White paper

# Important aspects to consider about GLP-1 and GIP

Reports showing that glucagon-like peptide (GLP-1) lowers glucose levels, and glucose-dependent insulinotropic polypeptide (GIP) stimulates insulin secretion led to the development of the first GLP-1 receptor agonist exenatide, followed by the dual GIP and GLP-1 receptor agonist tirzepatide. As we continue to learn about the actions of GLP-1 and GIP, the story keeps evolving. However, it is important to use accurate quantitative methods to ensure that scientists can precisely measure and analyze these molecules.

This white paper focuses on some of the significant analytical factors that should be considered when measuring circulating GLP-1 and GIP.

## Incretin hormones

The two major incretin hormones are glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide (GIP) [1,2]. Incretin hormones are released in the gut and stimulate glucose-dependent insulin secretion in response to food intake. They execute their actions by binding to their respective receptors (GLP-1R and GIP-R) and activating signalling cascades inside target cells. Both hormones stimulate insulin secretion, but a major difference between them is that GIP enhances the postprandial glucagon response, while GLP-1 suppresses it.

Because of GIP and GLP-1's ability to decrease glucose levels in a glucose-dependent manner by enhancing insulin secretion and suppressing the glucagon response, GIP and GLP-1 receptor agonists have attracted attention for their potential treating type 2 diabetes mellitus (T2DM) patients [2,3]. However, in T2DM patients, the incretins effect is reduced despite their relatively normal secretion, where the insulinotropic effects of GLP-1 are mildly impaired and GIP has almost no acute insulinotropic activity [2].

It is important to mention that GIP and GLP-1 have been described as satiety-signalling hormones also [4,5]. Patients suffering from obesity can have high levels of GLP-1 and still not feel satisfied, indicating that they may suffer from GLP-1 insensitivity, much like T2DM patients are insensitive to insulin [6,7,8]. In this scenario, the ability for GIP agonism to reduce GLP-1-induced illness behaviours may offer a solution in for the treatment of obesity and diabetes [5]. GLP-1 satiety-related signalling is likely to be mediated through the nervous system via the vagus nerve [9,10].

## Processing of proglucagon to GLP-1

GLP-1 is derived from proglucagon, which is also the precursor for several other peptides such as glucagon, GLP 2, glicentin, oxyntomodulin, and major proglucagon fragment (MPGF). MPGF shares sequences with both GLP-1 and GLP-2, and it is a product released mainly from pancreatic cells. Depending on the type of prohormone convertase (PC) present in the cell, proglucagon takes different paths in its post-translational processing. The L-cells in the gastrointestinal tract predominantly express PC 1/3 and process proglucagon into GLP-1 as well as GLP-2, oxyntomodulin and glicentin. The L-cells secrete GLP-1 at low basal levels during fasting or interprandial state. Pancreatic α-cells primarily express PC2 while PC 1/3 is expressed at lower levels. They secrete glicentin-related pancreatic polypeptide (GRPP), MPGF, and glucagon [11,12] (Figure 1). Depending on the N-terminally truncated products, a glycine extended peptide GLP-1(7–37) and GLP-1(7–36) amide can be detected by the pancreatic receptor, and are the active species *in vivo* [12].

## Processing of proGIP to GIP

The glucose-dependent insulinotropic peptide (GIP), the first incretin to be described, is a 42-amino-acid hormone secreted in response to food intake [13,14]. This incretin is derived from the post-translational processing of a 153-amino acid precursor encoded by the *gip* gene, proGIP, by PC1/3 in enteroendocrine K cells [15].

Mercodia

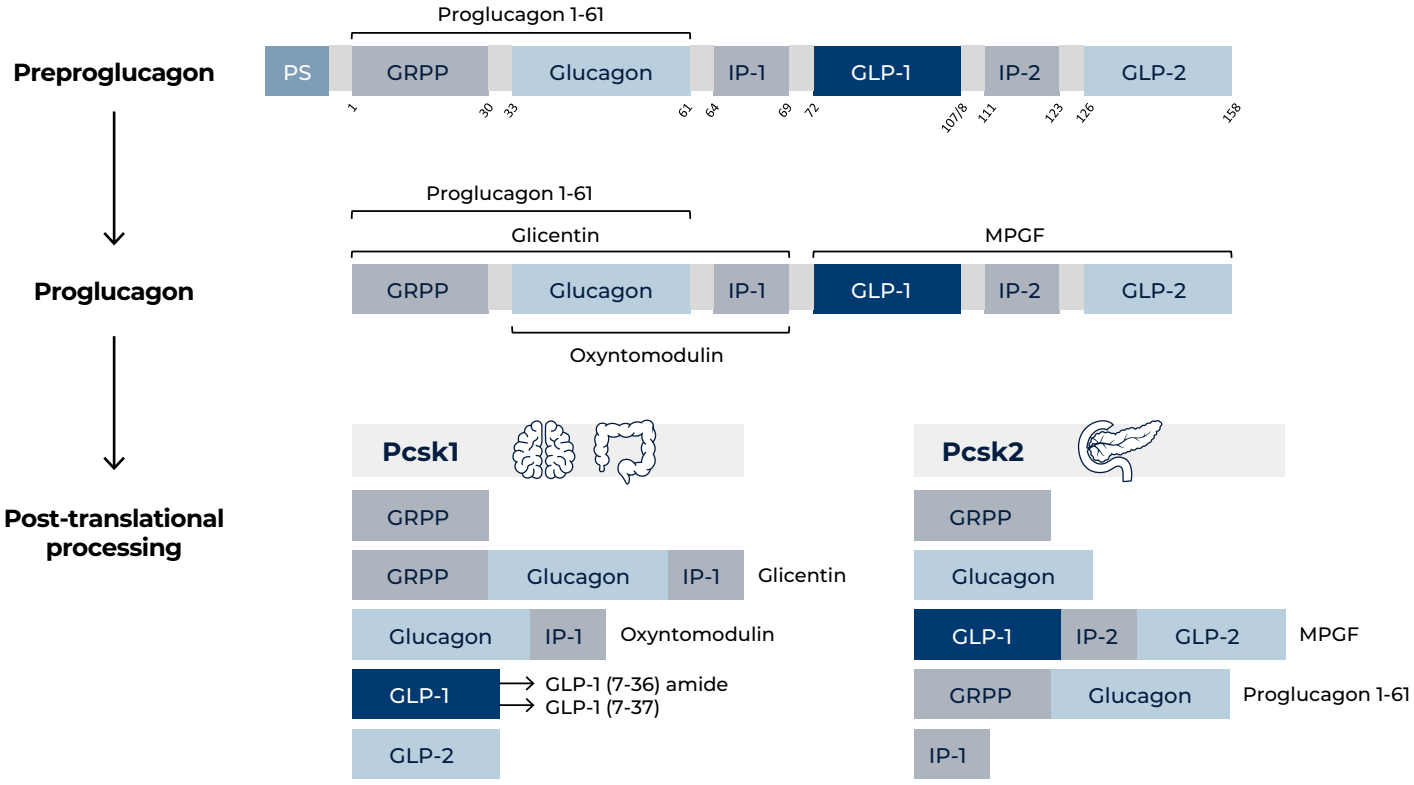


**Figure 1.** Schematic processing of proglucagon, showing post-translational processing by Pcsk1 (brain and intestinal L-cells) or Pcsk2 (Pancreatic α-cells). PS: Signal peptide; GRPP: glicentin-related polypeptide; IP-1: intervening peptide-1; GLP-1: glucagon-like peptide-1; IP-2: intervening peptide-2; GLP-2: glucagon-like peptide-2; MPGF: major proglucagon fragment; PCSK1: prohormone convertase 1/3; PCSK2: prohormone convertase 2 (modified from [11,12]).

GIP is a member of a family of structurally related hormones that includes secretin, glucagon, and vasoactive intestinal peptide [15]. It is synthesized and secreted from K cells of the upper small intestine and acts directly on pancreatic islets to stimulate insulin secretion from pancreatic β cells [13,14]. It has been shown however, that endogenous GIP may stimulate glucose-dependently insulin secretion in gastrectomized patients [13].

## GLP-1 amidation

GLP-1(1-37) corresponds to amino acid residues 72-108 of proglucagon, an inactive form of GLP-1. For it to be active, needs to be further processed into GLP-1(7-37) or GLP-1(7-36) amide, with the latter version being amidated after removal of the C-terminal glycine residue. Both isoforms have been shown to be equally potent in activating the GLP-1R, and the active forms are sometimes also referred to as “intact” GLP-1 [16,17,18].

GLP-1(7-36) amide is the major secreted isoform from the gut in humans, and it has been shown that levels of circulating amidated GLP-1 change significantly upon stimulation, while the levels of glycine-extended GLP-1(7-37) remain relatively unchanged [13,16]. The amidated forms of GLP-1, (x-36) amide, rise in circulation postprandially, while there is very little change in the glycine-extended isoforms (x-37)1 [16].

When GLP-1 secretion needs to be measured, it is important to accurately detect the amidated isoforms, since they predominate. It has been established that some commercially available assays lack specificity to detect the amidated isoforms, and as a consequence these assays will underestimate the true levels of GLP-1 [18,19].

## DPP-4 degradation of GLP-1

Upon stimulation, GLP-1(7-37) and GLP-1(7-36) amide are secreted. However, GLP-1 presents a short half-life of only a couple of minutes after been cleaved by the enzyme dipeptidyl peptidase IV (DPP-4), which is expressed near the site of GLP-1 secretion from the enteroendocrine L-cells.

DPP-4 is responsible for creating the metabolites GLP-1(9-37) and GLP-1(9-36) amide. Traditionally, the metabolites have been considered inactive, but several studies performed in dogs, rats and mice suggest that GLP-1(9-36) amide have cardioprotective effects [20,21,22]. Other studies point out that GLP-1R stimulation by exendin-4 [23] and treatment with GLP-1(9-36) amide have protective effects in neurodegenerative disease models improving stroke outcome by reducing the inflammatory response, in both cultured cells and animal models [24,25,26].

Since GLP-1(7-36) amide is rapidly degraded, its concentration in plasma is very low and small meals resulting in minor changes in GLP-1 concentrations can be difficult to detect. However, measuring both the concentration of (7-36) amide and the metabolite (9-36) amide, together called “total” GLP-1, provides a better chance of detecting small changes. In fact, for most applications it is best to measure total GLP-1, since it will not only

reflect the levels of secretion but also provide a better picture of the total effects of GLP-1 [27]. Detecting circulating GLP-1(9-36) amide provides information about the secretion of GLP-1 and that the brain received its signal via the vagus nerve [28]. Thus, studying both secretion and actions give better information and in a more comprehensive way. Certainly, for some applications, specific (7-36) amide assays may be needed, e.g., when studying DPP-4 inhibitors [29].

Several commercial assays measuring GLP-1 were evaluated in a publication by Bak *et al*. in 2014, both examining performances of the assays and the implications for clinical studies [19]. The results showed that the specificity and sensitivity of commercially available kits for the analysis of GLP-1 levels varied considerably. One assay detected none of the tested synthetic GLP-1 isoforms (GLP-1(1-36) amide, (7-36) amide, (9-36) amide, (1-37), (7-37) and (9-37)). Other assays had low recovery of non-active forms in plasma, and some only detected amidated GLP-1 [19]. This indicates that the variable performance of the tested assays should be considered when selecting which assay to use and when comparing data from different studies.

The molecule (7-36) amide will have the same chance to be detected as the (9-36) amide. This is, of course, only true if the specificity to GLP-1(7-36) amide is the same as to GLP-1(9-36) amide. If the assay specificity is only 50% to the metabolite, the advantage is gone. GLP-1 levels will then be underestimated, and any changes could go unnoticed, making such an assay suboptimal.

## DPP-4 degradation of GIP

DPP-4 is a serine protease that rapidly inactivates the incretin peptides to modulate postprandial islet hormone secretion and glycemia [30]. This means that similarly to GLP-1, GIP has also a short half-life in plasma of approximately 7 minutes in healthy individuals, and 5 minutes in individuals with type 2 diabetes [31]. This is due to its inactivation by DPP-4 into GIP(3-42) [14]. Like GLP-1, GIP in circulation is degraded by cleavage of the N-terminal two amino acids very efficiently from DPP-4, this results in the elimination of the glucoregulatory action due to a decrease in the receptor's affinity (GIP-R) [30].As described by Trzaskalski *et al*. degradation occurs within the vessels draining the mesentery and within the portal circulation and hepatic bed [30].

For detection of different fragments, some immunoassays have employed antisera directed towards the C-terminus or the mid-region of the GIP molecule. This means that such assays are unable to differentiate between intact GIP (1–42) and the N-terminally truncated peptide [32]. Nevertheless, the improvement of assays with time allowed further investigation of intact GIP and the cleaved form, making possible a better understanding of the actions in healthy humans. Moreover, this allowed a way to address to what extent DPP-4 played a physiological role *in vivo* [32].

## When to measure total GLP-1 and GIP?

Measurement of the products of proglucagon gene expression in plasma requires specific assays; as stated by professor Jens Juul Holst from the University of Copenhagen in his 2007 review, "assays for at least eight different peptides, three from the pancreas (glucagon, GRPP, major proglucagon fragment) and five from the intestine (glicentin, oxyntomodulin, GLP-1, GLP-2, and intervening peptide 2)" [18]. Regarding GLP-1, almost all intestinal GLP-1 is amidated in humans, and assays directed against the amidated form are the only ones that could reliably measure intestinal GLP-1 secretion. However, a contribution of GLP-1 (1–36) amide from the pancreas cannot be excluded [18].

When it comes to GIP, different processing of the molecule together with later enzymatic cleavage of the circulating products may lead to the existence of several different immunoreactive fragments. Some of these fragments possess biological activity [32]. This results in a complicated task for the measurement of GIP levels in an accurate way, due to the cross-reactivity with multiple fragments. Thus, identifying the right assay for measuring intact GIP (1–42) K-cell secretion might be complicated because the primary (inactive) metabolite, GIP (3–42), is often expressed in higher levels [32].

Having in consideration the characteristics of GLP-1 and GIP, and the products obtained after the induced-degradation by DPP-4, it is important not only to understand the expression levels of the molecules, but also to regard the distribution of their receptors in different organs and tissues. It has been shown that there are seven specific-transmembrane G protein-coupled receptors for GIP and GLP-1. These can be found in the islets of Langerhans in the pancreas, in the brain, and in other tissues where GIP and GLP-1 can exert biological activities. This has been elegantly shown in a review by Nauck *et al.* in 2021 (Figure 2) [2].

Further, the measurement of the activity of GLP-1 and GIP can be relevant for different treatments. Such is the case of GIP receptor agonism and antagonism, which has been highlighted for reduce weight or prevent obesity [2]. Other treatments involve lowering the effects of DPP-4 by using DPP-4 inhibitors resulting in lowering glucose levels [30,32]. Similarly, the antagonism of the GLP-1 receptor with exendin 9–39, described to block the glucose-lowering and insulinotropic effects of DPP-4 inhibition (using sitagliptin or vildagliptin) in patients with T2DM [32]. In other cases, osteoclasts depletion through treatment with denosumab has been reported to reduce circulating DPP-4 and increase GLP-1 levels [30].

Other therapies have aimed for exploiting GLP-1 and GIP and their receptors, including agonists and antagonists, and combinations with GLP-1. This is the case of the dual glucose-dependent insulinotropic polypeptides (GIP/GLP-1) receptor agonist tirzepatide. Tirzepatide is the most advanced unimolecular dual GIP/GLP-1 receptor agonist approved by the European Medicines Agency (EMA) for the treatment of T2DM patients [33].

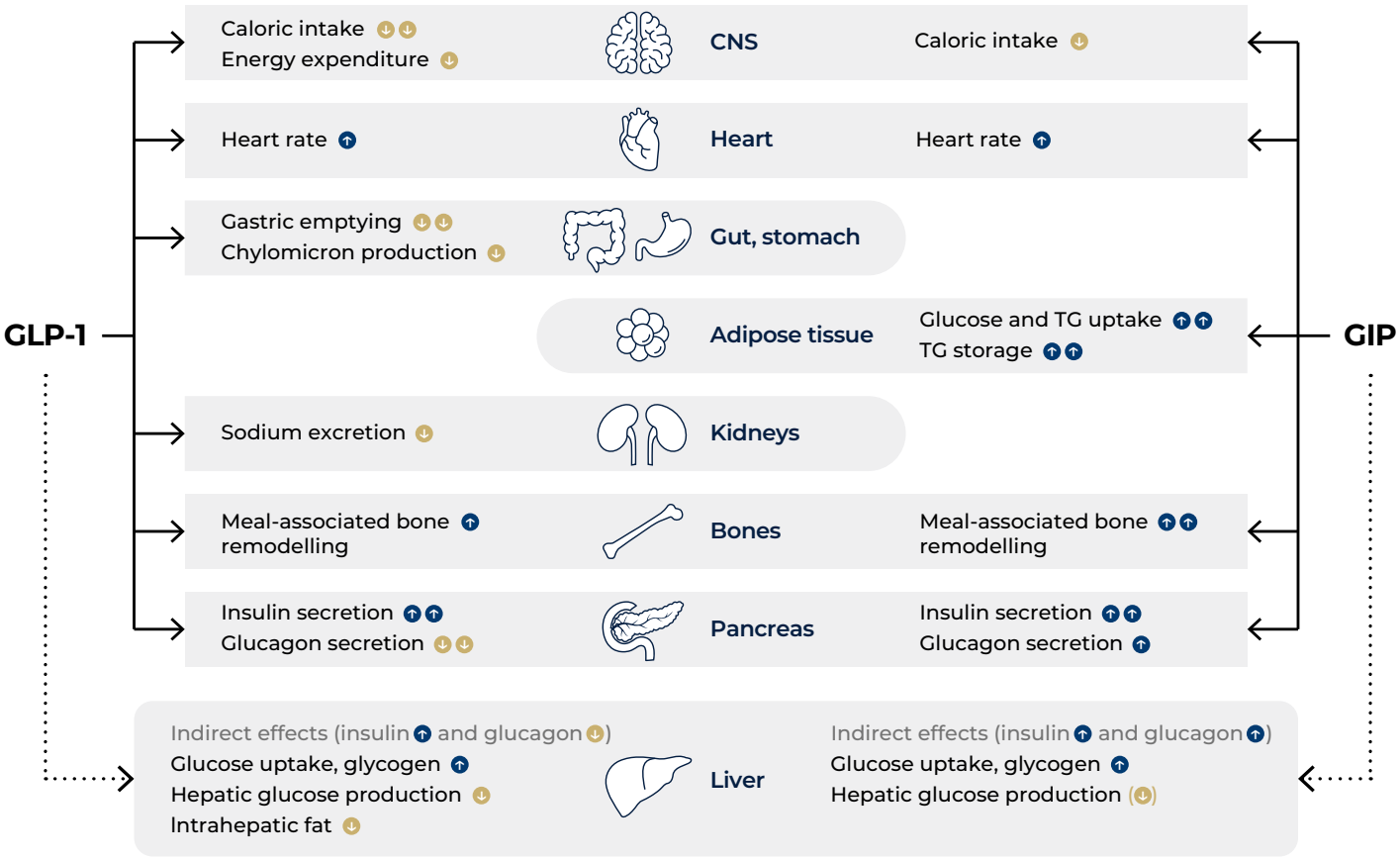


**Figure 2.** Biological effects of GLP-1 and GIP in different organs (modified from [2]).

## Wide range of physiological actions

GLP-1 and GIP are being studied in many different research settings due to the variety of physiological processes where they seem to be involved. Although the pancreatic islet cells are the major targets for GLP-1, the molecule also inhibits gastrin-induced acid secretion [34], slows gastric emptying, inhibits motility of the stomach [35,36], and affects food intake and body weight [37]. All of these actions combined with GLP-1's role in insulin stimulation and glucagon inhibition have established GLP-1 as a critical metabolic hormone.

It has also been shown that GLP-1 improves flow mediated dilation (a phenomenon in which a blood vessel dilates or expands when blood flow increases through it) and has cardiovascular protective effects [38], as well as other functions such as expansion and preservation of pancreatic β-cell mass [39,40,41], bone metabolism [42] and neuroprotection [43].

Similarly, GIP presents a variety of functions within different organs. In adipose tissue, GIP plays an important role ensuring that ingested lipids are preferentially targeted to adipocytes instead of the liver and pancreas, where they would cause lipotoxicity [14]. In the skeletal muscle, it has been suggested to facilitate the formation of new bone [14]. And in the central nervous system it has been shown to have neuroprotective effects in neurodegenerative diseases models of Alzheimer's and Parkinson's disease [14].

## Different physiological levels of GLP-1 and GIP

GLP-1 circulates at low concentrations, where "fasting plasma concentrations of total GLP-1 (including metabolites generated by DPP-4 degradation) are typically in the range of 5-10 pmol/L and can increase up to 40 pmol/L in response to a meal" [44]. Since the GLP-1 levels in healthy individuals are low, there is a strong need for sensitive methods to accurately detect GLP-1 as a biomarker in human plasma.

In certain patient groups, GLP-1 is present in abnormal concentrations. Patients which have undergone bariatric surgery show highly increased levels of GLP-1 after a meal, with concentrations up to 300 pmol/L [45,46]. Considering the unquestionable effect of bariatric surgery on GLP-1 levels in these individuals, combined with the fact that insulin levels normalize in most patients within days after surgery (long before any significant weight loss has occurred) it has been of interest to follow research in this field as more facts about GLP-1 and its actions are revealed. These findings have contributed to the understanding of how to develop better drugs for treatment of both diabetes and obesity, emphasizing the importance of accurate measurement of GLP-1.

Another patient group with reported abnormal GLP-1 levels is T2DM patients. However, the deviation from normal levels is far from what has been reported in the bariatric surgery patient population and is not always consistent across studies. It has been suggested that it is not the fasting GLP-1 levels that differ between diabetic and normal glucose tolerant patients, but rather the postprandial GLP-1 levels are significantly lower in the diabetic group [47,48]. This implies an impaired GLP-1 secretion in this group of patients.

For GIP, secretion levels have been described to be correlated to blood nutrient levels. This has been shown by analyzing fasting levels of GIP, which were measured at around 10 pmol/L, while after 1 hour of ingestion of carbohydrate and lipid-rich meals, peak up to 70-150 pmol/L [48,49]. Taking this into consideration, diet plays a role in GIP secretion and levels, where a high-fat diet has shown to increase the *gip* gene expression and hyperplasia resulting in increased levels in K cells and intestinal GIP [49]. This has been observed in other studies focused in T2DM patients, where it was found that the individuals presented increased fasting GIP levels compared to control groups [50,51].

## Treatments addressing GLP-1 and GIP

Due to the blood glucose lowering effect and the impact of GLP-1 and GIP on several important metabolic processes, the interest in therapeutically targeting this system has expanded over the last decades. Since both GLP-1 and GIP are degraded by DPP-4 within minutes of secretion, efforts have also been taken to develop drugs inhibiting the activity of DPP-4.

Currently the GLP-1 receptor agonists exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide and tirzepatide have been approved and used for treatment of patients suffering from T2DM [52,53,54]. Similarly, several DPP-4 inhibitors (also known as gliptins) have been launched and approved in different parts of the world, including alogliptin, sitagliptin, vildagliptin, saxagliptin, teneligliptin, gemigliptin, linagliptin, anagliptin, denagliptin, omarigliptin, evogliptin and trelagliptin [52,55]. The functional mechanism of all these drugs is to increase the physiological actions of GLP-1. GLP-1 receptor agonists (GLP-1 RA) are also approved for the treatment of obesity, because of GLP-1's satiety-signaling effects.

Taking into consideration the interaction between GLP-1 and GIP, research has focused as well on the creation of GIP analogs such as D-GIP$_{1–30}$, N-AcGIP(LysPAL16) and N-AcGIP(LysPAL37) [49] and GIP receptor agonists and antagonists with peptides such as Acyl GIP, LA-agonist, GIPg013, 7, and mGIP-Ant-1 [56].

Additional strategies have been evaluated to further enhance the GLP-1 effect by developing dual agonists (e.g., GLP-1/GIP receptor agonists) [57,58,59]. Dual incretin agonists are sometimes referred to as "twincretins", describing the combined activation of GLP-1- and GIP-receptors from one molecule. Among them MAR709 and tirzepatide, being tirzepatide considered "the first twincretin". For tirzepatide, the molecule has been based on the human GIP sequence and in which GLP-1R residues were introduced to yield a fivefold greater potency at the human GIPR relative to GLP-1R [60,61].

Other dual targets have focused on combining studies of GLP-1/glucagon combinational therapies, which have indicated that combining the effects of GLP-1 with the lipolytic effects of sustained glucagon receptor activation lower body weight more than what is seen with a single selective GLP-1 agonist [62].

Other studies have focused on triple agonist treatment. In 2015, Brian Finan and colleagues published a study with a triple agonist acting on the GLP-1R, GIPR and glucagon receptor [63]. The triple agonist effectively reduced body weight and diabetic complications in rodent models of obesity, and was proven to be superior to any existing dual co-agonists and best available mono-agonists [63,64]. The positive results and the advantages observed with the dual agonist therapies have also reinvigorated the development of triagonist peptides [65]. As mentioned by Alessandro Pocai in his 2023 Review, it is possible that "addressing the translatability and the mechanism(s) involved in the anti-emetic actions of GIP, may lead to next generation therapeutics without the onerous titration and the tolerability issues of current therapeutics" [65].

## Conclusions

In the last few years, expansion within the incretin field has led to new insights about GLP-1 and GIP function and relevance. The key role of these two molecules in many metabolic processes and the complex physiological interplay they present, has opened a window for new promising therapeutic approaches to the treatment of diabetes and obesity. To continue these advancements, methods to measure GLP-1 and GIP must be chosen carefully and the high demands for specificity and sensitivity must be met.

## References


1. Nauck MA, Meier JJ. Incretin hormones: Their role in health and disease. Diabetes Obes Metab. 2018;20 Suppl 1:5-21. doi:10.1111/dom.13129
2. Nauck MA, Quast DR, Wefers J, Pfeiffer AFH. The evolving story of incretins (GIP and GLP-1) in metabolic and cardiovascular disease: A pathophysiological update. Diabetes Obes Metab. 2021;23 Suppl 3:5-29. doi:10.1111/dom.14496
3. Rizvi AA, Rizzo M. The Emerging Role of Dual GLP-1 and GIP Receptor Agonists in Glycemic Management and Cardiovascular Risk Reduction. Diabetes Metab Syndr Obes. 2022;15:1023-1030. Published 2022 Apr 5. doi:10.2147/DMSO.S351982
4. Holst JJ. Incretin hormones and the satiation signal. Int J Obes (Lond). 2013;37(9):1161-1168. doi:10.1038/ijo.2012.208
5. Hayes MR, Borner T, De Jonghe BC. The Role of GIP in the Regulation of GLP-1 Satiety and Nausea. Diabetes. 2021;70(9):1956-1961. doi:10.2337/dbi21-0004
6. Højberg PV, Vilsbøll T, Rabøl R, *et al.* Four weeks of near-normalisation of blood glucose improves the insulin response to glucagon-like peptide-1 and glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes. Diabetologia. 2009;52(2):199-207. doi:10.1007/s00125-008-1195-5
7. Knop FK, Aaboe K, Vilsbøll T, *et al.* Impaired incretin effect and fasting hyperglucagonaemia characterizing type 2 diabetic subjects are early signs of dysmetabolism in obesity. Diabetes Obes Metab. 2012;14(6):500-510. doi:10.1111/j.1463-1326.2011.01549.x
8. Sandoval DA, D'Alessio DA. Physiology of proglucagon peptides: role of glucagon and GLP-1 in health and disease. Physiol Rev. 2015;95(2):513-548. doi:10.1152/physrev.00013.2014
9. Abbott CR, Monteiro M, Small CJ, *et al.* The inhibitory effects of peripheral administration of peptide YY(3-36) and glucagon-like peptide-1 on food intake are attenuated by ablation of the vagal-brainstem-hypothalamic pathway. Brain Res. 2005;1044(1):127-131. doi:10.1016/j.brainres.2005.03.011
10. Bucinskaite V, Tolessa T, Pedersen J, *et al.* Receptor-mediated activation of gastric vagal afferents by glucagon-like peptide-1 in the rat. Neurogastroenterol Motil. 2009;21(9):978-e78. doi:10.1111/j.1365-2982.2009.01317.x
11. Hurtado, V., Roncero, I., Blazquez, E., Alvarez, E., & Sanz, C. (2013). Glucagon-Like Peptide-1 and Its Implications in Obesity. InTech. doi: 10.5772/54221
12. Diz-Chaves Y, Mastoor Z, Spuch C, González-Matías LC, Mallo F. Anti-Inflammatory Effects of GLP-1 Receptor Activation in the Brain in Neurodegenerative Diseases. Int J Mol Sci. 2022;23(17):9583. Published 2022 Aug 24. doi:10.3390/ijms23179583
13. 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
14. Guccio N, Gribble FM, Reimann F. Glucose-Dependent Insulinotropic Polypeptide-A Postprandial Hormone with Unharnessed Metabolic Potential. Annu Rev Nutr. 2022;42:21-44. doi:10.1146/annurev-nutr-062320-113625
15. Kim W, Egan JM. The role of incretins in glucose homeostasis and diabetes treatment. Pharmacol Rev. 2008;60(4):470-512. doi:10.1124/pr.108.000604
16. Orskov C, Rabenhøj L, Wettergren A, Kofod H, Holst JJ. Tissue and plasma concentrations of amidated and glycine-extended glucagon-like peptide I in humans. Diabetes. 1994;43(4):535-539. doi:10.2337/diab.43.4.535
17. Drucker DJ. The biology of incretin hormones. Cell Metab. 2006;3(3):153-165. doi:10.1016/j.cmet.2006.01.004
18. Holst JJ. The physiology of glucagon-like peptide 1. Physiol Rev. 2007;87(4):1409-1439. doi:10.1152/physrev.00034.2006
19. Bak MJ, Wewer Albrechtsen NJ, Pedersen J, *et al.* Specificity and sensitivity of commercially available assays for glucagon-like peptide-1 (GLP-1): implications for GLP-1 measurements in clinical studies. Diabetes Obes Metab. 2014;16(11):1155-1164. doi:10.1111/dom.12352
20. Nikolaidis LA, Elahi D, Shen YT, Shannon RP. Active metabolite of GLP-1 mediates myocardial glucose uptake and improves left ventricular performance in conscious dogs with dilated cardiomyopathy. Am J Physiol Heart Circ Physiol. 2005;289(6):H2401-H2408. doi:10.1152/ajpheart.00347.2005
21. Sonne DP, Engstrøm T, Treiman M. Protective effects of GLP-1 analogues exendin-4 and GLP-1(9-36) amide against ischemia-reperfusion injury in rat heart. Regul Pept. 2008;146(1-3):243-249. doi:10.1016/j.regpep.2007.10.001
22. Ban K, Noyan-Ashraf MH, Hoefer J, Bolz SS, Drucker DJ, Husain M. Cardioprotective and vasodilatory actions of glucagon-like peptide 1 receptor are mediated through both glucagon-like peptide 1 receptor-dependent and -independent pathways [published correction appears in Circulation. 2008 Jul 22;118(4):e81]. Circulation. 2008;117(18):2340-2350. doi:10.1161/CIRCULATIONAHA.107.739938
23. Li Y, Duffy KB, Ottinger MA, *et al.* GLP-1 receptor stimulation reduces amyloid-beta peptide accumulation and cytotoxicity in cellular and animal models of Alzheimer's disease. J Alzheimers Dis. 2010;19(4):1205-1219. doi:10.3233/JAD-2010-1314

24. Ma T, Du X, Pick JE, Sui G, Brownlee M, Klann E. Glucagon-like peptide-1 cleavage product GLP-1(9-36) amide rescues synaptic plasticity and memory deficits in Alzheimer's disease model mice. J Neurosci. 2012;32(40):13701-13708. doi:10.1523/JNEUROSCI.2107-12.2012

25. Li Y, Glotfelty EJ, Karlsson T, Fortuno LV, Harvey BK, Greig NH. The metabolite GLP-1 (9-36) is neuroprotective and anti-inflammatory in cellular models of neurodegeneration. J Neurochem. 2021;159(5):867-886. doi:10.1111/jnc.15521

26. Huang J, Liu Y, Cheng L, *et al.* Glucagon-like peptide-1 cleavage product GLP-1(9-36) reduces neuroinflammation from stroke via the activation of insulin-like growth factor 1 receptor in astrocytes. Eur J Pharmacol. 2020;887:173581. doi:10.1016/j.ejphar.2020.173581

27. Larsen MP, Torekov SS. Glucagon-Like Peptide 1: A Predictor of Type 2 Diabetes?. J Diabetes Res. 2017;2017:7583506. doi:10.1155/2017/7583506

28. Brierley DI, de Lartigue G. Reappraising the role of the vagus nerve in GLP-1-mediated regulation of eating. Br J Pharmacol. 2022;179(4):584-599. doi:10.1111/bph.15603

29. Helmstädter J, Keppeler K, Küster L, Münzel T, Daiber A, Steven S. Glucagon-like peptide-1 (GLP-1) receptor agonists and their cardiovascular benefits-The role of the GLP-1 receptor. Br J Pharmacol. 2022;179(4):659-676. doi:10.1111/bph.15462

30. Trzaskalski NA, Fadzeyeva E, Mulvihill EE. Dipeptidyl Peptidase-4 at the Interface Between Inflammation and Metabolism. Clin Med Insights Endocrinol Diabetes. 2020;13:1179551420912972. Published 2020 Mar 20. doi:10.1177/1179551420912972

31. Kasina SVSK, Baradhi KM. Dipeptidyl Peptidase IV (DPP IV) Inhibitors. [Updated 2023 May 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK542331/

32. Deacon CF. Metabolism of GIP and the contribution of GIP to the glucose-lowering properties of DPP-4 inhibitors. Peptides. 2020;125:170196. doi:10.1016/j.peptides.2019.170196

33. Scheen AJ. Dual GIP/GLP-1 receptor agonists: New advances for treating type-2 diabetes. Ann Endocrinol (Paris). 2023;84(2):316-321. doi:10.1016/j.ando.2022.12.423

34. Schjoldager BT, Mortensen PE, Christiansen J, Orskov C, Holst JJ. GLP-1 (glucagon-like peptide 1) and truncated GLP-1, fragments of human proglucagon, inhibit gastric acid secretion in humans. Dig Dis Sci. 1989;34(5):703-708. doi:10.1007/BF01540341

35. Schirra J, Göke B. The physiological role of GLP-1 in human: incretin, ileal brake or more?. Regul Pept. 2005;128(2):109-115. doi:10.1016/j.regpep.2004.06.018

36. Marathe CS, Rayner CK, Jones KL, Horowitz M. Effects of GLP-1 and incretin-based therapies on gastrointestinal motor function. Exp Diabetes Res. 2011;2011:279530. doi:10.1155/2011/279530

37. Gutzwiller JP, Göke B, Drewe J, *et al.* Glucagon-like peptide-1: a potent regulator of food intake in humans. Gut. 1999;44(1):81-86. doi:10.1136/gut.44.1.81

38. Sheikh A. Direct cardiovascular effects of glucagon like peptide-1. Diabetol Metab Syndr. 2013;5(1):47. Published 2013 Aug 29. doi:10.1186/1758-5996-5-47

39. Stoffers DA, Kieffer TJ, Hussain MA, *et al.* Insulinotropic glucagon-like peptide 1 agonists stimulate expression of homeodomain protein IDX-1 and increase islet size in mouse pancreas. Diabetes. 2000;49(5):741-748. doi:10.2337/diabetes.49.5.741

40. Farilla L, Hui H, Bertolotto C, *et al.* Glucagon-like peptide-1 promotes islet cell growth and inhibits apoptosis in Zucker diabetic rats. Endocrinology. 2002;143(11):4397-4408. doi:10.1210/en.2002-220405

41. Li Y, Hansotia T, Yusta B, Ris F, Halban PA, Drucker DJ. Glucagon-like peptide-1 receptor signaling modulates beta cell apoptosis. J Biol Chem. 2003;278(1):471-478. doi:10.1074/jbc.M209423200

42. Zhao C, Liang J, Yang Y, Yu M, Qu X. The Impact of Glucagon-Like Peptide-1 on Bone Metabolism and Its Possible Mechanisms. Front Endocrinol (Lausanne). 2017;8:98. Published 2017 May 3. doi:10.3389/fendo.2017.00098

43. Hölscher C. Potential role of glucagon-like peptide-1 (GLP-1) in neuroprotection. CNS Drugs. 2012;26(10):871-882. doi:10.2165/11635890-000000000-00000

44. Müller TD, Finan B, Bloom SR, *et al.* Glucagon-like peptide 1 (GLP-1). Mol Metab. 2019;30:72-130. doi:10.1016/j.molmet.2019.09.010

45. Dimitriadis GK, Randeva MS, Miras AD. Potential Hormone Mechanisms of Bariatric Surgery. Curr Obes Rep. 2017;6(3):253-265. doi:10.1007/s13679-017-0276-5

46. Madsbad S, Holst JJ. Glycaemic control and weight loss with semaglutide in type 2 diabetes. Lancet Diabetes Endocrinol. 2017;5(5):315-317. doi:10.1016/S2213-8587(17)30094-3

47. Toft-Nielsen MB, Damholt MB, Madsbad S, *et al.* Determinants of the impaired secretion of glucagon-like peptide-1 in type 2 diabetic patients. J Clin Endocrinol Metab. 2001;86(8):3717-3723. doi:10.1210/jcem.86.8.7750

48. Vilsbøll T, Krarup T, Deacon CF, Madsbad S, Holst JJ. Reduced postprandial concentrations of intact biologically active glucagon-like peptide 1 in type 2 diabetic patients. Diabetes. 2001;50(3):609-613. doi:10.2337/diabetes.50.3.609

49. Sekar R, Singh K, Arokiaraj AW, Chow BK. Pharmacological Actions of Glucagon-Like Peptide-1, Gastric Inhibitory Polypeptide, and Glucagon. Int Rev Cell Mol Biol. 2016;326:279-341. doi:10.1016/bs.ircmb.2016.05.002

50. Calanna S, Christensen M, Holst JJ, *et al.* Secretion of glucose-dependent insulinotropic polypeptide in patients with type 2 diabetes: systematic review and meta-analysis of clinical studies. Diabetes Care. 2013;36(10):3346-3352. doi:10.2337/dc13-0465

51. Suh S, Kim MY, Kim SK, *et al.* Glucose-Dependent Insulinotropic Peptide Level Is Associated with the Development of Type 2 Diabetes Mellitus. Endocrinol Metab (Seoul). 2016;31(1):134-141. doi:10.3803/EnM.2016.31.1.134

52. Butler PC. Glucagon-like Peptide 1 Drugs as Second-line Therapy for Type 2 Diabetes [published correction appears in JAMA Intern Med. 2016 Oct 1;176(10):1579]. JAMA Intern Med. 2016;176(10):1-3. doi:10.1001/jamainternmed.2016.1523

53. Latif W, Lambrinos KJ, Rodriguez R. Compare and Contrast the Glucagon-Like Peptide-1 Receptor Agonists (GLP1RAs) [Updated 2023 Mar 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK572151/

54. Wojtara M, Mazumder A, Syeda Y, Mozgała N. Glucagon-Like Peptide-1 Receptor Agonists for Chronic Weight Management. Adv Med. 2023;2023:9946924. Published 2023 Sep 20. doi:10.1155/2023/9946924

55. Saini K, Sharma S, Khan Y. DPP-4 inhibitors for treating T2DM - hype or hope? an analysis based on the current literature. Front Mol Biosci. 2023;10:1130625. Published 2023 May 23. doi:10.3389/fmolb.2023.1130625

56. Davies I, Tan TMM. Design of novel therapeutics targeting the glucose-dependent insulinotropic polypeptide receptor (GIPR) to aid weight loss. Expert Opin Drug Discov. 2023;18(6):659-669. doi:10.1080/17460441.2023.2203911

57. Tamargo IA, Bader M, Li Y, *et al.* Novel GLP-1R/GIPR co-agonist "twincretin" is neuroprotective in cell and rodent models of mild traumatic brain injury. Exp Neurol. 2017;288:176-186. doi:10.1016/j.expneurol.2016.11.005

58. Skow MA, Bergmann NC, Knop FK. Diabetes and obesity treatment based on dual incretin receptor activation: 'twincretins'. Diabetes Obes Metab. 2016;18(9):847-854. doi:10.1111/dom.12685

59. 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

60. Tan Q, Akindehin SE, Orsso CE, *et al.* Recent Advances in Incretin-Based Pharmacotherapies for the Treatment of Obesity and Diabetes. Front Endocrinol (Lausanne). 2022;13:838410. Published 2022 Mar 1. doi:10.3389/fendo.2022.838410

61. Fanshier AV, Crews BK, Garrett MC, Johnson JL. Tirzepatide: A Novel Glucose-Dependent Insulinotropic Polypeptide/Glucagon-Like Peptide 1 Receptor Agonist for the Treatment of Type 2 Diabetes: The First Twincretin. Clin Diabetes. 2023;41(3):367-377. doi:10.2337/cd22-0060

62. Day JW, Ottaway N, Patterson JT, *et al.* A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. Nat Chem Biol. 2009;5(10):749-757. doi:10.1038/nchembio.209

63. Finan B, Yang B, Ottaway N, *et al.* A rationally designed monomeric peptide triagonist corrects obesity and diabetes in rodents. Nat Med. 2015;21(1):27-36. doi:10.1038/nm.3761

64. Jall S, Sachs S, Clemmensen C, *et al.* Monomeric GLP-1/GIP/glucagon triagonism corrects obesity, hepatosteatosis, and dyslipidemia in female mice. Mol Metab. 2017;6(5):440-446. Published 2017 Mar 1. doi:10.1016/j.molmet.2017.02.002

65. Pocai A. G protein-coupled receptors and obesity. Front Endocrinol (Lausanne). 2023;14:1301017. Published 2023 Dec 14. doi:10.3389/fendo.2023.1301017

**mercodia.com**



32-5036 v1 01/2024