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CLINICAL PRACTICE UPDATE IN
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Introducing GIP – Clinical Insights on Incretin Co-agonists

Megha Poddar MD, FRCPC, ABOM

Endocrinologist & Clinical Director, LMC Medical Weight Management Program
Toronto, Ontario, Canada

Glucagon-like peptide 1 (GLP-1) and gastric inhibitory polypeptide (GIP), the two main incretin hormones, are released in the gastrointestinal tract in response to a food bolus and are responsible for glucose dependent insulin secretion1. GLP-1 receptor agonists have dramatically changed the treatment paradigm of type 2 diabetes due to their robust A1c lowering, weight loss and cardiovascular protection benefits. GIP receptor agonist have not shown this same therapeutic benefit in early studies and thus further research was essentially abandoned. However, the recent development of a new molecule, which activates both the GIP and GLP-1 receptors together has shown impressive A1c lowering and weight loss benefits above and beyond that seen with GLP-1RAs alone. This has led to exciting new research to better identify the mechanism of action of GIP and the likely synergistic properties of this new GIP/GLP1 dual agonist which has opened the doors to a promising new class of anti hyperglycemic agent in the management in type 2 diabetes.

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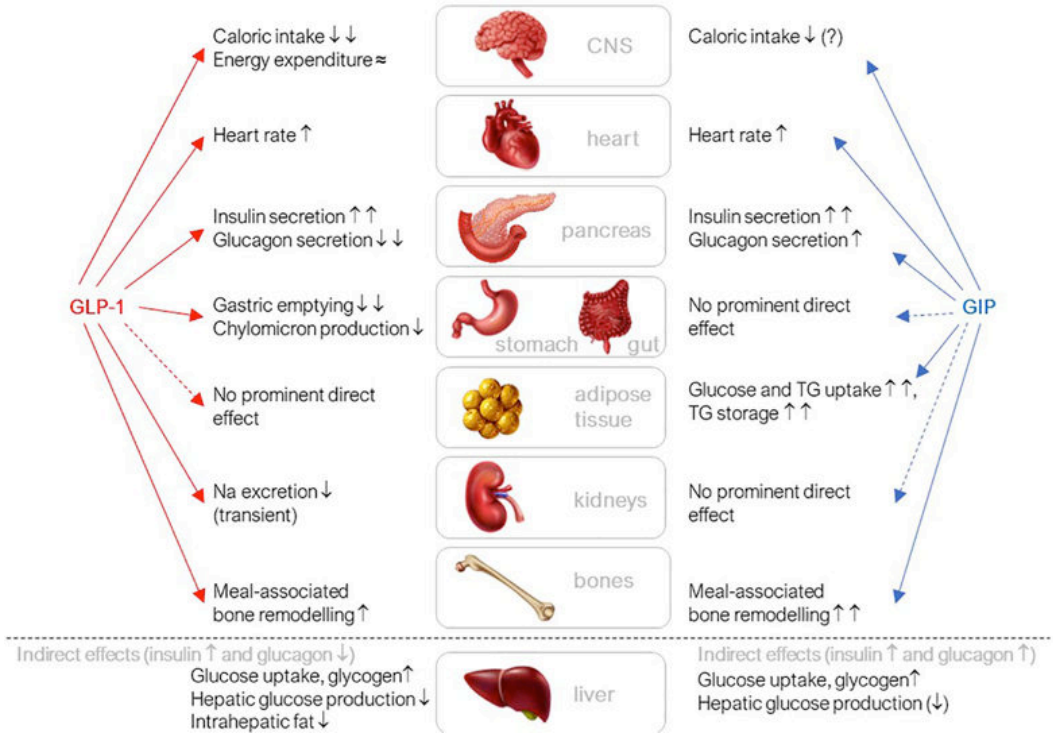
Mechanism of Action of Incretin Hormones

The incretin hormones are released in the gut by nutrient-induced secretion and work to regulate the endocrine pancreas and its secretion of insulin. The initial discovery of these hormones showed that the gut-endocrine-pancreatic pathway must be functional to maintain glucose regulation and that oral glucose ingestion resulted in greater secretion of insulin than IV glucose through the "incretin effect"[1]. Importantly, this incretin effect is blunted in the pathology of type 2 diabetes and results in impaired insulin secretion from the pancreas.

Each of the two incretin hormones, GLP-1 and GIP have their own receptors which are responsible for their individual downstream action, however they both primarily act on the beta cells of the pancreas to secrete insulin in a glucose dependent manner which gives them the distinct advantage of low rates of hypoglycemia when used in the treatment of type 2 diabetes. Interestingly, it has also been shown that there is only a small increase in insulin secretion with GIP in a hyperglycemic state, this may be one reasons that GIP receptor agonism alone failed as a therapeutic agent for type 2 diabetes.

Although GIP and GLP-1 are very similar, they do have some differences. Both GIP and GLP-1 have receptors in fat tissue, bone and the brain. GIP is unique in that it enhances the postprandial glucagon response, has receptors on adipose tissue and promotes bone formation whereas GLP-1 suppresses postprandial glucagon (in a glucose dependent manner) and inhibits bone formation. Both these incretin molecules have a beneficial effect in appetite regulation and both have receptors in the central nervous

Figure 1



system, acting on the hypothalamus to increase satiety[2]. Gastric emptying is slowed down by with GLP-1, however GIP does not seem to have a robust effect on this mechanism[3]. Despite the presence of GIP receptors in CNS regions involved in appetite regulation, GIP administered independently has not been shown to reduce food intake or appetite in human studies. However, its increase in the release of glucagon may have a beneficial effect of appetite reduction when both GIP and GLP-1 receptor are activated compared to when the individual GIP or GLP-1 receptors are activated alone[1]. There is more research that is needed to fully understand the mechanisms of action for the benefit of co-stimulating these two receptors.

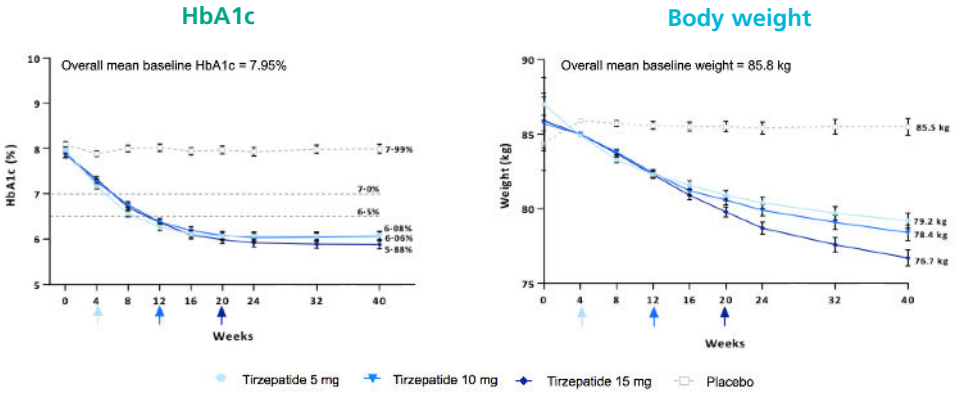


Figure 2. Effect of once weekly Tirzepatide vs Placebo in patients with Type 2 Diabetes, summary of results from the SURPASS-1 Trial

Introducing Tirzepatide, a dual GIP/GLP-1 receptor agonist

Tirzepatide is a 39 amino acid multifunctional peptide that is modified to bind to both GIP and GLP-1 receptors. Because of its relatively long half-life of 5 days, it is administered once weekly by subcutaneous injection via 6 different doses, 1 titration dose (2.5mg), and 5 therapeutic doses (5mg, 7.5mg, 10mg, 12.5mg and 15mg), and is titrated up every 4 weeks until the desired therapeutic dose is reached.[4]

Tirzepatide has shown remarkable efficacy in A1c and weight lowering in patients with type 2 diabetes in its phase 3 clinical trial programs called SURPASS. These programs are a series of randomized control trials looking at Tirzepatide in various clinical scenarios including monotherapy against placebo, other GLP-1RA (semaglutide 1mg) as well as basal insulins and as add on therapy to basal insulin, with some studies still pending completion. Tirzepatide is still being studied in persons with obesity with and without Type 2 diabetes in the SURMOUNT clinical trial program and with preliminary data suggest efficacy for chronic weight management in people without diabetes as well. The SURMOUNT program also includes specific outcomes of interest in patients with obesity including sleep apnea, renal disease and HfpEF.

A1c reduction of greater than 2%

The summaries of these clinical trials are shown in Figure 2 and 3, however in general the A1c lowering potential of this new molecule in almost all treatment arms (including the lowest therapeutic dose of 5mg) led to an average A1c reduction of greater than 2%. Similarly, the weight loss

Tirzepatide in Obesity (No T2D) SURMOUNT-1

	Placebo	TZP 5mg	TZP 10 mg	TZP 15 mg
Baseline Weight	105 kg			
Primary endpoint	72 weeks			
Weight Change (mean)	**-2 kg**	**-16 kg**	**-22 kg**	**-24 kg**
% Weight Change from baseline (mean)	**-2.4%**	**-16%**	**-21.4%**	**-22.5%**
% Achieving Wt Loss ≥5%	28%	89%	96%	96%
% Achieving Wt Loss ≥10%	13.5%	73%	86%	90%
% Achieving Wt Loss ≥15%	6%	50%	74%	78%
% Achieving Wt Loss ≥20%	1.3%	32%*	55%	63%

Figure 3. Effect of once weekly Tirzepatide vs Placebo in patients with Obesity, summary of results from the SURMOUNT-1 Trial

benefit in both patients with and without type 2 diabetes was greater than placebo and greater than the most effective GLP-1RA (Semaglutide 1mg, in the SURPASS 2 trial). The much-awaited cardiovascular outcome trial is still underway and due to be completed in October 2024, however a meta-analysis of pooled patients on Tirzepatide vs. pooled comparators (including placebo, semaglutide, degludec and glargine), and time to first occurrence of MACE showed a non-statistically significant HR of 0.8 (95% CI 0.57-1.11) showing likely cardiovascular safety with Tirzepatide.

In SURPASS-1 (Figure 2), the main placebo-controlled study of Tirzepatide, 478 patients with relatively recently onset (treatment naïve) type 2 diabetes were treated with Tirzepatide at randomly selected therapeutic doses of 5mg, 10mg or 15 mg vs placebo. At the end of the 40-week trial,

87-92%
of patients were able to get their A1c to
less than 7%

all doses showed superiority with A1c lowering and weight compared with placebo. Also, most impressively 87-92% of patients were able to get their A1c to less than 7% compared to 20% with placebo. Like most GLP-1RA's gastrointestinal side effects were the most common with nausea seen in 12-18% of patients on Tirzepatide and only 6% in the placebo group. This is similar to other GLP-1RA and usually occurred during the dose escalation period. The treatment discontinuation was 21.5% at the 15mg per week dose vs 14.8% with placebo and were noted to be due to non-adverse events for most trial participants. No level 2 hypoglycemia (<3mmol/L) was seen with Tirzepatide[5].

63% of participants were able to
reduce their weight by 20% or more[6].
This rivals the weight benefit of 20-30% typically seen with bariatric surgery

The SURMOUNT-1 clinical trial (Figure 3) focused on Tirzepatide as a treatment for obesity and had a very similar structure to the SURPASS trials. It Included 2539 patients with obesity without diabetes, treated with Tirzepatide in a 1:1:1:1 ratio with the same doses as the SURPASS trials compared to placebo for 72 weeks. The baseline mean BMI was 38. The results showed an impressive weight loss of 16.0% at the 5mg dose, 21.4% at the 10mg dose and 22.5% at the 15mg dose of Tirzepatide compared to 2.4% with placebo. At the 15mg per week dose, 96% of patients were able to reduce their weight by 5% and 63% of participants were able to reduce their weight by 20% or more[4]. This rivals the weight benefit of approximately 20-30% seen with bariatric surgery and is certainly far more effective than any anti-obesity medication that is currently available. The adverse events were similar to those seen in the SURPASS program and to other GLP-1RA.

Tirzepatide, an exciting new development in the Management of Type 2 diabetes and Obesity

The incretin family of hormones has led to impressive outcomes in the field of both diabetes and obesity. Patients have benefitted from the many GLP-1RA agents available in both subcutaneous and oral, daily, and weekly formulations. More research is needed to understand the underlying mechanism of action of this dual GIP/GLP1 agonist, however the remarkable outcomes in both A1c lowering and weight loss in both patient with and without diabetes is promising to help more patients reach their therapeutic goals. It is also paving the way for the development of other agents including triple agonists (GIP/GLP-1/Glucagon) in the pipeline.

Tirzepatide has already been approved by the FDA for use in Type 2 diabetes and is available in the US. It is anticipated to be approved by Health Canada, initially for Type 2 diabetes only, and should be available for our patients in the very near future.

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Eligible patients must be:

- Age: 50+
- Medically stable (no major medication changes or recent medical diagnosis)

***Note: Additional eligibility criteria will also apply**

Do you have patients that might be interested in participating? Enrollment has already started in Toronto, Burlington, Montreal and Quebec City.

If you are interested in referring your patients to this study, please contact:

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