GLP-1/GIP analogs: potential impact in the landscape of obesity pharmacotherapy

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Keywords: Obesity; therapy; peptide; unimolecular; GLP-1; GIP

Abstract

Introduction: Obesity is recognised as a major healthcare challenge. Following years of slow progress in discovery of safe, effective therapies for weight management, recent approval of glucagon-like peptide 1 receptor (GLP-1R) mimetics, liraglutide and semaglutide, for obesity has generated considerable excitement. It is anticipated these agents will pave the way for similar application of tirzepatide, a highly effective glucose-dependent insulinotropic polypeptide receptor (GIPR), GLP-1R co-agonist recently approved for management of type 2 diabetes mellitus.

Areas covered: Following promising weight loss in Phase III clinical trials, liraglutide and semaglutide were approved for weight management without diabetes. Tirzepatide has attained Fast Track designation for obesity management by the US Food and Drug Association. This narrative review summarises experimental, preclinical and clinical data for these agents and related GLP-1R/GIPR co-agonists, prioritising clinical research published within the last 10 years where possible.

Expert Opinion: GLP-1R mimetics are often discontinued within 24-months, owing to gastrointestinal side-effects, meaning long-term application of these agents in obesity is questioned. Combined GIPR/GLP-1R agonism appears to induce fewer side-effects, indicating GLP-1R/GIPR co-agonists may be more suitable for enduring obesity management. After years of debate, this GIPR-biased GLP-1R/GIPR co-agonist highlights the therapeutic promise of GIPR modulation for diabetes and obesity.

Keywords: Obesity; therapy; peptide; unimolecular; GLP-1; GIP

1. Introduction

According to their most recently published global figures in 2016, the World Health Organisation (WHO) estimates there are over 1.9 billion adults currently overweight, while 650 million are considered clinically obese [1]. Given the uncurbed prevalence of excess body weight gain, it is likely these figures will have been exceeded at the time of writing. Indeed, according to more recent estimates from the World Obesity Atlas 2022, it is predicted that over 1 billion people will be clinically obese by 2030 [2], equating to 1 in 5 women and 1 in 7 men globally. More recent regional WHO data for Europe indicate a rise in overweight and obesity prevalence in children and adolescents during the COVID-19 pandemic, which have been compounded by decreases in physical activity and increases in the consumption of foods high in fat, sugar and salt [3]. Importantly, the report indicates that obesity will surpass smoking as the major risk factor for preventable cancer in many European countries in the coming decades [3].

1.1 Pharmacological management of obesity

While recognised as a major risk factor for stroke and cardiovascular disease [4], type 2 diabetes mellitus (T2DM) [5] and now increasingly implicated as an environmental driver of cognitive decline in the development Alzheimer's Disease [6, 7], the American Medical Association and National Institutes of Health officially recognise obesity as a complex, chronic disease in its own right [8, 9]. As such, pharmacological intervention for obesity is becoming increasingly accepted.

However, it is important to note that lifestyle intervention, namely increasing physical activity and reducing calorie intake, remains the first line option for managing patients with obesity [10]. While bariatric surgery can also be employed in more extreme cases [11], it is usually reserved for patients with a BMI of 40 kg/m^2 or more or patients with a BMI of 35

kg/m^2 or above and a comorbidity such as type 2 diabetes or high blood pressure [12]. Thus, pharmacological intervention is a more universally applicable option if lifestyle intervention fails. Unfortunately, prescribing options have remained remarkably limited for obesity, owing to a chequered past of many small molecule agonists previously employed for the disease. Agents such as sibutramine, lorcaserin and rimonabant have been withdrawn in the vast majority or regions, due to safety concerns such as increased cardiovascular risk and adverse behavioural effects [13-15]. Until relatively recently, the lipase inhibitor orlistat, has been the only universal mainstay in obesity management [16]. However, the well documented unpleasant gastrointestinal (GIT) side-effects of orlistat limit patient uptake and compliance. Thus, there has been real optimism following the recent demonstrated effectiveness and approval of glucagon-like peptide-1 (GLP-1) mimetics, liraglutide and semaglutide [17, 18], for management of obesity, with hope that the genuine success of these peptide agents in type 2 diabetes (T2DM) can be translated to obesity.

2.0 Glucagon-like peptide-1 mimetics

GLP-1 is a gut-derived, 29 amino acid residue hormone, released post-prandially from intestinal L-cells, particularly following meals rich in fat and carbohydrate [19, 20]. GLP-1 secretion is biphasic, with an early phase occurring 10-15 min after meal ingestion and a second, more prolonged, phase occurring 30-60 min post meal [21]. The primary biologically active form of the peptide is GLP-1(7-36)-amide, generated by tissue-specific post-translational processing of the proglucagon gene by prohormone convertase enzymes [22]. Upon binding to the GLP-1 receptor (GLP-1R) on pancreatic beta-cells, GLP-1 promotes glucose-dependent insulin secretion via stimulation of intracellular cAMP-mediated events and also encourages glucose-induced biosynthesis of insulin, resulting in replenishment of insulin stores within beta-cells [21, 23; Figure 1]. Furthermore, there is evidence to suggest that GLP-

1R activation enhances pancreatic beta-cell growth and survival, at least in rodents [25, 26; Figure 1]. In addition, GLP-1 is also known to supress glucagon secretion, with some debate as to whether this is related to a direct effect on alpha-cells or mediated indirectly through increased somatostatin secretion from islet delta-cells [24]. As a result of these combined positive effects on glucose modulating islet-derived hormones, sustained activation of GLP-1R has seen successful clinical application in the management of T2DM.

2.1 GLP-1 mimetics in type 2 diabetes

Endogenous GLP-1 is subject to extremely rapid N-terminal degradation by the ubiquitous serine protease dipeptidyl peptidase-4 (DPP-4) [27], which cleaves an N-terminal dipeptide to generate GLP-1(9-36), a weak GLP-R antagonist. Ultimately, this means that the insulinotropic effects of the native peptide are rapidly lost in the circulation, rendering it unsuitable for therapeutic utilisation.

In order to combat this rapid enzymatic inactivation, various long-acting GLP-1 analogues have been developed for the management of T2DM. The first such analogue was exendin-4, originally isolated from the saliva of the venous Gila monster (*Heloderma suspectum*) lizard [28]. Exendin-4 is a potent agonist for mammalian GLP-1Rs, effectively bringing about GLP-1R-mediated benefits on glycaemia [28, 29], and importantly also possesses inherent resistance to DPP-4 inactivation [30]. Synthetic exendin-4, exenatide, attained clinical approval for T2DM in 2005 (Byetta), and has since become a widely prescribed second- and third-line agent for this disease. Subsequent medicinal chemistry and drug formulation innovation has seen the successful development of liraglutide, which is a stable once-daily GLP-1 mimetic based on the structure of human GLP-1, and even longer-acting GLP-1 analogues that allow for once weekly delivery. These second-generation drugs include exenatide extended-release as well as semaglutide and dulaglutide analogues that are

based on the sequence of human GLP-1 [31-33]. While all these GLP-1 mimetics are injectable agents, it is noteworthy that an oral version of semaglutide (Rybelsus) formulated with sodium N-(8-[2-hydroxybenzoyl] amino) caprylate to protect against stomach degradation, is now available as a once-daily tablet [34], but requires extremely high doses of semaglutide to provoke effective glucose-lowering actions.

2.2 GLP-1 mimetics in obesity

In addition to the positive effects of GLP-1 on insulin secretion and beta-cell survival [21, 23; Figure 1], the hormone has long been understood to play an important role in delaying gastric transit and promoting satiety [Figure 1]. These actions are linked to activation of GLP-1Rs at central and peripheral enteric neurons to slow gastric emptying and intestinal transit, as well as suppress appetite at the level of the hypothalamus, together influencing a mechanism termed the "ileal brake" [35; Figure 1]. It is clear that a complex gut-brain relationship is at play given the presence of releasable stores of GLP-1 and its target receptors in both peripheral and central locations [35,36; Figure 1]. Indeed, satiety is influenced by activation of GLP-1R present in both the central nervous system, while the gut is further modulated by vagal-derived cholinergic signals [36]. It has been suggested that centrally, modulation of the anorexigenic proopiomelanocortin (POMC) neurons is responsible for satiating effects, given they possess GLP-1Rs and are present in the nucleus tractus solitarius (NTS), the site of GLP-1 production in the brain [36]. This complex interplay likely explains why an intact vagus nerve is required for the satiating effects of exogenous GLP-1 when delivered by intraperitoneal injection, but not when delivered intravenously [35,36]. Promotion of satiety has been demonstrated to impart significant weight loss in T2DM patients receiving GLP-1 analogues [36], hence enthusiasm in repurposing of GLP-1 analogues as anti-obesity agents, in the absence of T2DM.

Such exploitation was realised in 2020 following the approval of liraglutide (marketed as Saxenda for obesity) as the first GLP-1 mimetic to gain regulatory consent for management of obesity, without concurrent diabetes [17]. Related phase III clinical trials (Satiety and Clinical Adiposity – Liraglutide Evidence in non-diabetic and diabetic individuals; SCALE) demonstrated a sustained 2-year weight loss of 5-10% in non-diabetic participants receiving liraglutide, when employed in addition to patient education on increased physical activity and some restriction of food intake [37; Table 1]. The increased dose of liraglutide for obesity as compared to diabetes, 1. 8 mg *vs*. 3.0 mg, respectively, has been a topic of some concern [17, 38]. As such, the SCALE trials indicated that when liraglutide was employed at a dose of 3.0 mg it was subject to largely the same GIT side-effects as the 1.8 mg dose used in T2DM but the incidence of severe adverse effects was increased [17]. Moreover, the trial confirmed that any positive effects in terms of decrease in body weight are lost upon drug discontinuation, necessitating long-term therapy. In this respect, in T2DM as many as 70% of patients in the US receiving GLP-1 therapies discontinue within 24 months, largely due to GIT related side-effects [39]. In good agreement, a related study indicated that over 60% of patients cite feelings of nausea or GIT discomfort as the primary reason for discontinuation of GLP-1 mimetics [40]. In that regard, it will be interesting to track how this adverse effect profile affects translation of longer-term GLP-1 benefits on obesity in the real-world setting, especially since both liraglutide and semaglutide are used at higher doses in obesity than for T2DM.

Following the successful approval of liraglutide for obesity, Phase III clinical trials (Semaglutide Treatment Effect in People with obesity; STEP) demonstrated that once weekly semaglutide induced an average weight loss of 14.9% following 68 weeks treatment in obese and overweight adults, with an acceptable adverse effect profile linked to anticipated GIT actions [41; Table 1]. Previous studies had already indicated that semaglutide elicited superior weight loss than liraglutide [42]. Injectable semaglutide gained FDA approval for obesity in

2021 (marketed as Wegovy), with subsequent approval by the MHRA and EMA following in 2022. As with liraglutide, the dose for obesity of 2.4 mg, is higher than the 2.0 mg employed in T2DM [43]. However, an 18-week titration window with injectable semaglutide may help partially alleviate discontinuation issues, by potentially reducing troublesome GIT adverse effects. Additionally, oral semaglutide has now been approved for T2DM and demonstrates promising body weight reductions and tolerability in the PIONEER 8 trials in T2DM patients [44]. Phase III clinical trials in obese individuals are set to be conducted in 2023, investigating the effects of 50 mg of oral semaglutide daily over a 68-week period [45; Table 1]. The significant dose increase from T2DM to obesity is notable but relates to the poor oral bioavailability of oral semaglutide, reported to be in the region of 0.8% [46].

3.0 GIP mimetics

Glucose-dependent insulinotropic polypeptide (GIP) is a 42-amino acid peptide hormone secreted from intestinal K-cells of the duodenum and proximal jejunum [47]. Like GLP-1 [19, 20; Figure 1,2], GIP is released in response to macronutrient load in the gut, working together with GLP-1 to induce the 'incretin-effect'. As such, GIP enhances glucose-stimulated insulin secretion following binding to GIP receptors (GIP-R) on the beta-cell [48; Figure 1], augmenting adenyl cyclase signal transduction pathways [49], similar in many respects to GLP-1 [50]. Further overlap exists with GLP-1, as GIP is also subject to rapid degradation by DPP-4, generating the inactive GIP(3-42) metabolite [51]. Indeed, this DPP-4 degradation fragment may even function as a weak GIPR antagonist, especially at high concentrations [52; 53]. Additionally, GIP and its receptor have been evidenced within the brain, with GIPR expression in the hypothalamus being implicated in the modulation of feeding, particularly within arcuate, paraventricular, and dorsomedial nuclei, hypothalamic regions associated with energy balance [54, 55; Figure 1] however the exact mechanisms at play within these regions are yet to be

confirmed. Moreover, the peripheral actions of GIP in improving insulin sensitivity in adipocytes and modulate overall lipid metabolism positively influence overall energy balance and can benefit weight loss [55]. Thus, given the complementary actions of these hormones, the development of a dual-acting GIPR/GLP-1R agonist is entirely logical.

In that respect, the antidiabetic efficacy of several first-generation GIP compounds with N-terminal modifications at positions Tyr^1 or Ala^2 were documented some 20 years previously [56]. These GIP analogues were highly effective in the preclinical setting using animal models of obesity and diabetes [57-59]. Furthermore, second-generation acylated versions of these GIP analogues with extended biological half-lives also exhibited impressive antidiabetic profiles in animal models of diabetes [60-63]. Moreover, advocation of GIPR agonist therapies in T2DM is supported by early studies that confirm GIP as the major incretin hormone [64, 65]. However, concerns over a postulated lack of bioactivity of GIP in human T2DM hindered clinical progression [66].

4.0 Tirzepatide, a GLP-1R/GIPR co-agonist

Considerable excitement has surrounded Eli Lilly & Co's next-generation peptide therapeutic for T2DM, namely tirzepatide (Mounjaro). Not unlike some of the above-mentioned therapies, tirzepatide is a synthetic, linear peptide containing 39 amino acids, also incorporating a C20 diacid fatty acid that directly contributes to a half-life of approximately 5 days [67; Figure 2], allowing for weekly dosing. However, tirzepatide sets itself apart from earlier peptide therapies through a dual-acting biological profile, functioning as an agonist at both GLP-1 and GIP receptors to elicit its biological actions [67]. Indeed, the structure of tirzepatide has strong parallels with GIP, together with sequence modifications to also encourage GLP-1R binding and activation [Figure 2], thus building on early preclinical work with GIP therapeutics [68].

In that regard, tirzepatide attained US Food and Drug Association (FDA) approval for the management of T2DM in May 2022 following impressive Phase III (SURPASS-3) clinical trial data, where the peptide induced superior HbA_{1c} reductions than dulaglutide (2.4-2.8% compared to 1.3%) following 52 weeks treatment [69; Table 1]. Interestingly, HbA_{1c} reductions were noted to be largely independent of age [70]. However, in this regard it is important to note that while over 1200 participants in the SURPASS program achieved HbA_{1c} levels of below 5.7%, these individuals tended to be both younger and have had a shorter duration of disease [71]. Doses of 5, 10 and 15 mg were employed in the SURPASS trials and the current recommended dose is 5 mg daily which can be titrated to a maximum dose of 15 mg in 2.5 mg increments [72].

Beyond glycaemic benefits, tirzepatide has been demonstrated to induce profound reductions in body weight. Phase II clinical trials in T2DM patients indicated highly impressive body weight reductions of 5-10% alongside substantial reductions in waist-circumference following 12 weeks administration [73]. Tirzepatide-induced reductions of body weight were over three times greater than with dulaglutide, being attributed to complementary benefits of GIPR/GLP-1R modulation on inhibition of appetite and gastric emptying, as well as the ability of GIPR to curb GLP-1 induced emesis, leading to improved overall effectiveness and tolerability [67]. It is important to note that appetite reduction was measured as a self-reported score, hence further study will be required to elucidate synergistic mechanisms between GLP-1/GIP centrally and in the periphery in regulating appetite. Such findings are supported by data arising from Phase III clinical trials (SURPASS-3), that demonstrated a 7.6-11.2% weight loss in participants receiving tirzepatide, in comparison to 5.7% induced by semaglutide alone [73,74]. Hence, tirzepatide is claimed to be a potential game changer in terms of pharmacological interventions for obesity. Indeed, on October 6th 2022, the FDA granted Fast Track designation for tirzepatide in obesity management, with the results of a current Phase III

clinical trial (SURMOUNT-MMO; 75), anticipated to be completed in April 2023, being the primary factor relating to how expedited this process will actually be.

Given the strong similarity of tirzepatide with the amino acid sequence of GIP [Figure 2], it is not unsurprising that *in vitro* mechanistic studies reveal strong bias towards the GIPR, activating this receptor with equipotency to native GIP whilst having 5-fold weaker affinity than native GLP-1 at GLP-1R [76; Figure 2]. This poses a question as to the importance of each receptor interaction in driving the pro-glycaemic and weight-loss effects of tirzepatide. When investigated in murine pancreatic islets lacking GLP-1R's, tirzepatide-stimulated insulin secretion was abolished when co-cultured with a GIPR antagonist [67]. Additionally, in islets from GIPR knock-out (KO) mice, tirzepatide-stimulated insulin secretion is completely blocked by GLP-1R antagonism [67], indicating the importance of both receptors for beneficial effects of the peptide in relation to insulin secretion. Although species-specific activity of GIP amino acid sequences [77], that is not observed with GLP-1, may make it difficult to interpret and translate exact receptor selectivity importance of tirzepatide from the rodent setting to humans. In addition, additive or even synergistic benefits of combined GLP-1R/GIPR signalling would not be fully quantifiable when using receptor KO models of individual receptor pathways, since signalling pathway interactions are unable to be examined. A similar paradigm has been noted when attempting to understand the additive benefits of GLP-1 alongside other related gut derived hormones, such as cholecystokinin or gastrin [78,79]. This could be particularly important when it comes to the side-effect profile of tirzepatide and long-term tolerability in patients. For example, it has been suggested that anti-emetic effects GIPR agonism combined with GLP-1R agonism improves tolerability of tirzepatide when compared to GLP-1 mimetic monotherapy [80], especially given the higher doses employed for GLP-1 mimetic monotherapy in obesity management. That said, the incidence of GIT side-effects were only modestly reduced in tirzepatide receiving subjects than in those receiving

semaglutide [74]. Although in this study, semaglutide was employed at a lower dose than is now recommended for obesity, meaning tirzepatide may have a competitive edge in this respect.

5.0 Further GLP-1R/GIPR co-agonists in development

While representing the first major success in terms of the clinical application of GLP-1/GIP-R co-agonism, it is important to note that tirzepatide builds on a considerable body of previous work exploring this combination. Indeed, the first chimeric GLP-1/GIP chimeric peptides were first described over 25 years ago [81], with other related dual-acting peptides only being characterised several years after this [82-84].

In this regard, preclinical studies in genetically obese-diabetic (*ob/ob*) mice indicated that combination therapy with a stable, N-terminally acylated GIP analogue, N-AcGIP, with the GLP-1R agonist exendin-4, elicited superior improvements in glucose tolerance and insulin sensitivity than exendin-4 alone [85]. Notably, no body weight reduction was observed over the sub-chronic, 14-day study with combined N-AcGIP and exendin-4 therapy [86]. However, the relatively short treatment period could be a factor in terms of lack of effect of the GIPR and GLP-1R agonist combination therapy on adiposity in the *ob/ob* mice. Indeed, the effectiveness of this approach was further endorsed through later studies utilising administration of an acylated GLP-1 and GIP preparations in the same mouse model [87]. The initial promise of GIPR and GLP-1R combination therapies led to the generation of a unimolecular molecule, termed N-Ac(d-Ala^2)GIP/GLP-1-exe, combining a N-AcGIP molecule with exendin-4 [84], which brought about significant body weight reduction in addition to improved glucose handling and insulin sensitivity in diet-induced obese (DIO) mice. Although, the receptor balance profile of N-Ac(d-Ala^2)GIP/GLP-1-exe has not yet been fully explored, making it

difficult to determine the relative impact of GIPR and GLP-1R signalling in these observed metabolic improvements [85,86].

Intriguingly, a balanced GLP-1/GIPR unimolecular co-agonist has been described in the literature, with development appearing to run largely in tandem with that of tirzepatide. Denominated in the literature as RG7697, or NNC0090-2746, this molecule was designed on a glucagon-based core, with residues from native GIP, GLP-1 and also exendin-4 incorporated into the sequence, to produce a balanced GIPR/GLP-1R binding profile [82; Table 1], although modest affinity for the glucagon receptor (GCGR) was retained. The molecule progressed as far as Phase II clinical trials [87; Table 1], with comparison against liraglutide (1.8 mg) noting similar reductions in HbA_{1c} following 12 weeks administration in subjects with T2DM, although body weight reductions were significantly improved over liraglutide [88]. While both molecules were employed at 1.8 mg, it is important to note that this is considerably lower than 3.0 mg currently utilised for liraglutide in obesity management [17]. It is unclear why RG7697 has not progressed further, but higher rates of discontinuation with RG7697 as compared to the liraglutide may be a factor [88], as well as requirement for once daily injection [67, 89, 90]. In addition, the combined impact of GIPR, GLP-1R and GCGR activation on the cardiovascular system, particularly in relation to elevated heart rate [74], could also be a factor that requires consideration. Moreover, it appears that Novo Nordisk is currently attempting to emulate their success with oral semaglutide, through the development of an oral GLP-1/GIPR agonist, reported to be undergoing Phase I trials [91, 92], but information on this molecule is sparse at the time of writing.

Beyond obesity and diabetes, it is worth documenting that GLP-1/GIPR co-agonism is also being explored in neurodegenerative diseases [Figure 1]. This is noteworthy given that obesity is becoming increasingly recognised as a risk factor for neurodegenerative disorders [6, 7]. A unimolecular GLP-1/GIPR co-agonist, DA5-CH, which crosses the blood brain barrier

(BBB) [93], was shown to improve cognition, memory retention and motor function in a superior manner to exendin-4, liraglutide or semaglutide in rodent models of Alzheimer's and Parkinson's disease [94, 95]. While no metabolic data was published for DA5-CH within these studies, it would be interesting to assess potential benefits in relation to glycaemia and weight loss, particularly given the increasing role assigned to obesity in the pathophysiology of neurodegenerative disorders [6, 7, 93]. In support of this, work with DA5-CH actually builds on findings relating to the neurological benefits of the aforementioned N-Ac(d-Ala^2)GIP/GLP-1-exe dual acting peptide, that was demonstrated to augment recognition memory, hippocampal neurogenesis, synapse formation and reduce neuronal oxidative stress in DIO mice, alongside benefits on metabolism [84]. In good harmony, earlier work had already confirmed cognitive benefits of up-regulation of either GIPR [96; Figure 1] or GLP-1R [97; Figure 1] signalling in obese mice with impaired memory and cognition.

Finally, there are established benefits of GIP on bone formation in both animal models and humans with T2DM [98, 99; Figure 1], with a suggestion that GLP-1 may also positively impact bone composition [100]. Indeed, similar to the picture with neurodegenerative disorders, obesity is also noted to have a negative impact on the osteocyte network and overall bone quality [101]. Thus, dual GIPR/GLP-1R activation may also lead to improvements in bone homeostasis as documented with DPP-4 inhibitors [102], which is relevant since T2DM is linked with increased bone fragility [103].

6.0 Conclusion

The approval of semaglutide and liraglutide for weight management has been met with considerable excitement [17, 18]. Conversely, given high discontinuation rates observed in T2DM [39], application of these medications for long-term management of obesity remains unclear. Importantly however, their successful clinical application has likely paved the way for

use of the first GLP-1R/GIP-R co-agonist, tirzepatide, in obesity [67, 75], following recent approval of this molecule in T2DM. Moreover, the success of this GIPR-biased molecule has finally highlighted the potential of GIPR-modulation for the treatment of obesity and T2DM [67], after decades of debate. Once considered the poorer relative of GLP-1, these new and exciting observations with GIPR modulation confirm the longstanding belief that GIP possess translatable benefits for human disease [68].

7.0 Expert Opinion

Amid many years of stagnation in the approval of new, safe and effective therapies for obesity, the considerable excitement surrounding the recent approval of GLP-1R mimetics liraglutide and semaglutide in 2021[Table 1] for the management of the condition is understandable. Indeed, such has been the popularity of these therapies for weight loss that global shortages of semaglutide have been witnessed in 2022, likely compounded by prior off-label use of the GLP-1R mimetic before regulatory approval of semaglutide in 2021 [43, 104]. In addition, the increased dose requirement for obesity, as well as for oral application in T2DM, have likely compounded semaglutide peptide supply issues. Furthermore, it is important to note that application of GLP-1 therapies for obesity is in relative infancy, with considerable intrigue surrounding the longevity of these agents, given the already high drug discontinuation rates in T2DM coupled with elevated doses employed for weight management [18, 37, 39]. In this respect, a reduced GIT side-effect profile with tirzepatide in T2DM is encouraging [74], suggesting prolonged treatment within the confines of obesity may be more achievable with tirzepatide than GLP-1 monotherapy counterparts.

Ethnic differences may play an important role in the universal application of GLP-1 mimetics for obesity. As such, in relation to T2DM management, concern over the use of GLP-1R mimetics has been noted in Asian populations who appear to be at increased risk of

sarcopenia [105], while the same could also be true for the elderly. Thus, GLP-1 induced weight-loss has thus far been primarily reported as a crude percentage of body weight or BMI reduction, rather than specific fat mass loss [18, 36]. In addition, the WHO BMI classifications have been defined as inappropriate for Asian populations [106]. Thus, the relative "quality" of GLP-1 mimetic induced weight loss, i.e., fat mass over lean or muscle mass reductions, may be pertinent in this regard. More positively, a recent study in rodents indicated semaglutide specifically reduced the accumulation of intramuscular fat, promoted muscle protein synthesis, increased skeletal muscle proportion and improved muscle function in DIO mice [107], although translation to the human setting is still required.

As highlighted above, the recent approval of GLP-1R mimetics for management of obesity will likely pave the way for application of tirzepatide in weight management. Assumed uptake of tirzepatide in the diabetes and obesity clinic may also lead to realisation of more complex unimolecular agonists, that modulate pathways beyond that of only GLP-1R and GIPR. In that respect, multiagonism more closely emulates the hormonal changes demonstrated following Roux-en-Y gastric bypass (RYGB) surgery, following which numerous gut hormones are upregulated and are becoming more recognised as major dictators of the T2DM remission and profound weight loss seen post-surgery [108]. Indeed, the therapeutic potential of other unimolecular peptidic agents has been reviewed recently [109]. Nonetheless, it appears that after many years of debate, tirzepatide has endorsed the therapeutic promise of GIPR modulation for diabetes. In addition, it is well recognised that obesity is as a major risk factor for stroke and cardiovascular disease as well as certain kinds of malignancy, thus GLP-1 mimetics or related dual agonists such as tirzepatide will likely improve outcomes in this respect. In keeping with this, GLP-1R mimetics are known to improve cardiovascular risk in T2DM, largely independent of their antihyperglycemic actions [110].

Interestingly, the discovery of GIP was made over a decade prior to that of GLP-1 [111, 112], hence it poses the question as to why its therapeutic application has taken this long to be realised? The answer is probably two-fold, and relates to a documented inefficacy of GIP in patients with T2DM [66], although this phenomenon appears to be reversible when glycaemia is returned to more normal values [113]. Secondly, a continuing debate remains as to whether GIPR agonism or antagonism is of most benefit in T2DM and obesity? In this regard, GIP was once referred to as an "obesity hormone", due to direct actions on GIPR present on adipocytes that promote lipid accumulation [114]. Additionally, GIPR KO mice were reported to be resistant to the adipogenic effects of a high fat diet [115], but this is also true for GLP-1R KO mice [116]. Conversely, the hormone has been demonstrated to also possess a lipolytic effect [117], albeit in *in vitro* settings. Either way, it is clear that GIP exerts important direct actions on lipid metabolism that merit further investigation [118, 119].

Taken together, modulation of GIP action presents something of a conundrum, in that antidiabetic and anti-obesity benefits of GIPR agonism and antagonism have been demonstrated. Indeed, obesity and hyperphagia are attenuated by central and/or peripheral injection of a GIPR-neutralising antibodies and GIPR antagonist peptides [120-123], while in preclinical studies, benefits of sustained GIPR blockade have been demonstrated alone and in combination GLP-1R mimetics. Thus, the partial GIPR antagonist, (Pro^3)GIP, has originally been demonstrated to improve obesity-related diabetes, reducing islet hypertrophy and improving insulin sensitivity [124], while also eliciting 8% weight loss following administration alone in obese mice [125]. These observations have been largely confirmed by others employing GIPR monoclonal antibodies [126]. Interestingly, there is a suggestion that the metabolic benefits of chronic GIPR agonism are related to desensitisation of the GIPR, thus mimicking GIPR antagonism [127]. Although, this GIPR desensitisation theory still requires significant further investigation and confirmation.

In terms of a combination approach for GIPR antagonism and GLP-1R agonism, related investigations demonstrate that co-administration of GIPR monoclonal antibody, with various GLP-1R mimetic therapies, elicits superior weight-loss over monotherapy in obese mice and non-human primates [128]. Similar, but less pronounced benefits of a peptide based GIPR antagonist in combination with liraglutide have subsequently been noted in DIO mice [129]. More recently, the peptidic GIPR antagonist, [Nα-Ac, L14, R18, E21] hGIP(5-31)-K11(γE-C16) has been described as potentiating the weight loss benefits of semaglutide alone, when administered over 28 days in DIO mice [130]. Furthermore, preclinical studies suggest an optimised scheduling to annul GIPR signalling and promote GLP-1R signalling at specific times during the day may be important for therapeutic benefits, interchanging between GIPR blockade during periods of inactivity and GLP-1R agonism during the active hours [131]. However, a more recent study has characterised a bi-specific antibody that combines GIPR antagonism and GLP-1R agonism within the same compound and revealed beneficial weight reducing actions in mice and monkeys [132], arguing against a scheduled daily dosing pattern.

Declaration of interests

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Article Highlights

Approval of GLP-1R mimetics liraglutide and semaglutide for weight management paves the way for peptide therapies in obesity.

FDA approval of tirzepatide for type 2 diabetes management has been met with considerable excitement owing to significant glycaemic and weight loss benefits.

It is anticipated tirzepatide will ultimately find clinical application in obesity management. Debate remains as to whether GIPR agonism or antagonism is of most metabolic benefit, but the pendulum is swinging towards agonism.

The therapeutic potential of GIPR modulation may now be realised in management of metabolic disease.

Figure legends

Figure 1. An overview of the biological actions of endogenous glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) in man. Tissue-specific effects of GLP-1 and GIP are provided for relevant organs in green or blue, respectively.

Figure 2. A peptidic structure analysis of glucose-dependent insulinotropic peptide (GIP) (1-42), glucagon-like peptide-1 (GLP-1) (7-36) and tirzepatide, a dual GIP/GLP-1 receptor co-agonist. Amino acid residues are provided as their single-letter abbreviations. Residues shared with GIP(1-42) are shaded in blue, shared with GLP-1(7-36) are shaded in green, residues shared with both GLP-1 and GIP are indicated in orange and those unique to tirzepatide are shaded in grey. The fatty acid modification of tirzepatide is indicated in yellow. Receptor affinities are also indicated based on values reported in the literature [75].

Figure 1

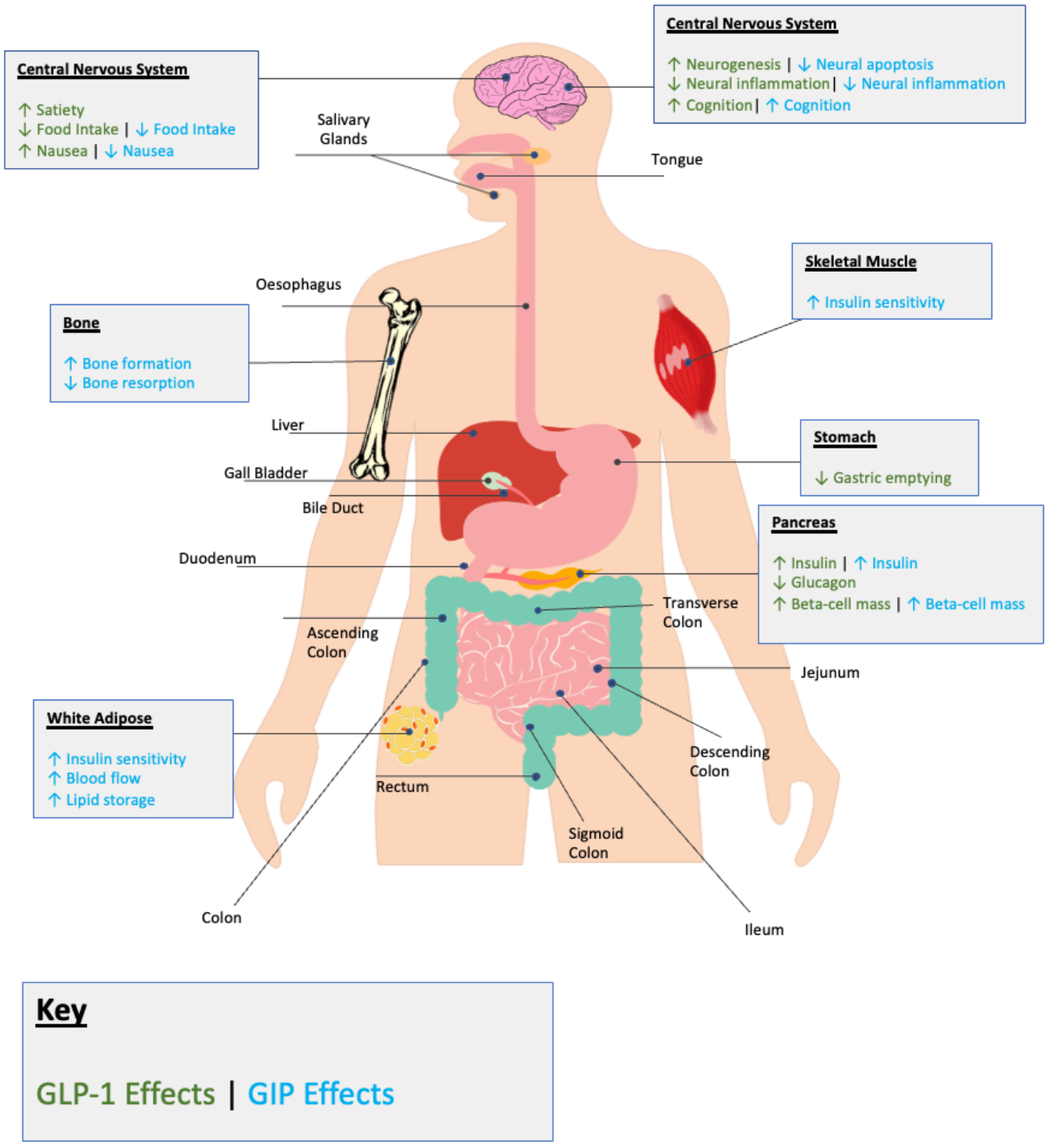
Central Nervous System
↑ Satiety
↓ Food Intake | ↓ Food Intake
↑ Nausea | ↓ Nausea
Central Nervous System
↑ Neurogenesis | ↓ Neural apoptosis
↓ Neural inflammation | ↓ Neural inflammation
↑ Cognition | ↑ Cognition
Salivary Glands
Tongue
Oesophagus
Skeletal Muscle
↑ Insulin sensitivity
Bone
↑ Bone formation
↓ Bone resorption
Liver
Stomach
↓ Gastric emptying
Gall Bladder
Bile Duct
Pancreas
↑ Insulin | ↑ Insulin
↓ Glucagon
↑ Beta-cell mass | ↑ Beta-cell mass
Duodenum
Transverse Colon
Ascending Colon
Jejunum
White Adipose
↑ Insulin sensitivity
↑ Blood flow
↑ Lipid storage
Descending Colon
Rectum
Sigmoid Colon
Colon
Ileum
Key
GLP-1 Effects | GIP Effects

Figure 2

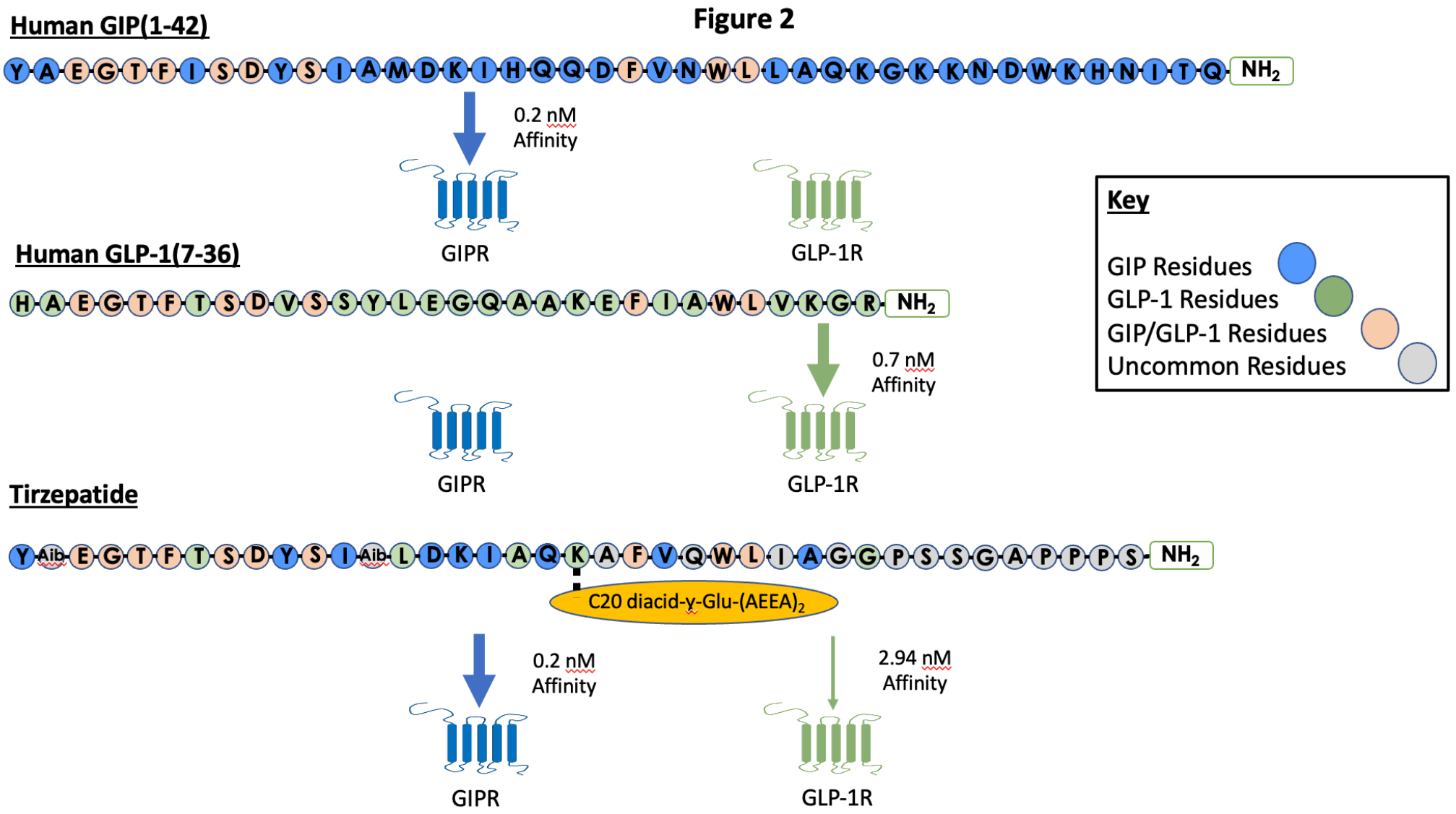
Human GIP(1-42)
Y A E G T F I S D Y S I A M D K I H Q Q D F V N W L L A Q K G K K N D W K H N I T Q NH2
0.2 nM Affinity
GIPR
GLP-1R
Human GLP-1(7-36)
H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R NH2
0.7 nM Affinity
GIPR
GLP-1R
Tirzepatide
Y Aib E G T F T S D Y S I Aib L D K I A Q K A F V Q W L I A G G P S S G A P P P S NH2
C20 diacid-γ-Glu-(AEEA)2
0.2 nM Affinity
2.94 nM Affinity
GIPR
GLP-1R
Key
GIP Residues
GLP-1 Residues
GIP/GLP-1 Residues
Uncommon Residues

Table 1. A summary of GLP-1R mimetics and GLP-1/GIPR co-agonists studied in obesity management

Therapeutic Name	Administration Route	Mechanism of Action	Regulatory Approval/Development Stage	Study Duration (months)	Cohort Size	Endpoints Assessed	Weight Loss Outcome (%bw loss)	Reference
Liraglutide (Saxenda)	Injectable	GLP-1R agonist	2019	24	846	BMI, WC, HbA1c, FPG, FPH, FPL, QOL	5-10	37
Semaglutide (Wegovy)	Injectable	GLP-1R agonist	2021	5.5	1961	BW, BC, QOL	14.9	41
Semaglutide (Rybelsus)	Oral	GLP-1R agonist	Phase III (commencing 2023)	5.5	198*	BMI, WC, VFM, HbA1c, FPL	-	45
Tirzepatide	Injectable	GLP-1R/GIPR co-agonist	Phase III (T2DM)	12	1879	BMI, WC, QOL, FPL, FPG, HbA1c, HOMA-IR	7.6-11.2	74
RG7697	Injectable	GLP-1/GIPR co-agonist	Phase II	3	108	BW, HbA1c, FPG, FPL, FPH	2.86	88

Assessed endpoints include body mass index (BMI), waist circumference (WC) measurement, glycated haemoglobin (HbA1c), fasting plasma glucose (FPG), fasting plasma hormones (FPH) encapsulating insulin, glucagon and c-peptide measurements, quality of life (QOL) questionnaires, body composition (BC) as measured by dual-energy X-ray absorptiometry, visceral fat measurement (VFM) as measured by CT-scan and homeostatic model assessment for insulin resistance (HOMA-IR).

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