagon-like peptides (GLPs) in insects and vertebrates.[134] Although these hormones are structurally different, they play similar roles in mobilising energy stores and mediating stress responses in both groups of animals. After binding to the receptor, GLPs activate signalling pathways that lead to the breakdown of glycogen and fat, making energy available for a fight or flight response. GLPs, particularly GLP-1, have also been implicated in stress responses, such as activation of hypothalamic corticotropic releasing neurons, leading to increased corticosterone secretion.[135,136] In these terms, beyond cardiovascular effects essential to ensure effective substrate delivery, incretins could also support physiological responses to stress. In non-mammalian species, incretins influence various activities related to stress responses. Similarly, in humans, incretin signalling is involved in stress hyperglycaemia,[137,138] suggesting an evolutionary link. For instance, GLP-1 is pivotal in managing chronic stress by influencing the hypothalamic–pituitary–adrenal (HPA) axis and related neuroendocrine pathways, with GLP-1 receptor signalling in the hypothalamic paraventricular nucleus being crucial for coordinating the neuroendocrine responses to stress.[136] Thus incretins could serve as a crucial evolutionary link between digestion and substrate oxidation, orchestrating substrate allocation to optimise the body's fight or flight response. This finely tuned mechanism underscores the importance of a robust cardiovascular system, essential for survival and peak physiological performances.

The transition from stress regulation in primitive species to metabolic control in mammals can be understood as a process whereby existing biological mechanisms are co-opted for new functions due to changing selective pressures. What began as a survival mechanism to cope with environmental stress in early organisms was later repurposed for energy balance and metabolic control in more complex species, where feeding and digestion became more central to survival. In modern eras, survival probabilities are less related to stress response and more related to nutrition and efficient metabolism of nutrients (figure 4). Thus, the evolutionary conservation of incretins reflects their fundamental importance in organismal survival, with their function adapting in time to fit the specific needs of different species. This conservation seems to be confirmed by the accumulating wealth of data showing that incretin-based therapies prolong survival; we propose that this is achieved by translating their digestive roles into organ protection.

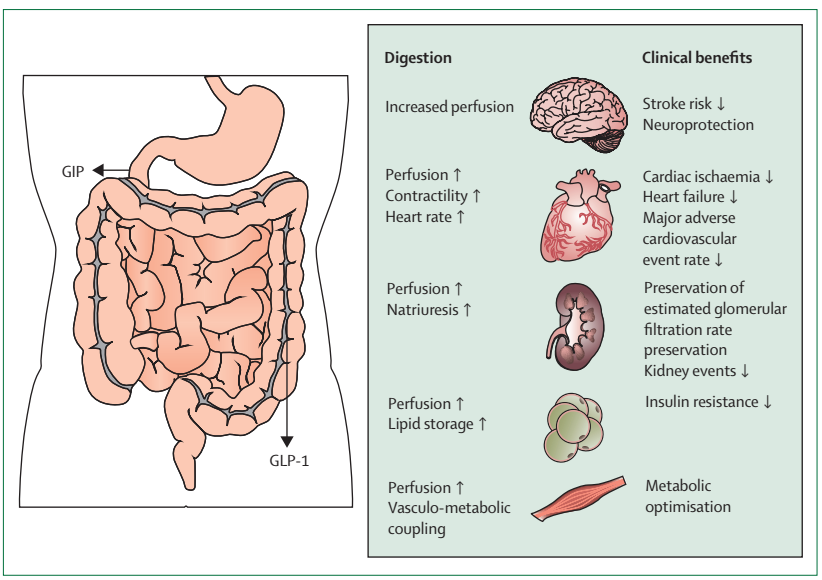

Figure 4: **Effects of incretins on digestion and the possible resulting clinical benefits**
Effects of incretins on digestion and the possibe resulting clinical benefits in the brain, heart, kidneys, adipose tissue, and muscles. GIP=glucose-dependent insulinotropic peptide. GLP-1=glucagon-like peptide-1.

Search strategy and selection criteria

References for this Review were initially identified from searches of PubMed for articles published from January, 1960, to Feb 28, 2025, with the search terms: (["GLP-1 receptor agonist" OR "glucagon-like peptide-1 receptor agonist" OR "liraglutide" OR "semaglutide" OR "tirzepatide" OR "exenatide" OR "Efpeglenatide" OR "dulaglutide"] AND ["cardiovascular protection" OR "cardiovascular disease"] AND ["metabolism" OR "oxidation" OR "tissue perfusion" OR "evolution"]). Articles resulting from these searches and relevant references cited in these articles were reviewed. Only articles published in English were selected.

Contributors
AA and GPF were responsible for conceptualisation, data curation, formal analysis, investigation, methodology, supervision, validation and verification of data, writing, and preparation, creation or presentation of data.

Declaration of interests
AA received honoraria for speaker activities, for serving on advisory boards, or consultancy from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Amarin, Bruno Farmaceutici, Amgen, Novo Nordisk, and Sanofi. GPF received honoraria for speaker activities, for serving on advisory boards, or consultancy from AstraZeneca, Boehringer Ingelheim, Eli Lilly, Guidotti, Novartis, Novo Nordisk, and Sanofi.

Acknowledgments
No funding was obtained for this Review. During the preparation of this work, the authors used WriteMe from ChatGPT to improve the editing of the manuscript. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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