Commentary

Tirzepatide: Novel Dual Targeted Treatment for Type 2 Diabetes Mellitus in Adults

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INTRODUCTION

Diabetes mellitus (DM) is a chronic progressive metabolic disorder in which either the body does not produce sufficient insulin (type 1) or uses it improperly due to insulin resistance (type 2), or both, which leads to hyperglycemia, glycosuria, hyperlipidaemia, negative nitrogen balance, and sometimes ketonemia.[1] WHO states that diabetes mellitus is a leading cause of death in the world with approximately 422 million people suffering from it globally.[2] India has approximately 77 million people (1 in 11 Indians) diagnosed with diabetes, which makes it the second most affected country in the world, after China.[3]

The purpose of therapy in diabetes mellitus is to restore the metabolism to normal, avoid symptoms due to hyperglycemia and glycosuria, and prevent short-term complications (infection, ketoacidosis, etc.) and long-term sequelae (cardiovascular, retinal, neurological, renal, etc.).[1] The treatment modalities mainly include orally administered Sulfonylureas, Meglitinides, Biguanides, Thiazolidinediones, α-glucosidase inhibitors, Sodium glucose co transporter 2 (SGLT2) inhibitors, and various injectable insulin preparations. These treatment options often provide desired efficacy by polytherapy rather than monotherapy. Common side-effects of these drugs are hypoglycemia, metallic taste, diarrhea, indigestion, bloating, abdominal cramps etc. Many studies have shown that these drugs can even take a toll on renal and hepatic function and can produce non-alcoholic fatty liver disease (NAFLD) and marked renal insufficiency as major adverse effects on prolonged repeated use at shorter intervals.[4]

To overcome this problem, normal physiology mimicking drugs with a longer duration of action have been discovered. These drugs act by release of endogenous hormones like glucagon-like peptide (GLP-1) and glucose-dependent insulinotropic peptide, also known as gastrin inhibitory peptide (GIP) in response to increased glucose; or their agonists. GIP is a 42 amino acid peptide hormone secreted by enteroendocrine K cells present throughout the intestine but present at a high density in the duodenum and upper jejunum, whereas GLP-1 is a 30 amino acid hormone produced by intestinal epithelial endocrine L cells in response to the increased glucose in intestine.[5,6] GLP-1 binds to its receptor (GLP-1R) and triggers a downstream signalling cascade to induce a potent stimulation of glucose stimulated insulin secretion (GSIS) in β-cells, as well as inhibition of α-cell glucagon release. Synthetic GLP-1 analogues, such as Liraglutide and Exendin-4, unlike endogenously produced GLP-1, are not rapidly degraded by dipeptidyl peptidase-4 (DPP-4) and therefore, can induce sustained therapeutic actions, that otherwise would not be possible due to the exceedingly short half-life of endogenous GLP-1 in circulation. It is to be noted that for the same plasma level of glucose, insulin secretion is more when glucose is administered orally rather than intravenously. This phenomenon is called the incretin effect, since GLP-1 and GIP are known as incretins as they are normally released from the intestine after oral glucose consumption. GIP is considered the most potent incretin hormone and it, together with glucagon-like peptide-1 (GLP-1), contributes to 25 to 70% of the postprandial insulin response.[5-7]

Thus, GIP and GLP-1 play an important role in maintaining the carbohydrate metabolism in healthy individuals by stimulating the release of insulin from β-cells of the pancreas. This released insulin then increases glucose uptake by muscles and decreases gluconeogenesis in the liver as shown in figure 1.[8] A few drugs that act via this pathway are Exenatides, Pramlintide, and DPP-4 inhibitors. DPP-4 inhibitors (Gliptins) prevent the breakdown of GIP and GLP-I via dipeptidyl peptidase-4 enzyme and hence indirectly lead to increased insulin availability.

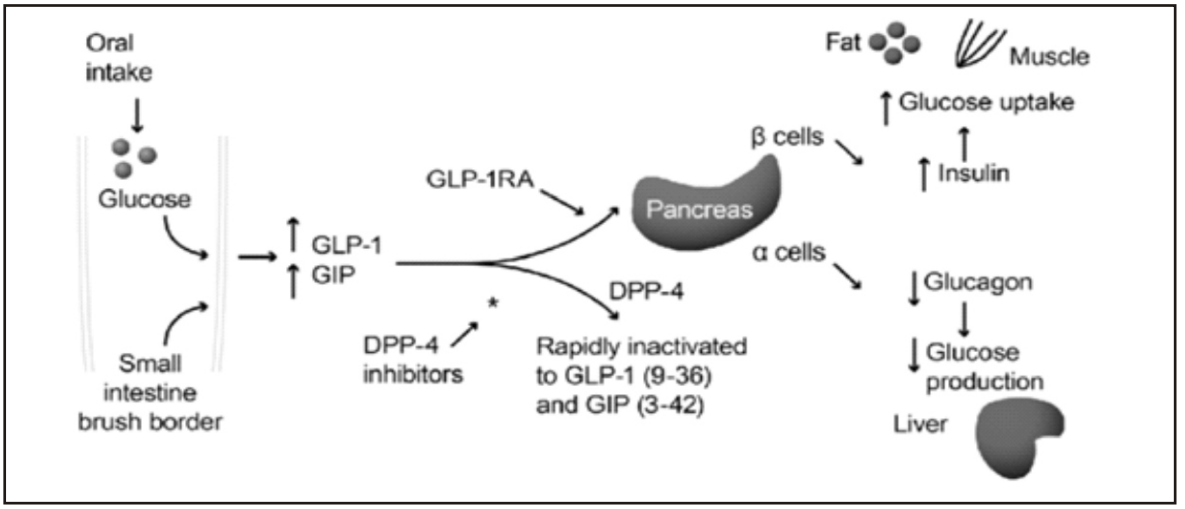

Figure 1: Mechanism of action of GIP and GLP-1.[8]

TIRZEPATIDE

In May 2022, the U.S. FDA approved a novel dual targeted treatment for type 2 diabetes mellitus- Tirzepatide after receiving priority review designation. Tirzepatide is first drug in the dual-target class, once-weekly-administered. It is an injectable therapy indicated for the management of type 2 diabetes mellitus (T2DM) in adults as an adjunct to diet and exercise.

Chemically, Tirzepatide is a linear polypeptide of 39 amino acids that has been chemically modified by lipidation to improve its uptake into cells and to stabilize it against metabolism to make it longer acting.

Mechanism of action: Tirzepatide acts by binding and stimulating both GIP and GLP-1 receptors on pancreatic cells. It improves the secretion of both first and second phase insulin and reduces glucagon in a glucose-dependent manner. The dual agonist behavior produces greater reductions in hyperglycemia compared to the GLP-1 receptor agonists alone. Tirzepatide has a greater affinity for GIP receptors than for GLP-1 receptors. However, at the GLP-1 receptor, Tirzepatide shows bias towards cAMP (a messenger associated with regulation of glycogen, sugar and lipid metabolism) generation, rather than β-arrestin recruitment. This combination of preference towards GIP receptor and distinct signaling properties at GLP-1 increases insulin secretion.

Clinical trials[9]: In total, five clinical trials have been conducted, namely- and SURPASS-1, SURPASS-2, SURPASS-3, SURPASS-4, and SURPASS-5.

SURPASS-1: Tirzepatide was evaluated as a monotherapy against placebo at three different doses: 5 mg, 10 mg, and 15 mg administered subcutaneously once weekly. The primary objective of this trial was to assess changes in HbA1c from baseline. With 121 participants in each arm, the maximum reduction in HbA1c was seen in the group with a 15 mg dose followed by 10 mg and then 5 mg. Nausea (24.6%, 33.3%, 31.0%), diarrhoea (18.7%, 21.2%, 23.0%), vomiting (8.3%, 10.7%, 12.2%), and constipation (16.8%, 17.1%, 11.7%) were more frequently experienced as compared to placebo (9.5% nausea, 7.3% diarrhea, 1.7% vomiting, and 5.8% constipation).

SURPASS-2: The test drug was compared against 1mg of Semaglutide (GLP-1 agonist) administered once weekly for 40 weeks with the same primary outcome as SURPASS-1 but comparing only two doses against Semaglutide. At the end of 40 weeks, a maximum reduction in HbA1c was seen with Tirzepatide 15 mg followed by Tirzepatide 10 mg.

SURPASS-3: This trial compared Tirzepatide (10 mg and 15 mg) against Insulin Degludec administered subcutaneously daily with the primary objective of comparing reduction in HbA1c. At the end of 52 weeks, the test drug with 15 mg was reported with a maximum reduction in HbA1c followed by 10 mg dose of Tirzepatide and the least reduction was seen with Insulin Degludec.

SURPASS-4: Tirzepatide 5 mg was compared against Insulin Glargine with titrated dose (according to protocol defined target dose) starting from 10 IU/day at bedtime. At the end of 52 weeks, Tirzepatide 5 mg was seen to reduce HbA1c more than Insulin Glargine.

SURPASS-5: Tirzepatide as an adjunct was compared with placebo in participants with type 2 diabetes inadequately controlled on Insulin Glargine with or without Metformin.

At the end of 40 weeks, Tirzepatide 10 mg and 15 mg showed a comparable reduction in HbA1c (-2.59) which was more than placebo (-0.93).

A meta-analysis of all randomized controlled trials with at least 26 weeks duration of study from the Tirzepatide T2DM clinical development program, was conducted with the primary objective to compare the time to first occurrence of confirmed four-component major adverse cardiovascular events (MACE-4; cardiovascular death, myocardial infarction, stroke, and hospitalized unstable angina) with that of controls. The results revealed that Tirzepatide did not increase the risk of major cardiovascular events in participants with T2DM versus controls.[10]

Other potential uses: Recently, Tirzepatide has also been approved as a weekly drug for obesity owing to its propensity to decrease food intake and increase energy expenditure.[11] The SURPASS programme showed that it resulted in greater weight loss than comparators and those who received higher doses of Tirzepatide reduced maximum weight loss of 25 lbs. In obese patients, it works by increasing the levels of adiponectin, an adipokine involved in the regulation of both glucose and lipid metabolism.

Tirzepatide is also being studied as a potential treatment for non-alcoholic steatohepatitis (NASH) and heart failure with preserved ejection fraction (HFpEF). Studies of Tirzepatide in obstructive sleep apnoea (OSA) and in morbidity/mortality in obesity are planned as well.[12]

Route and dosage: 5-15 mg once weekly by subcutaneous route.

Adverse effects: The mild adverse effects reported with the drug are nausea, diarrhoea, reduced appetite, constipation, upper abdominal discomfort, and abdominal pain. However, in rats, this drug was seen to cause thyroid cell tumors. However, the drug has not been tested in humans for tumors. Also, this drug has not been tested in patients with pancreatitis and is not indicated for use in type-1 diabetes mellitus.[13]

CONCLUSION

Tirzepatide is a novel dual-receptor agonist which acts on GIP and GLP-1 receptors and shows robust improvements in glycemic control and body weight, without increased risk of hypoglycemia. The consistent efficacy and safety profile make it a potential monotherapy candidate for type 2 diabetes mellitus.

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