International Journal of Trend in Innovative Research (IJTIIR)
Available Online @ www.ijtiir.com | ISSN: 2582-0354

The Efficacy and Future of Tirzepatide in Treating Type 2 Diabetes and Obesity: A Comprehensive Review

[1]Gunti Nikitha, [2]Kukkala Anusha, [3]Gandu Rachana
[1,2,3]Pharm D 4th Year Department of Pharmacy Practice, Prathap Narender Reddy College of Pharmacy

Corresponding:
Gunti Nikitha
Pharm D 4 th Year, Department of Pharmacy Practice
Prathap Narender Reddy College of Pharmacy
Email: guntinikitha64@gmail.com

Abstract--

Background:
Tirzepatide, a dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, represents a significant advancement in the treatment of type 2 diabetes (T2D) and obesity. Its unique mechanism offers superior glycemic control and substantial weight loss compared to conventional treatments.

Objective:
To comprehensively review the pharmacodynamics, efficacy, safety profile, and potential future applications of tirzepatide in managing T2D and obesity.

Methods:
A systematic review of 90 articles was conducted using databases such as PubMed, Scopus, and SciFinder®. Articles were selected based on clinical trial data, meta-analyses, and systematic reviews relevant to tirzepatide and its applications in diabetes and obesity management.

Results:
Tirzepatide improves glycemic control through enhanced insulin secretion, suppressed glucagon release, and delayed gastric emptying. It also reduces weight by promoting satiety and addressing insulin resistance. Clinical trials demonstrate significant HbA1c reductions and weight loss with once-weekly subcutaneous administration. Adverse effects are primarily gastrointestinal, with rare reports of hypoglycemia and renal complications.

Conclusion:
Tirzepatide is a promising therapy for T2D and obesity, offering multifaceted benefits, including improved metabolic health and reduced cardiovascular risks. However, challenges such as cost, injection administration, and long-term safety data must be addressed. Continued research is essential to optimize its use and establish its role in personalized medicine for chronic metabolic diseases.

I. INTRODUCTION

Tirzepatide is an innovative pharmacological agent, functioning as a dual-action receptor agonist for glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which has been developed for the therapeutic management of type 2 diabetes and has recently garnered approval for the treatment of obesity. This agent signifies a significant advancement in the domain of metabolic disease management, presenting prospective advantages in comparison to conventional GLP-1 receptor agonists. The distinctive dual mechanism of Tirzepatide effectively engaging both GIP and GLP-1 signaling pathways has exhibited encouraging efficacy in clinical investigations aimed at enhancing glycemic regulation and facilitating weight reduction. This review seeks to consolidate the most recent clinical evidence regarding Tirzepatide pharmacodynamics, effectiveness, safety profile, and prospective developments, with the objective of assessing its position within the therapeutic landscape for type 2 diabetes and obesity **(1)**. Tirzepatide, an emergent dual receptor agonist for glucose-dependent insulin tropic peptide (GIP) and glucagon-like peptide-1 (GLP-1), has obtained regulatory approval for the management of type 2 diabetes (T2D) and is presently under investigation for its potential in sustained weight management. Our objective is to examine the safety and efficacy of administering once-weekly subcutaneous tirzepatide for weight loss in individuals diagnosed with T2D or obesity.

The pathophysiology of T2D involves a complex interplay of insulin resistance, beta-cell dysfunction, and metabolic disturbances, with obesity being both a cause and a consequence of the disease. Diet and satiety are crucial factors in managing T2D, as excessive caloric intake and disrupted hunger signals exacerbate insulin resistance. The roles of GLP-1 and GIP in regulating insulin secretion, glucose metabolism, and appetite make them essential components in the treatment of both T2D and obesity. Dual agonists like Tirzepatide, which target both GLP-1 and GIP receptors, offer a promising therapeutic strategy for improving glycemic control and promoting weight loss in individuals with T2D and obesity **(2).**

Type 2 Diabetes, Insulin Resistance, Diet, Satiety, Obesity, and the Role of GIP and GLP-1 in Both Diabetes and Obesity:

Type 2 Diabetes and Insulin Resistance: Insulin resistance and decreased insulin secretion by pancreatic beta cells combine to cause type 2 diabetes (T2D), a chronic metabolic disease marked by high blood glucose levels (hyperglycemia). The pancreas secretes the hormone insulin, which lowers blood sugar levels by assisting cells in absorbing glucose from the bloodstream. The cells in the body, mainly the muscle, liver, and fat cells, lose their ability to react to insulin when they have type 2 diabetes. The pancreas first tries to overcome the resistance by producing more insulin (a condition called hyperinsulinemia). The pancreatic beta cells eventually wear out and lose their capacity to secrete enough insulin, which exacerbates hyperglycemia, dysregulation of lipid metabolism, increased risk of complications.

Diet and Satiety in Type 2 Diabetes: Diet plays a crucial role in the management of T2D. The types of foods consumed directly influence blood sugar levels, insulin resistance, and the overall metabolic state. Key dietary considerations for individuals with T2D include:

- **Carbohydrate management**: Carbohydrates are broken down into glucose, which can cause blood sugar levels to spike. Low-glycemic index (GI) foods that are digested slowly can help control post-meal glucose surges.
- **Protein and fat intake**: Protein-rich foods, along with healthy fats (monounsaturated and polyunsaturated), are important for stabilizing blood glucose levels and preventing rapid fluctuations.
- **Caloric restriction**: Managing overall calorie intake is vital to avoid excess weight gain, which can exacerbate insulin resistance **(3).**

Satiety and the Impact of Food Intake Satiety, or the feeling of fullness after eating, is an important aspect of diabetes management, particularly when managing weight. Overeating and constant hunger can lead to weight gain and worsen insulin resistance. In T2D, disruptions in the mechanisms regulating hunger and satiety often occur, leading to increased food intake despite adequate or high calorie consumption. This can be influenced by several factors:

- **Hormonal regulation of hunger**: Hormones like ghrelin (which stimulates appetite) and leptin (which signals fullness) play key roles in regulating food intake. In insulin resistance and obesity, these signals may become dysregulated, contributing to overeating.
- **GIP and GLP-1 role**: These hormones, which are released from the gut after eating, influence both insulin secretion and appetite regulation. Dysregulation of these hormones in T2D may contribute to overeating and poor blood sugar control **(4).**

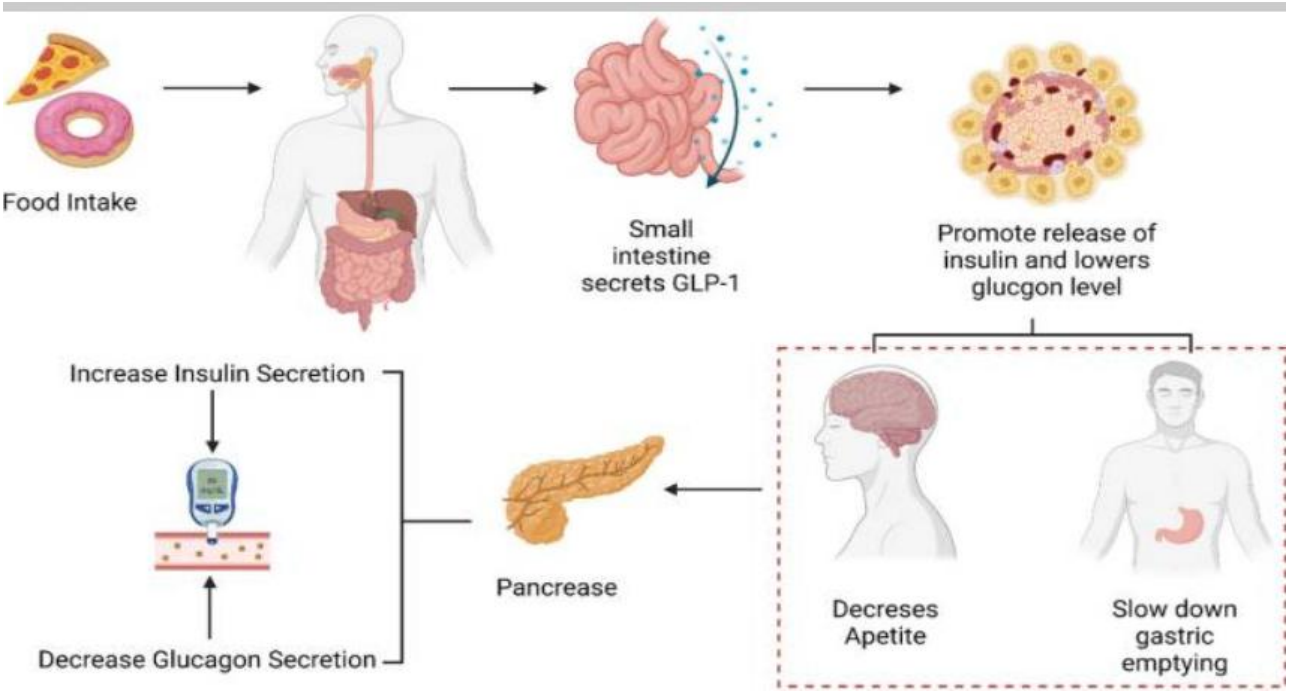

Figure 1: Role of GLP-1 in humans

Obesity in Type 2 Diabetes

Obesity is both a cause and a consequence of T2D. Excess fat, particularly visceral fat (fat stored around internal organs), exacerbates insulin resistance. This occurs because fat cells release various inflammatory mediators (adipokines) and fatty acids, which interfere with the normal action of insulin.

- **Visceral fat**: This type of fat is particularly harmful in T2D because it is metabolically active and releases inflammatory substances that worsen insulin resistance.
- **Insulin resistance and weight gain**: Over time, the progression of insulin resistance and chronic hyperinsulinemia can lead to increased fat storage, particularly in the abdominal area, which further worsens the metabolic state **(5).**

The Role of GIP and GLP-1 in Diabetes and Obesity

GIP (Gastric Inhibitory Polypeptide) and **GLP-1 (Glucagon-Like Peptide-1)** are incretin hormones released from the gut in response to food intake. They play important roles in glucose metabolism and appetite regulation, making them critical targets for diabetes and obesity therapies **(6).**

GLP-1:

Insulin secretion: GLP-1 enhances insulin secretion from the pancreas in a glucose-dependent manner. This means it helps to increase insulin levels when blood glucose is elevated, and has a minimal effect when blood glucose levels are normal or low, reducing the risk of hypoglycemia.

Inhibition of glucagon secretion: GLP-1 suppresses the release of glucagon, a hormone that raises blood glucose levels, helping to prevent excess glucose production by the liver.

Appetite regulation: GLP-1 also acts on the brain to reduce hunger and promote satiety, which can lead to decreased food intake and weight loss.

Gastric emptying: GLP-1 slows gastric emptying, contributing to prolonged feelings of fullness after meals.

GIP:

Insulin secretion: GIP also stimulates insulin release from the pancreas but is considered less effective in individuals with T2D due to insulin resistance at the GIP receptor level.

Appetite regulation: While GIP's role in appetite regulation is less well understood than GLP-1, it appears to influence hunger and food intake to some extent. In combination with GLP-1, GIP's effects on appetite may be more potent.

The Synergistic Effect of GLP-1 and GIP in Diabetes and Obesity

Tirzepatide's Dual Action: Tirzepatide is a dual GIP and GLP-1 receptor agonist that combines the benefits of both hormones. This dual agonism has been shown to improve insulin sensitivity, reduce blood glucose levels, promote weight loss, and enhance satiety. Tirzepatide's ability to simultaneously enhance insulin secretion, suppress glucagon, slow gastric emptying, and reduce appetite makes it a promising treatment for both T2D and obesity.

Impact on Obesity: By improving insulin sensitivity and reducing hunger and food intake, GLP-1 and GIP receptor activation can help combat obesity, which is a major risk factor for the development and progression of T2D. The weight loss effects are particularly beneficial for individuals with T2D who often struggle with managing both their weight and blood sugar levels simultaneously **(7).**

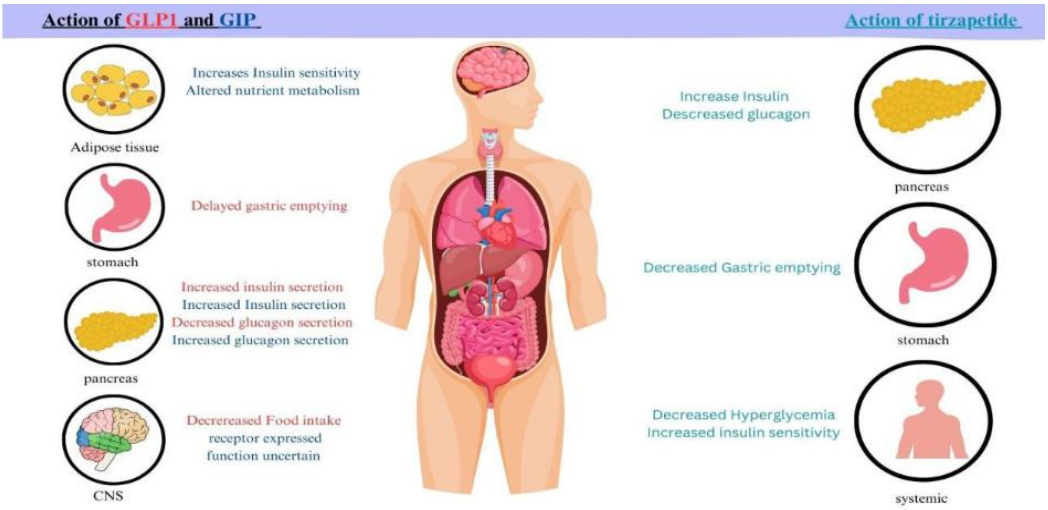

Figure 2: Mechanism of action of Tirzepatide

II. METHODOLOGY

For the preparation of this review, we carried out a literature search using SciFinder®, PubMed, Scopus and WOS. The key words 'tirzepatide and Diabetes', 'Tirzepatide and Obesity', 'novel antidiabetics' were used to search the related articles. In total, 90 articles were found containing the two concepts 'tirzepatide' and 'Diabetes/Obesity' closely associated with one another. From these, we included those articles that employed synthetic methods, clinical trial data, research articles, meta analysis, systematic reviews or discussion of tirzepatide. No conference abstracts or book chapters were included, and only papers written in English language were included.

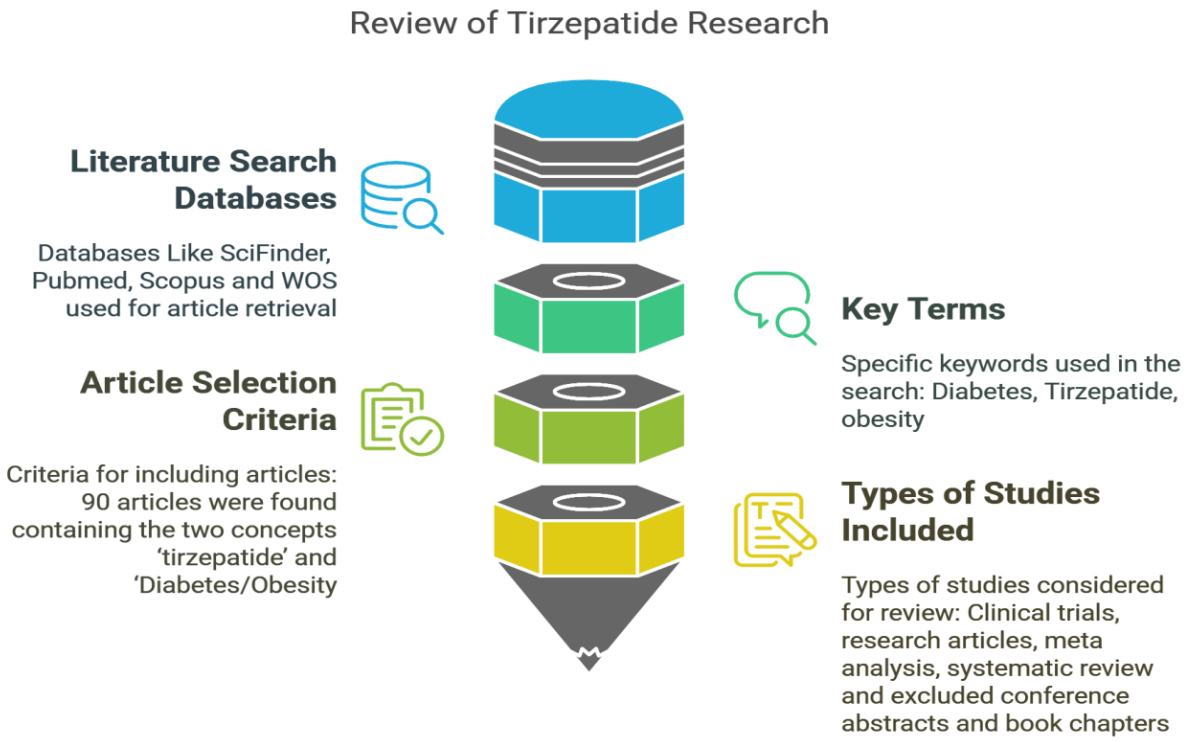

Figure 3: Methodology Process

III. DISCUSSION

Eli Lilly and Company (Indianapolis, IN, USA) used tirzepatide as a glycemic control technique for the first time in early 2016. Eli Lilly achieved yet another milestone on May 14, 2022, when the US FDA approved Mounjaro® (tirzepatide), a much-anticipated anti-diabetic medication. Tirzepatide is a synthetic peptide compound that functions as a receptor agonist on both GIP and GLP-1 receptors. It also goes by the name "twincretin" because of this special dual activity characteristic. Since it has a half-life of roughly five days, subcutaneous dosing once a week is sufficient.

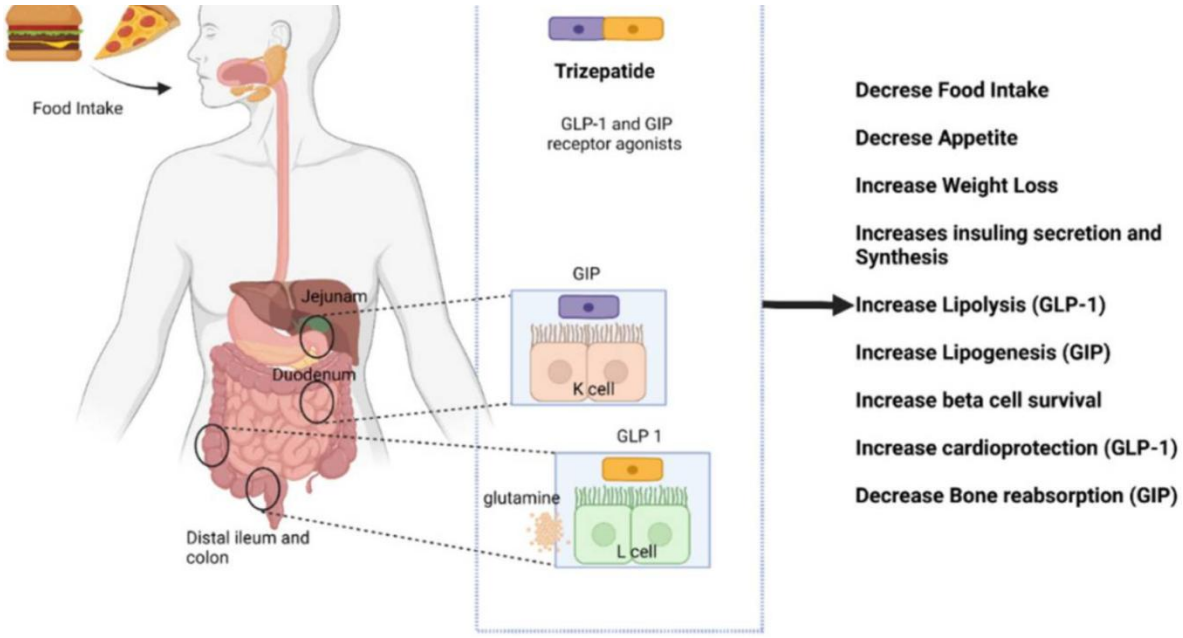

Figure 4: Mechanisms of Tirzepatide

Mechanism of Tirzepatide:

The specific mechanisms through which tirzepatide modulates glycemic control and assists in weight management in individuals with type 2 diabetes remain inadequately elucidated. It is well-established that the agonism of GLP-1 receptors plays a significant role in facilitating these advantageous pharmacodynamic effects. Analogous to selective GLP-1 receptor agonists, tirzepatide exhibits central effects that diminish food consumption by enhancing insulin secretion from pancreatic beta-cells in response to glucose (referred to as the incretin effect) while concurrently suppressing glucagon secretion from pancreatic alpha-cells, thereby contributing to decreased nutrient intake and fostering weight reduction. Tirzepatide is characterized as a synthetic peptide that functions as an agonist for both GLP-1 and GIP receptors. It serves as an analog of gastric inhibitory polypeptide and comprises a sequence of 39 amino acids. Functionally, it stimulates the pancreas to augment insulin secretion, consequently resulting in a decrease in blood glucose levels. Moreover, tirzepatide is associated with an increase in the concentration of adiponectin. In contrast to the administration of GLP-1 agonist medications in isolation, its dual agonistic properties significantly curtail appetite and markedly diminish hyperglycemic states **(8).**

Tirzepatide in diabetes management

Tirzepatide is a novel medication that acts as a dual agonist of the glucagon-like peptide-1 (GLP-1) receptor and the glucose-dependent insulinotropic polypeptide (GIP) receptor. By stimulating these receptors, tirzepatide enhances insulin secretion in response to meals while simultaneously suppressing glucagon release, leading to improved glycemic control. The clinical significance of tirzepatide lies in its ability to not only lower blood sugar levels but also promote weight loss and reduce cardiovascular risk factors, making it a comprehensive treatment option for patients with type 2 diabetes. Its unique mechanism of action allows tirzepatide to address multiple aspects of type 2 diabetes management, providing both metabolic benefits and improved patient outcomes in a population that often struggles with obesity and related complications. This multifaceted approach positions tirzepatide as a promising therapeutic agent in the evolving landscape of diabetes care, potentially transforming how clinicians manage this complex condition.

The ongoing research and clinical trials will further elucidate its long-term efficacy and safety, paving the way for broader adoption in diabetes treatment protocols. As healthcare professionals continue to explore the full potential of tirzepatide, its integration into standard treatment regimens could lead to significant advancements in patient care and overall health outcomes. Such advancements may not only enhance glycemic control but also support weight loss and reduce cardiovascular risks, addressing the multifactorial nature of type 2 diabetes comprehensively. The multifaceted benefits of tirzepatide highlight the importance of personalized medicine, allowing clinicians to tailor treatment strategies that align with individual patient needs and preferences. This approach not only empowers patients in their healthcare journey but also fosters a collaborative environment between providers and individuals, ultimately leading to more effective management of type 2 diabetes **(9).**

As the field of healthcare perpetuates its advancement, the continuous pursuit of research and clinical trials will be pivotal in enhancing our comprehension of the enduring

implications of tirzepatide, thereby guaranteeing that its deployment remains both secure and efficacious for a heterogeneous array of patient demographics. Clinical trials will be pivotal in enhancing our comprehension of the enduring implications of tirzepatide, thereby guaranteeing that its deployment remains both secure and efficacious for a heterogeneous array of patient demographics. As the field of healthcare perpetuates its advancement, the continuous pursuit of research and clinical trials will be pivotal in enhancing our comprehension of the enduring implications of tirzepatide, thereby guaranteeing that its deployment remains both secure and efficacious for a heterogeneous array of patient demographics.

Tirzepatide in obesity management:

Obesity has emerged as a critical global health dilemma, possessing profound ramifications for morbidity and mortality rates. The effective management of obesity necessitates the implementation of innovative therapeutic paradigms that address the fundamental physiological mechanisms involved. Tirzepatide, a groundbreaking dual agonist of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors, signifies a noteworthy advancement in the management of obesity. Its distinctive mechanism of action encompasses the facilitation of insulin secretion contingent upon nutrient ingestion, the inhibition of glucagon secretion, and the promotion of satiety, which collectively foster enhanced glycemic regulation and weight reduction. Empirical studies have substantiated that tirzepatide not only engenders considerable weight loss but also confers supplementary metabolic advantages, including amelioration of lipid profiles and attenuation of cardiovascular risk factors. This introduction endeavors to examine the multifaceted role of tirzepatide in the management of obesity, elucidating its mechanistic underpinnings and clinical relevance in confronting this ubiquitous health challenge **(10).**

As the incidence of obesity continues to escalate on a global scale, the comprehension and application of innovative treatments such as tirzepatide become increasingly paramount for public health endeavors and clinical practices. The ongoing investigation into the long-term effects and safety profile of tirzepatide will further elucidate its potential as a foundational element in the combat against obesity, thereby facilitating more personalized treatment approaches. This dynamic landscape of obesity treatment accentuates the necessity of amalgamating pharmacological interventions with lifestyle modifications, thereby ensuring a holistic strategy that optimizes patient outcomes and fosters enduring weight management. The collaborative engagement between healthcare practitioners, researchers, and patients will be indispensable in refining these strategies, ultimately culminating in an enhanced quality of life for individuals affected by obesity. As new empirical data emerges, it will be essential to perpetually evaluate the efficacy of these integrated strategies and modify them in accordance with individual patient responses and the latest scientific insights. Sustained research and innovation within this domain will not only broaden our comprehension of obesity but also empower patients with the requisite tools to attain enduring health improvements. This ongoing dedication to research will pave the way for novel therapeutic modalities and interventions that address the intricate nature of obesity, recognizing it as a multifaceted condition shaped by genetic, environmental, and behavioral determinants.

Tirzepatide occupies a prominent position in the realm of innovative methodologies for the management of obesity, distinguished by its dual functionality as an agonist for both GIP and GLP-1 receptors. This distinctive mechanism not only promotes substantial weight reduction but also confers various metabolic advantages, thereby tackling the complex challenges associated with obesity. The clinical relevance of tirzepatide is accentuated by its capacity to enhance glycemic regulation, improve lipid profiles, and potentially mitigate cardiovascular risks, rendering it an indispensable instrument in modern obesity treatment frameworks. As the incidence of obesity continues to rise, the incorporation of tirzepatide into therapeutic approaches, in conjunction with lifestyle alterations, signifies a holistic strategy aimed at optimizing patient outcomes. Ongoing investigations into its prolonged effects and safety profile will further solidify tirzepatide position as a foundational element in the management of obesity, ultimately contributing to an enhanced quality of life for individuals impacted by this intricate condition. The collaborative endeavors of healthcare practitioners, researchers, and patients will be crucial in refining treatment methodologies, ensuring they are customized to individual requirements and anchored in the most current scientific literature. This dedication to enhancing our comprehension of obesity and its therapeutic interventions will facilitate future advancements, empowering patients to attain sustainable health improvements amidst this global health crisis **(11).**

Route of administration:

Tirzepatide is administered subcutaneously, typically once weekly, which offers convenience for patients compared to daily oral medications. Its clinical significance lies in its dual action as a GLP-1 receptor agonist and a glucose-dependent insulinotropic polypeptide (GIP) receptor agonist, potentially providing superior glycemic control and weight loss compared to existing treatments for type 2 diabetes. While the advantages of tirzepatide include its efficacy in reducing HbA1c levels and promoting significant weight loss, potential disadvantages may

include gastrointestinal side effects and the need for injection, which some patients may find less desirable than oral medications Tirzepatide, is available as a subcutaneous injection solution. It is commercially available under the brand name of Mounjaro ® **(12).**

Dose and dosages:

Tirzepatide Dosing Protocol:

1. **Starting Dose: 2.5 mg once weekly**
    - The initial dose is 2.5 mg once weekly for the first 4 weeks. This low starting dose helps the body adjust to the medication and reduces the likelihood of side effects like gastrointestinal issues (nausea, vomiting, etc.).
2. **Dose Escalation:**
    - After the first 4 weeks, the dose is increased to 5 mg once weekly for the next 4 weeks.
    - Following this, the dose is further escalated to 7.5 mg once weekly for the subsequent 4 weeks.
    - If the therapeutic effect is insufficient and the patient tolerates the medication well, the dose can be increased to 10 mg once weekly.
3. **Maximum Recommended Dose: 15 mg once weekly**
    - The maximum dose is 15 mg once weekly. This is the highest dose recommended for patients who need additional efficacy in managing their type 2 diabetes or obesity.

The gradual increase in Tirzepatide dose over several weeks allows for better tolerance and minimizes side effects, particularly gastrointestinal discomfort. Not every patient will require the maximum dose of 15 mg, so the dose should be adjusted based on individual needs, treatment goals, and tolerance. Tirzepatide is administered once a week as a subcutaneous injection, and patients should be educated on how to properly inject the medication. This dosing schedule provides a clear path for titration based on patient tolerance and therapeutic response, ensuring effective management of blood sugar levels while minimizing adverse effects **(13).**

Tirzepatide offers several advantages, including its dual action as a GLP-1 and GIP receptor agonist, which provides superior glycemic control compared to some existing treatments and significant weight loss effects. The once-weekly dosing regimen adds convenience for patients, and there is also potential for cardiovascular benefits. However, there are some disadvantages to consider. Tirzepatide requires injection, which may be off-putting for some patients, and it can cause gastrointestinal side effects such as nausea, vomiting, and diarrhea. Additionally, it is more expensive than some older diabetes medications and has limited long-term safety data. There is also a potential risk of thyroid C-cell tumors based on animal studies, and it is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2 **(14).**

Clinical Significance:

Tirzepatide, a novel dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, offers significant clinical benefits in both diabetes and obesity management. In diabetes, it demonstrates superior glycemic control, with greater HbA1c reductions compared to some existing treatments, potentially leading to better long-term outcomes. Additionally, it may provide cardiovascular benefits, addressing the common complications of diabetes, and their weight losses effects help manage the comorbidity of obesity. The once-weekly dosing regimen simplifies the treatment, improving adherence and quality of life for patients. In obesity, tirzepatide offers a significant weight loss option, potentially reducing obesity-related comorbidities, and provides metabolic improvements, including better insulin sensitivity, lipid profiles, and blood pressure. It also serves as a non-surgical alternative for patients who are not candidates for or prefer to avoid bariatric surgery. Moreover, tirzepatide addresses both weight management and glycemic control in patients with comorbid obesity and type 2 diabetes. However, considerations such as the need for injections, potential side effects, and limited long-term safety data must be weighed against these advantages when determining its use for individual patients.

Pharmacokinetics:

Tirzepatide is administered subcutaneously once a week and is slowly absorbed, reaching maximum plasma concentrations in approximately 5 days. Its absolute bioavailability is about 80%, and it has a large volume of distribution (approximately 10.3 L), indicating extensive tissue distribution. The drug is highly protein-bound (>99%) in plasma and is primarily metabolized through proteolytic cleavage of the peptide backbone and beta-oxidation of the fatty acid side chain. It is eliminated via both renal and hepatic routes, with a mean apparent clearance of approximately 0.061 L/h. Tirzepatide has a long elimination half-life of about 5 days, supporting its once-weekly dosing schedule, and steady-state concentrations are reached after about 4 weeks of administration. Its pharmacokinetics is dose-proportional across the therapeutic range, and no significant differences are observed in patients with mild to moderate renal or

hepatic impairment. Age, sex, race, and body weight do not significantly affect its pharmacokinetics, and no clinically significant drug-drug interactions have been noted with commonly co-administered medications in patients with type 2 diabetes **(15).**

ADRs related to Tirzepatide:

According to the information currently available, the majority of users do not experience significant adverse pharmacological responses. The most frequent adverse effects that have been reported are gastrointestinal issues, while other side effects have also been reported. Reduced hunger is frequently seen, even though this is most likely a contributing factor to intentional weight loss.

Skin: Allergic reaction at the site of administration

GI: It is common to have a decrease in appetite. 10 percent or so of people may have symptoms of diarrhea and nausea, with sporadic reports of vomiting and gastroesophageal reflux. Furthermore, several people have mentioned experiencing constipation. The absorption of some oral drugs is hampered by delayed stomach emptying. This is especially important for people who already have delayed stomach emptying because it may make their symptoms worse.

Renal: There have been rare reports of acute renal impairment, which is most likely caused by dehydration from gastrointestinal losses. Both healthy individuals and those who currently have chronic renal illness are susceptible to them. To prevent kidney injury, it is probably better to watch for signs of dehydration.

Hypoglycemia is a rare and dose-dependent endocrine complication. Those starting insulin therapy or taking sulfonylureas are less at risk. In certain situations, it is necessary to explain the implicit symptoms of hypoglycemia. It is well recognized that GLP-1 medications raise the risk of acute pancreatitis. The level of risk associated with tirzepatide is similar to that of GLP-1 agonist medications. Patients undergoing tirzepatide therapy should be encouraged to seek treatment at their local emergency room if they have severe stomach discomfort. Some patients have asymptomatic lipase increases.

CONCLUSION

Tirzepatide marks a transformative step in managing type 2 diabetes (T2D) and obesity through its dual agonism of GIP and GLP-1 receptors, offering enhanced glycemic control, improved insulin sensitivity, and significant weight loss. Its once-weekly subcutaneous administration provides convenience, while its multifaceted benefits address both metabolic disorders effectively. Clinical evidence demonstrates its potential to reduce HbA1c levels, cardiovascular risks, and obesity-related complications, making it a valuable tool for comprehensive care. However, challenges such as gastrointestinal side effects, injection-related preferences, high costs, and limited long-term safety data must be addressed. Future research should focus on these limitations, emphasizing its long-term safety, cost-effectiveness, and suitability across diverse patient populations. As a pioneering therapy, tirzepatide exemplifies the potential of personalized medicine, enabling tailored treatments and fostering better health outcomes. Its development highlights the importance of holistic approaches in tackling chronic diseases, setting a new standard for metabolic disease management **(16).**

References

[1] Kanaujia KA, Shukla AK, Yadav VK, Yadav MK, Kumar S. BEYOND BORDERS: TIRZEPATIDE UNVEILED-A COMPREHENSIVE REVIEW OF DUAL TARGETING THERAPIES IN DIABETES AND OBESITY MANAGEMENT. Biochemical & Cellular Archives. 2024 Oct 1;24(2).

[2] Muzurović EM, Volčanšek Š, Tomšić KZ, Janež A, Mikhailidis DP, Rizzo M, Mantzoros CS. Glucagon-like peptide-1 receptor agonists and dual glucose-dependent insulinotropic polypeptide/glucagon-like peptide-1 receptor agonists in the treatment of obesity/metabolic syndrome, prediabetes/diabetes and non-alcoholic fatty liver disease—current evidence. Journal of Cardiovascular Pharmacology and Therapeutics. 2022 Dec 22;27:10742484221146371.

[3] Chavda VP, Ajabiya J, Teli D, Bojarska J, Apostolopoulos V. Tirzepatide, a New Era of Dual-Targeted Treatment for Diabetes and Obesity: A Mini-Review. *Molecules*. 2022;27(13):4315. Published 2022 Jul 5. doi:10.3390/molecules27134315

[4] Engin A. The Unrestrained Overeating Behavior and Clinical Perspective. Obesity and Lipotoxicity. 2024 Sep 18:167-98.

[5] Goyal R, Singhal M, Jialal I. Type 2 Diabetes. 2023 Jun 23. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025 Jan–. PMID: 30020625.

[6] Baggio LL, Drucker DJ. Biology of incretins: GLP-1 and GIP. Gastroenterology. 2007 May 1;132(6):2131-57.

[7] Bergmann NC, Lund A, Gasbjerg LS, Meessen EC, Andersen MM, Bergmann S, Hartmann B, Holst JJ, Jessen L, Christensen MB, Vilsbøll T. Effects of combined GIP and GLP-1 infusion on energy intake, appetite and energy expenditure in overweight/obese individuals: a randomised, crossover study. Diabetologia. 2019 Apr;62:665-75.

[8] Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van der

Velden WJ, Stutsman C, Cardona GR, Urva S. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. JCI insight. 2020 Sep 9;5(17).

[9] Karagiannis T, Avgerinos I, Liakos A, Del Prato S, Matthews DR, Tsapas A, Bekiari E. Management of type 2 diabetes with the dual GIP/GLP-1 receptor agonist tirzepatide: a systematic review and meta-analysis. Diabetologia. 2022 Aug;65(8):1251-61.

[10] Fareed A, Ghanem L, Vaid R, Iftikhar Z, Rehman AU, Sarwar A, Asif MI. Charting New Territories in Obesity Management-Traditional Techniques to Tirzepatide. Endocrine Practice. 2024 Sep 13.

[11] Lu W, Zhou Z, Jiang N, Han J. An updated patent review of GLP-1 receptor agonists (2020-present). Expert Opinion on Therapeutic Patents. 2023 Sep 2;33(9):597-612.

[12] Baker DE, Walley K, Levien TL. Tirzepatide. Hospital Pharmacy. 2023 Jun;58(3):227-43.

[13] Heise T, Mari A, DeVries JH, Urva S, Li J, Pratt EJ, Coskun T, Thomas MK, Mather KJ, Haupt A, Milicevic Z. Effects of subcutaneous tirzepatide versus placebo or semaglutide on pancreatic islet function and insulin sensitivity in adults with type 2 diabetes: a multicentre, randomised, double-blind, parallel-arm, phase 1 clinical trial. The Lancet Diabetes & Endocrinology. 2022 Jun 1;10(6):418-29.

[14] Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Landó LF, Mao H, Cui X, Karanikas CA, Thieu VT. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. The Lancet. 2021 Jul 10;398(10295):143-55.

[15] Gastaldelli A, Cusi K, Landó LF, Bray R, Brouwers B, Rodríguez Á. Effect of tirzepatide versus insulin degludec on liver fat content and abdominal adipose tissue in people with type 2 diabetes (SURPASS-3 MRI): a substudy of the randomised, open-label, parallel-group, phase 3 SURPASS-3 trial. The lancet Diabetes & endocrinology. 2022 Jun 1;10(6):393-406.

[16] Mishra R, Raj R, Elshimy G, Zapata I, Kannan L, Majety P, Edem D, Correa R. Adverse events related to tirzepatide. Journal of the Endocrine Society. 2023 Apr 1;7(4):bvad016.