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Viewpoint

SURMOUNTing body weight barriers in type 2 diabetes

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The emergence of GIPR:GLP-1R co-agonists has heralded a renaissance of anti-obesity medication. In the recent SURMOUNT 2 trial, Garvey and colleagues set out to examine the weight loss efficacy of the GIPR:GLP-1R co-agonist tirzepatide in patients with obesity and type 2 diabetes, reporting that tirzepatide has unprecedented efficacy in a magnitude historically considered almost unattainable.[1]

Cardiovascular, gastrointestinal, and endocrine conditions are all linked to the preceding obesogenic state. Although addressing obesity undoubtedly offers a means to positively impact the development of interconnected comorbidities, historic pharmacological interventions have generally proven ineffective in curbing the obesity epidemic. Consequently, bariatric surgery has been considered an ultimate solution for achieving lasting improvements in obesity and its major associated comorbidity, type 2 diabetes (T2D). In the recent decade, we have witnessed a renaissance in obesity pharmacology, as evidenced by the development of long-acting glucagon-like peptide 1 (GLP-1) receptor agonists such as liraglutide and semaglutide. In particular, Wegovy (semaglutide 2.4 mg) has been approved for the treatment of obesity in the United States as of 2021 and has demonstrated effective reductions in placebo-corrected body weight by an average of −12.4% in overweight and obese patients in the non-diabetic state over 68 weeks.[2] Yet, comparatively, in overweight and obese patients with concurrent T2D, semaglutide becomes less efficacious, achieving just −6.2% body weight reduction with the same 2.4-mg dosage.[3] Tirzepatide is an unimolecular hybridized peptide containing amino acid residues from GLP-1 and its incretin counterpart, the glucose-dependent insulinotropic polypeptide (GIP), and is preferentially biased 5:1 toward the GIP receptor (Figure 1). Beyond their classical role to stimulate insulin secretion from pancreatic beta cells, both GLP-1 and GIP act at their cognate receptors in the CNS to incur satiety and reduce body weight.[4] The concept of using unimolecular GIPR:GLP-1R co-agonism for synergistic body weight reduction was born in 2013 by the collaborative work of Richard DiMarchi and Matthias Tschöp.[5] The concept has subsequently been refined and taken to phase 3 clinical trials in the form of tirzepatide. The SURMOUNT-1 phase 3 clinical trial in non-diabetic overweight and obese individuals demonstrates the average body weight-lowering effect of 10 mg and 15 mg tirzepatide to be −19.5% and −20.9%, respectively,[6] and now impressively, the SURMOUNT-2 phase 3 clinical trial demonstrates a retention of double-digit placebo-corrected body weight percentage-lowering effects within the context of T2D.[1]

From around the world, 938 participants with a BMI ≥ 27 kg/m^2 and a hemoglobin A1c (HbA1c) of 7%–10% participated in the SURMOUNT-2 clinical trial, which aimed to assess the body weight-lowering efficacy of 10 mg and 15 mg tirzepatide over the course of 72 weeks. Remarkably, the placebo-corrected percentage change in total body weight on average was −9.6% and −11.6% for 10 mg and 15 mg (Figure 1), while 79% and 83% of patients in the respective treatment groups achieved >5% body weight loss. In the diabetic obese state, a general consideration is that 15% body weight loss is desired for substantial improvements in both glycemia and obesity-related complications. Approximately half (48%) of the patients in the 15-mg treatment arm achieved >15% body weight reduction, setting the endpoint well within the therapeutic proximity of influencing obesity-derived co-morbidities. Placebo-corrected reductions in HbA1c percentage were approximately −1.6% for both patients receiving 10 mg and 15 mg, with the majority of the improvement occurring in the first 24 weeks and plateauing despite continued reductions in body weight over the course of 72 weeks. Additionally, akin to risk improvements in obesity-associated comorbidities, reductions were observed in placebo-corrected fasted glucose (−37.9 mg/dL for both 10-mg and 15-mg treatments), insulin (−15.6% and −25.9%), systolic blood pressure (−5.1 mm Hg as a pooled 10-mg/15-mg effect), and triglycerides, VLDL-C, and free fatty acids (>20% reductions).

Expectedly, side effects generally consisting of nausea, vomiting, and diarrhea have hampered dose escalations of GLP-1R mono-agonists.[4] GIPR co-agonism with GLP-1 not only acts synergistically to reduce food intake[5] but also contributes an anti-emetic effect in pre-clinical models,[7,8] thereby likely

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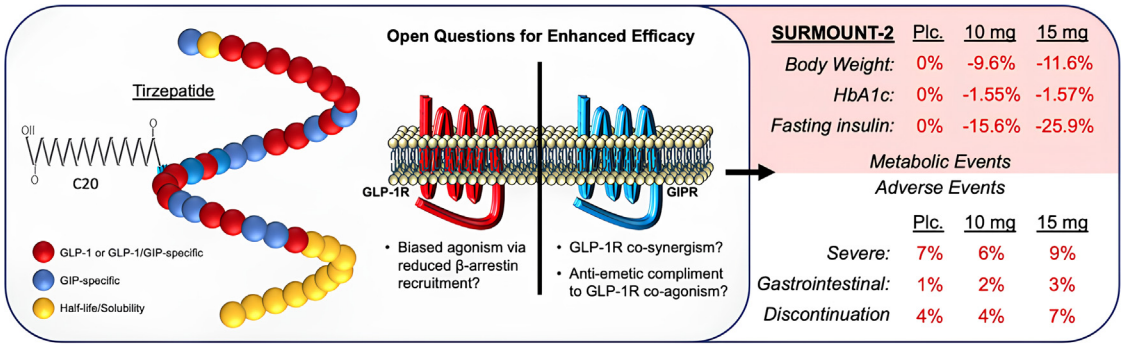

Figure 1. Schematic of the tirzepatide structure, open questions on the potential mode of action, and key results from the SURMOUNT-2 study

lowering emetic episodes attributed to chronic GLP-1R agonism. In the SURMOUNT-2 trial, there were no significant differences reported for total or serious adverse events between 10 mg and 15 mg tirzepatide and placebo (Figure 1).[1] This data is generally in line with the earlier SURMOUNT-1 trial[6] and is similar to that of semaglutide in the STEP-2 trial.[3] However, important distinctions may add nuance to the apparent lack of discrepancy between tirzepatide and semaglutide on adverse event outcomes. This subtlety pertains to dosing; tirzepatide is dosed 3- to 5-fold higher than 2.4 mg semaglutide, suggesting tirzepatide's allowance for higher dosing, higher effect size, and maintenance of a similar gastrointestinal adverse event profile to that of semaglutide. Does this pharmacological profile of tirzepatide call to the benefits of GIPR co-agonism? Alternatively, is the capacity for higher effect size due to a unique interaction between tirzepatide's unique sequence at the GLP-1R? Or is it both?

The future of GLP-1R/GIPR pharmacology following the SURMOUNT-2 clinical trial

GIP at work

Tirzepatide is more efficacious at 10 mg and 15 mg on body weight-lowering parameters than semaglutide in both diabetic and non-diabetic obese humans. Is the GIP component driving this differential effect? It is clear the GIP component of tirzepatide is active in human tissue. Based on antagonist experiments, the GIP component of tirzepatide seems to be driving the majority of insulin secretion in extracted non-diabetic human islets, while the GLP-1 component alone seems to not be involved.[8] This, however, does not discount the role of the GLP-1 component in humans, as GLP-1R mono-agonism drives anti-diabetic and anti-obesogenic effects in obese individuals with diabetes, while the effects of GIPR mono-agonism in the diabetic obese are muted.[4] So why is tirzepatide so efficacious on body weight endpoints in the diabetic obese? It is difficult to tease out whether the contribution of the GIP component is due to (1) simultaneous and synergistic activation of distinct GLP-1 and GIP receptor expressing neural populations involved in suppression of food intake, (2) subsequent GLP-1/GIP synergistic action following an initial antecedent body weight reduction driven by GLP-1, or (3) complementing anti-emetic properties of GIP allowing for higher dosing of the GLP-1 component. The future holds much to be uncovered regarding the potential mechanisms through which tirzepatide's GIP entity may mediate the drug's potent actions.

Biased GLP-1R action

If GIP acts as only an anti-emetic complement to GLP-1R-mediated food-intake suppression, this would suggest tirzepatide to have strong partial-to-full agonism at the GLP-1R. Surprisingly, tirzepatide is minimally efficacious for Gα recruitment at both the mouse and human GLP-1R.[8,9] Despite minimal Gα recruitment, tirzepatide exhibits seemingly biased properties in that it retains maximal efficacy for cAMP production while minimizing recruitment of the Gα signaling brake β-arrestin to the GLP-1R. Importantly, these unique dynamics are associated with minimal GLP-1R internalization and subsequent lysosomal co-localization during stimulation, indicating that the drug leads to a higher presence of ligand-bound GLP-1R at the plasma membrane. This *in vitro* characterization of tirzepatide at the GLP-1R is reminiscent of the GLP-1R mono-agonist exendin4-Phe1, which displays potent insulinotropic properties in mice over that of exendin4.[9] Is the unique signaling and trafficking profile of tirzepatide generating a "super" GLP-1R agonist?

Recapitulating bariatric surgery

Pharmacological efforts toward mimicking the effects of bariatric surgery have centered around the simultaneous utilization of GLP-1 and GIP—and the addition of an energy expenditure-enhancing component glucagon. Retatrutide is a unimolecular hybridized peptide containing amino acid residues from all three separate peptides, resulting in a peptide that favors GIPR activity but has balanced activity between GLP-1R and the glucagon receptor.

Retatrutide (12 mg) recently achieved approximately one quarter (−24.2%) total body weight loss over the course of 48 weeks in overweight and obese patients without T2D,[10] which is relative to the −20.9% reduction by tirzepatide in 72 weeks during the SURMOUNT-1 trial.[6] Retatrutide seems to be a leading candidate to induce massive body weight reduction in the shortest amount of time and represents the leading candidate to equivalate, or perhaps surpass, the achievements of bariatric surgery. The leading question for retatrutide is as follows: have we pharmacologically solved acute and safe body weight reductions?

The SURPASS-2 trial represents the development of a critical GIP-centric paradigm in obesity management within concurrent T2D in which the maximal therapeutic capacity is only recently being uncovered. Perhaps these findings pave the way for obesity to be characterized as a therapeutic field in that different treatments (GLP-1R mono-agonism, GIPR:GLP-1R co-agonism, or GLP-1R:GIPR:GcgR triple-agonism) may be applicable to the different degrees of required obesity and diabetes management. However, questions still remain regarding practical implementation, patient tolerance, affordability, and insurance coverage. Nonetheless, the current field of drug discovery in obesity may hold promise for positively affecting the multitude of comorbidities that drive the negative valence on the obesity epidemic.

In essence, over the course of only a decade, we've seen a remarkable resurgence of potent anti-obesity medications. This resurgence gives us reason to be cautiously hopeful that these pharmaceutical treatments could, in the near future, match the effectiveness of bariatric surgery or possibly surpass it.

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