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A Novel Insight of Tirzepatide for Diabetes Mellitus and Overweight

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ABSTRACT

The chronic metabolic disease known as type 2 diabetes mellitus (DM) has been becoming more common worldwide. This trend is causing the disease to spread swiftly to additional parts of worldwide, and it is estimated that an ageing population will cause the disease to impact twice as many individuals in the ten years to come. Overweight and obesity are dangerous illnesses that have been linked to heart disease, stroke, diabetes, and other major causes of death. Healthcare workers will have an even greater workload as a result of this, particularly in developing nations. Tirzepatide is a new medication that the FDA has approved to treat type 2 diabetes mellitus. Due to Tirzepatide's potent weight-loss effects, it is utilised as an off-label treatment for obesity. By functioning as a dual GLP-1 and GIP agonist, it optimises benefits akin to those of GLP-1 medications like semaglutide. Similar to GLP-1 medications, it is currently given as a once-weekly subcutaneous injection as a second-line diabetic medication. The FDA approved Tirzepatide in May 2022. The most commonly reported side effects are gastrointestinal problems i.e diarrhea and nausea. Tirzepatide lowers blood sugar levels in people with type 2 diabetes by slowing the passage of food through the intestines, limiting the amount of sugar the liver produces, and assisting in the release of insulin when blood sugar levels are high. The introduction, mechanism of action, adverse effects, contraindications, and important takeaways of Tirzepatide are covered in this article.

Keywords: Tirzepatide, Diabetic, Type 2 DM, Clinical outcome, Cell action.

INTRODUCTION

A dangerous chronic illness that progresses and relapses is obesity.[1]. The cornerstone of managing obesity is lifestyle modifications, yet maintaining weight loss from calorie restriction based on lifestyle might be difficult. People will gain weight from taking any growth hormone because insulin is a growth hormone. It's also probable that you lost a substantial amount of weight fast after being diagnosed, since weight loss is one of the symptoms of diabetes and weight gain is a key component of recovery. Therefore, in order to encourage weight loss, make weight maintenance easier, and enhance health outcomes for those who suffer from obesity, the most recent guidelines suggest supplementary antiobesity drugs.[2-4] So far, randomised investigations on the withdrawal of antiobesity drugs have repeatedly shown that stopping therapy can result in a clinically significant increase in body weight.[5,6] Additionally, there is evidence that anti-obesity drugs such as orlistat, naltrexone/bupropion, phentermine/topiramate, and long-acting glucagon-like peptide-1 (GLP-1) receptor agonists may aid in maintaining weight loss that has been accomplished.[7-12].

Tirzepatide is a novel medication that has been approved by the US Food and Drug Administration (FDA) to treat type 2 diabetes mellitus (T2DM). Because of this drug's effectiveness in helping people lose weight, it is being used off-label to treat obesity. As a dual agonist, tirzepatide binds to the glucagon-like peptide-1 (GLP-1) receptor as well as the glucose-dependent insulinotropic polypeptide (GIP) receptor. In individuals with type 2 diabetes, the medication greatly improves glycaemic control and reduces body weight, with results comparable to those of GLP-1 drugs like semaglutide.

As with GLP-1 drugs such as semaglutide, tirzepatide is currently prescribed as a second-line treatment for diabetes. It is injected subcutaneously once a week, with gradual dosage increases. Tirzepatide has not been studied in individuals with pancreatitis and is not authorised for the treatment of type 1 diabetic mellitus (T1DM). The gastrointestinal side effects of the medication, such as nausea, vomiting, and diarrhoea, are the most often reported side effects.

Tirzepatide is a single compound that combines GLP-1 receptor agonism [13] and glucose-dependent insulinotropic polypeptide (GIP) to provide a synergistic effect on appetite, food intake, and metabolic processes [14–16]. In several countries, including the US, EU, and Japan, tirzepatide is approved for use as a once-weekly subcutaneous injection to treat type 2 diabetes. It is also approved for the treatment of obesity in the US and UK [16–18]. When tirzepatide was used for 72 weeks, people with obesity or overweight but not diabetes experienced mean decreases in body weight of up to 20.9% in a placebo-controlled experiment.[17,18]

One noteworthy finding from the SURMOUNT-4 trial is that participants ended the research with a significant drop in body weight (9.9%) after switching to a placebo for a year. But a large portion of their initial reduction in risk variables related to cardiometabolism has been undone. To fully comprehend the possible hazards and benefits (i.e., legacy effects) of such short-term therapy, more research is required. Studies of incretin-based therapies that have been approved for the treatment of obesity and overweight have also shown a safety profile consistent with the health benefits of prolonged treatment at the maximum tolerated dose of tirzepatide during this study. These trials include SURMOUNT and SURPASS [18, 19]. A summary of the indications, mechanism of action, side effects, contraindications, and crucial factors to take into account when taking tirzepatide is given in this activity. Additionally, this exercise helps physicians become more adept at managing patients' type 2 diabetes and giving tirzepatide, which improves patient care and safety overall.

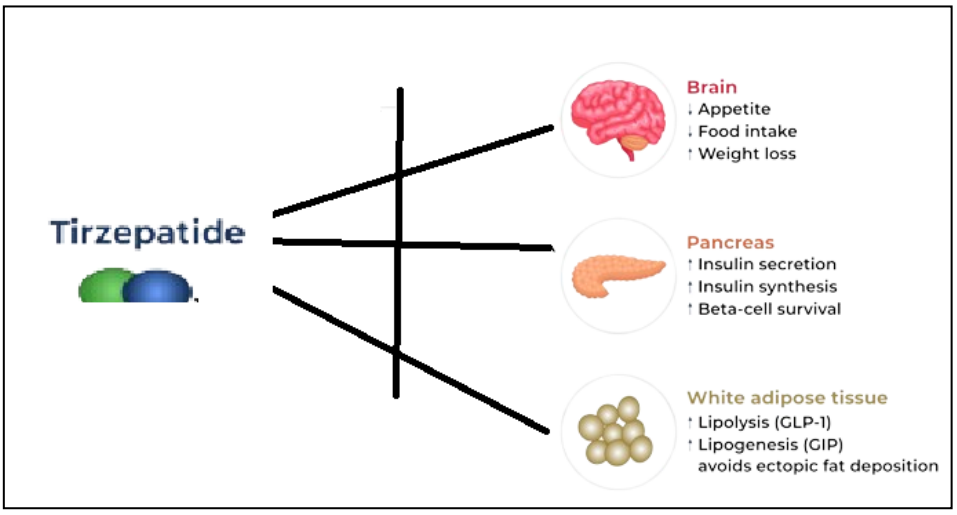

Fig.1 (Role of Tirzepatide)

Mechanism of Action:

A synthetic polypeptide dual agonist for GLP-1 and GIP is called tirzepatide. "Twincretin," or tirzepatide, differs from GLP-1 receptor agonists in a number of ways [20]. The drug is an analogue of the gastric inhibitory polypeptide and consists of 39 amino acids. In terms of function, tirzepatide lowers hyperglycemia and encourages the pancreas to secrete insulin. Furthermore, tirzepatide raises adiponectin levels as well.

Compared to GLP-1 agonist medications, the dual agonism ability dramatically lowers hyperglycemia and decreases hunger in the patient [21]. Tirzepatide 5 to 15 mg once weekly was given to non-diabetic patients to manage obesity. Over a 72-week period, the patients' body weight decreased significantly, from 16.5% to 22.4%. Based on post hoc assessments of fasting biomarkers, tirzepatide significantly improved markers of β-cell activity and insulin sensitivity [22].

Pharmacokinetic profile:

About 80% of tirzepatide is bioavailable. It can take as little as eight to seventy-two hours to achieve peak serum levels. Tirzepatide's mean constant state volume of distribution is roughly 10.3 L. The drug has a 99% binding strength to plasma albumin. The structure of peptide is breaked by proteolytic cleavage upon injection. Additionally, amide hydrolysis and β-oxidation are applied to the C20 fatty diacid composition. Tirzepatide is a modified polypeptide that is metabolised into individual amino acids in the liver and other organs [23]. Tirzepatide is excreted as metabolites in the urine and faeces and has a half-life of five days, which makes weekly dosage easier [24].

Indications:

The FDA authorised Tirzepatide, a novel medicine, in May 2022 for the treatment of type 2 diabetic mellitus (T2DM). Tirzepatide is a synthetic polypeptide that acts as a dual agonist on the GLP-1 (glucagon-like peptide) and GIP (glucose-dependent insulinotropic polypeptide) receptors. Therefore, the medicine maximises advantages similar to GLP-1 treatments like semaglutide and leads to dramatically improved glycaemic control and weight loss in people with T2DM.[1] Similar to GLP-1 medications like semaglutide, tirzepatide is being used as a second-line diabetic treatment. It is injected subcutaneously (SQ) once a week, with gradual dosage modifications [25].

The outcomes of the SURPASS studies show that tirzepatide, in contrast to other agonists (dulaglutide and semaglutide GLP-1 receptor), insulin glargine, produces clinically meaningful benefits in glycaemic management and weight loss. As a result, tirzepatide is rated as a very successful treatment by the American Diabetes Association (ADA) for glycaemic management and weight loss [26,27].

Tirzepatide has a more effective mechanism of action than GLP-1 drugs. Its ability to reduce weight and non-toxicity to the liver suggest that it may play a supporting role in the management of nonalcoholic fatty liver disease [28]. Before the treatment is authorised for steatotic liver disease linked to metabolic dysfunction, more investigation is necessary [28].

Dosage and administration:

Oral Tirzepatide is not yet a viable option; it is injected subcutaneously (SQ). 10 mg/0.5 mL, 12.5 mg/0.5 mL, 7.5 mg/0.5 mL, 5 mg/0.5 mL, 10 mg/0.5 mL, and 15 mg/0.5 mL are the available dose strengths for Tirzepatide.

The recommended dose is normally taken once a week; however, during follow-up visits, it may be raised based on efficacy, which is determined by body weight, HbA1c levels, and side effects. The dose titration process is heavily influenced by the patient's capacity to endure side effects. Tirzepatide is started at a dose of 2.5 mg given subcutaneously once a week, with the main focus being on commencement rather than glycaemic control. Increase to 5 mg SQ once weekly after 4 weeks. After taking the current dosage for at least 4 weeks, increase the dosage by 2.5 mg for more control. The maximal dosage of Tirzepatide is 15 mg SQ once every week. Tirzepatide must be taken within 4 days (96 hours) if a dosage is missed.

Toxicity Profile:

Patients who take too much Tirzepatide should have their clinical state closely watched. Patients may need ongoing monitoring because of the extended half-life of this medicine. Clinicians should get in touch with poison control; they might also need to speak with a toxicologist. Since there is currently no cure for Tirzepatide overdose, supportive care is the most helpful course of action.

Data currently available indicate that the majority of consumers do not have notable adverse medication responses. Although gastrointestinal side effects are the most common adverse effect, there have been occasionally been reports of other side effects. It is common to hear about decreased hunger, yet this could be a contributing factor in purposeful weight loss.

Interaction with Drug:

Tirzepatide shouldn't be given to people who are already taking other GLP-1 medications, such as liraglutide or semaglutide. To reduce the risk of hypoglycemia, insulino therapy peoples on can be started on Tirzepatide medication and have their dose of insulin gradually lowered [28].

Due to the decreased effectiveness (hormonal contraceptives oral), patients should be recommended to utilise barrier contraceptives for four weeks following initiation and to increase their dosage of Tirzepatide. Tirzepatide slows down the emptying of the stomach, which affects how well oral drugs taken at the same time are absorbed. Since it might exacerbate symptoms, this is especially crucial for those who already have delayed stomach emptying. Tirzepatide and other oral drugs having a narrow therapeutic index (TI) or that rely on threshold concentrations should be used with caution [29].

Patient Monitoring:

During follow-up visits, patients should have their body weight and HbA1c measured. The local standard of care for the treatment of obesity and diabetes determines the intervals between follow-up visits. Generally, HbA1c monitoring is done every three months, based on the patient's HbA1c target. The assessment of responsiveness can also be done with continuous glucose monitoring [30, 31].

It could be essential to keep an eye out for adverse effects, such symptoms connected to the digestive system, particularly when the recommended dosages rise. Furthermore, patients on tirzepatide may have asymptomatic elevations in lipase and amylase levels. Clinical evidence, however, do not support the usefulness of tracking these markers in the absence of symptoms.

Prohibited to use:

In patients with medullary thyroid carcinoma, tirzepatide should not be administered. In patients are multiple endocrine neoplasia syndrome-2 (MEN-2), tirzepatide is likewise contraindicated. Additionally, as tirzepatide has been linked to serious hypersensitivity events such anaphylaxis and oedema, its usage is not advised in individuals who are known to be severely allergic to it or any of its excipients [31]. Patients should utilise tirzepatide cautiously who have previously had angioedema or anaphylaxis as a result of GLP-1 receptor agonists.

Clinical Outcomes:

A new drug called Tirzepatide has been licensed to treat DM-2 and also helps patients lose weight. After first-line therapy, clinicians are likely to recommend it for uncontrolled diabetes. Tirzepatide is a highly effective medication for lowering body weight and decreasing HbA1c levels, according to recent clinical research [32].

For many nonpregnant adults, a HbA1c goal of <7% is suitable, according to the ADA guidelines [33]. If the HbA1c target is not reached after three months of metformin alone, guidelines suggest that metformin can be used with a GLP-1 receptor agonist (recommended in patients with a compelling need for weight loss) or other drugs based on comorbidities and collaborative decision-making [34]. Depending on the dosage and the local standard of care for the management of diabetes, clinicians may follow up with patients at predetermined intervals after starting tirzepatide therapy, which could be as early as 4 weeks or as late as 12 weeks. Pharmacists provide assistance to patients on tirzepatide by doing certain tasks, such as giving the drug, advising patients about possible side effects, and periodically checking their haemoglobin HbA1c levels.

Pharmacists are included in certain care teams' diabetes treatment strategies. The expected first point of contact when discussing the side effects of tirzepatide is expected to be nurses. Additionally, clinicians must to inform patients about the warning signs of hypoglycemia, which include tremors, disorientation, and irritability.

Like GLP-1 drugs, tirzepatide is probably also prescribed in weight loss clinics. In order to optimise patient outcomes, obesity treatment clinics frequently integrate multidisciplinary care with the assistance of social workers or dietitians. Tirzepatide's high levels of reported efficacy suggest that it will likely attain a similar level of appeal among physicians and patients as semaglutide did in weight loss clinics. Clinical studies, however, indicate that weight loss appears to be dose-dependent; the patient's capacity to tolerate larger tirzepatide dosages may be the limiting factor in managing weight loss.

A recent systematic review study found that patient-reported outcomes in patients with type 2 diabetes are considerably improved by interprofessional teamwork between specialists, physicians, nurses, and other healthcare staff [35]. Maintaining meticulous documentation in the patient's medical file is essential to guaranteeing that all team members have access to current, accurate patient data for making decisions.

Conclusion:

The FDA authorised Tirzepatide, a novel medicine, in May 2022 for the treatment of T2-DM. Tirzepatide is a synthetic polypeptide that acts as an additional agonist on the GLP-1 (glucagon-like peptide) and GIP (glucose-dependent insulinotropic polypeptide) receptors.. It is need to determine whether patients, given their clinical profile and desired course of treatment, are good candidates for tirzepatide therapy. Evaluate the patient's reaction to tirzepatide therapy by keeping a close eye on weight fluctuations and glycaemic control. For individuals with complicated medical histories or diabetes that is resistant to treatment, choose the best combination therapies or alternate therapy alternatives. Work together with interdisciplinary healthcare teams to plan follow-up appointments and care transitions so that tirzepatide therapy can continue while long-term results are tracked.

Conflict of interest: None

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