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TIRZEPATIDE: A DUAL RECEPTOR AGONIST IN DIABETES AND OBESITY MANAGEMENT — A REVIEW OF ITS MECHANISMS AND PHARMACOLOGICAL ACTIONS

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ABSTRACT

Tirzepatide is a novel dual incretin receptor agonist that targets both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Approved by the FDA in May 2022 under the brand name Mounjaro, it represents a significant advancement in the treatment of type 2 diabetes mellitus (T2DM). Tirzepatide improves glycemic control, enhances insulin secretion, suppresses glucagon release, and contributes to weight loss by modulating appetite and energy balance.

The increasing prevalence of T2DM is closely linked to obesity, poor dietary habits, and sedentary lifestyles. Incretin hormones, particularly GLP-1 and GIP, play a critical role in glucose metabolism by stimulating insulin secretion and regulating lipid metabolism. Tirzepatide's dual mechanism amplifies these effects, leading to superior glycemic control and metabolic benefits compared to single-hormone therapies.

Chemically, tirzepatide is a 39-amino acid synthetic peptide with a fatty acid modification that prolongs its half-life, allowing for once-weekly administration. It preferentially binds to the GIP receptor while retaining biased signaling at the GLP-1 receptor, contributing to its efficacy in glucose regulation and weight management. The drug also enhances insulin sensitivity, reduces fasting triglyceride levels, and positively impacts lipid metabolism.

Furthermore, tirzepatide mitigates β-cell dysfunction, which is a hallmark of T2DM, by reducing oxidative and endoplasmic reticulum stress. Clinical studies have demonstrated significant reductions in glycosylated hemoglobin (HbA1c) and body weight, positioning tirzepatide as a promising therapeutic option for diabetes and obesity management.

This review highlights the pharmacological, molecular, and clinical aspects of tirzepatide, emphasizing its unique mechanism of action, potential advantages over existing therapies, and its role in addressing the twin epidemics of obesity and diabetes.

Keywords: Tirzepatide, GLP-1, Types 2 Diabetes, Obesity, Incretin.

I. INTRODUCTION

Tirzepatide is a groundbreaking medication for diabetes that has received approval from the Food and Drug Administration (FDA) on May 13, 2022, for the treatment of type 2 diabetes (T2DM) under the Mounjaro brand. It was the first authorised medication for diabetes that targeted two gut hormone receptors. Tirzepatide, developed by Eli Lilly and Company, aids in blood glucose regulation and promotes weight loss. It is the first drug of its kind to function as a dual receptor agonist, targeting both the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptors.[1][2].

Tirzepatide is a promising option for enhancing the incretin effect, which is often diminished in individuals with diabetes. Besides improving glycemic control, it provides benefits such as reductions in glycosylated hemoglobin (HbA1c), weight loss, cardiovascular protection, and favorable changes in lipid profiles.[1]

The incidence of Type 2 diabetes (T2D) has significantly increased in recent years, primarily as a result of factors like poor eating habits, decreased physical activity, and rising obesity rates. The number of T2D diagnoses increased fourfold between 1980 and 2014, and the number of deaths from diabetes increased by 5% during that same period. According to the International Diabetes Federation (IDF), 537 million adults aged 20 to 79 had diabetes as of 2021. By 2045, this number is expected to increase to 783 million. Significant regional variations in the disease burden are highlighted by the fact that the rise in T2D is not uniform across regions, with Europe predicted to see an increase of 13% and sub-Saharan Africa potentially seeing a much higher increase of 134%.[3]

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Obesity and diabetes are chronic illnesses that cause significant morbidity and high mortality rates globally, particularly in wealthy nations. These are regarded as the 21st century's twin epidemics. Both conditions are complicated health issues that combine behavioral, genetic, and epigenetic variables, as well as socioeconomic and environmental effects. Obesity is defined by the World Health Organization (WHO) as an abnormal or excessive accumulation of fat that may result in various health complications. It is defined by body mass index (BMI), which is calculated by weight (kg) divided by the square of height, in adults over 30 kg/m^2.[4]

Obesity can lead to an increased risk of type 2 diabetes and hypertension; it can affect bone health and reproduction, and it increases the risk of certain cancers. It can also influence the quality of living, such as sleeping or physical movement[5]. Individuals with type 2 diabetes (T2DM) are often characterized by obesity or a higher percentage of body fat, particularly in the abdominal area. The risk factors for T2DM are multifactorial, involving a combination of genetic, metabolic, and environmental influences that work together to increase its prevalence.[6]

Type 2 diabetes interferes with the way your body processes glucose (sugar) for energy. It impairs the body's ability to manage insulin effectively, which can cause elevated blood sugar levels if not addressed. If left uncontrolled, type 2 diabetes can progressively harm vital organs, especially the nerves and blood vessels[7]. Insulin is continuously produced by the pancreatic β-cells and stored for release when blood glucose levels rise. It allows cells, including those in muscle and fat tissue, to take in glucose and aids in converting it into glycogen for storage in the liver and muscles. When blood glucose decreases, insulin secretion slows, and glucagon from the α-cells is released, prompting the breakdown of glycogen into glucose to raise blood sugar levels.[8]

Additionally, in the early 1970s, it was discovered that the human body produces substances called "incretins," also referred to as "incretin hormones," which cause beta cells to release insulin. The intestinal secretion of these chemicals impacts beta-cell activity. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the two most well-known incretins[4].

The therapeutic effects of Tirzepatide are mainly driven by its interaction with the GLP-1 receptor (GLP-1R), a member of the class B family of G protein-coupled receptors. This receptor is present in a variety of cell types, including pancreatic beta cells, various cells within the gastrointestinal tract, and neurons found in both the central nervous system (CNS) and the peripheral nervous systems.[9]

II. TIRZEPATIDE

Tirzepatide was developed by combining the activity of glucagon-like peptide-1 (GLP-1) with glucose-dependent insulinotropic polypeptide (GIP). In individuals with Type 2 diabetes mellitus (T2DM), GLP-1 levels are typically lower following dietary intake, although pharmacological GLP-1 infusion has similar insulinotropic effects in both diabetic and healthy individuals. Additionally, GLP-1 agonists have been shown to promote feelings of satiety[1].

The GIP receptor, primarily found in white adipose tissue, plays a role in regulating circulating lipids. Activation of the GIP receptor is believed to enhance the capacity of adipocytes to clear dietary triglycerides (TAG) more efficiently and support long-term lipid storage by fostering healthy growth in white adipose tissue. Furthermore, GIP activity in the brain may offer additional metabolic benefits, including reducing energy expenditure, especially when combined with GLP-1 [10].

Administering both GIP and a GLP-1 receptor agonist together in healthy individuals has a synergistic effect that boosts insulin secretion, compared to administering each hormone separately [11]. The synergistic impact of GIP and GLP-1 was first described by Finan et al., who created a dual agonist molecule for these two receptors, thus coining the term "twincretin". This improvement in patient health supports the idea that combining GLP-1 therapy with GIP's action enhances glucose control by stimulating pancreatic cells, leading to improved insulin secretion. Moreover, GIP contributes to the functionality of white adipose tissue and produces a potent appetite-suppressing effect in the brain through the activation of these receptor pathways [6]. Additionally, tirzepatide has shown significant reductions in fasting triglyceride levels, and analysis using the homeostasis model assessment for insulin resistance (HOMA2-IR) indicates an improvement in insulin sensitivity[1].

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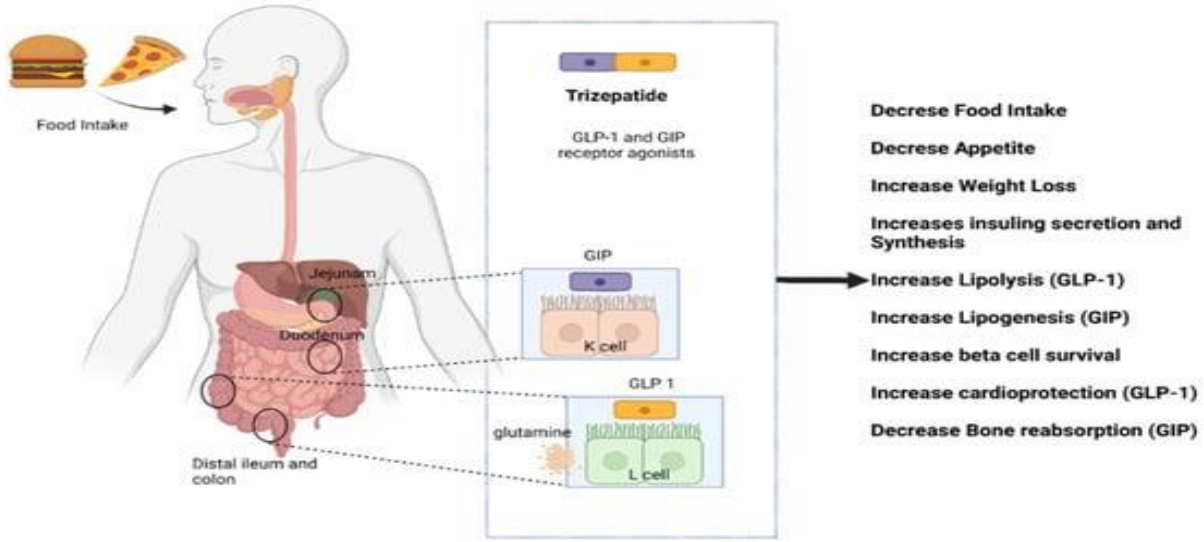

Figure 1: Main physiological actions of the dual GIP and GLP-1 agonist.[1]

III. MECHANISM OF ACTION

Tirzepatide's exact mechanism of action has not been completely elucidated; however, current research suggests that it exerts its effects through dual activation of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. This dual engagement contributes to both weight reduction and improved glycemic control. Compared to the effects of single hormone therapies, simultaneous stimulation of GIP and GLP-1 receptors enhances insulin sensitivity and suppresses glucagon secretion, findings that align with previous studies [12]. By activating these pathways, tirzepatide promotes insulin release in response to glucose levels. Additionally, it exhibits a stronger binding affinity for the GIP receptor than the GLP-1 receptor, suggesting that it may mimic the natural activity of GIP more effectively, potentially leading to better control of blood sugar levels [13].

In adipose tissue, tirzepatide's activity primarily involves GLP-1 receptor activation and improvements in insulin sensitivity. This results in the breakdown of stored triglycerides (lipolysis) within fat cells, releasing free fatty acids and glycerol into the bloodstream for energy use [14]. By facilitating this process, tirzepatide reduces fat accumulation and supports weight management. Enhanced insulin sensitivity in fat tissue also improves glucose uptake, helping to lower blood glucose levels and contributing to overall metabolic health. Furthermore, GLP-1 receptor activation plays a key role in slowing gastric emptying and regulating appetite by acting on the central nervous system. This appetite suppression leads to decreased food intake and prolonged feelings of fullness, which contribute to weight loss and reduced caloric consumption. Together, these actions make tirzepatide a promising therapeutic option for addressing both obesity and type 2 diabetes[2].

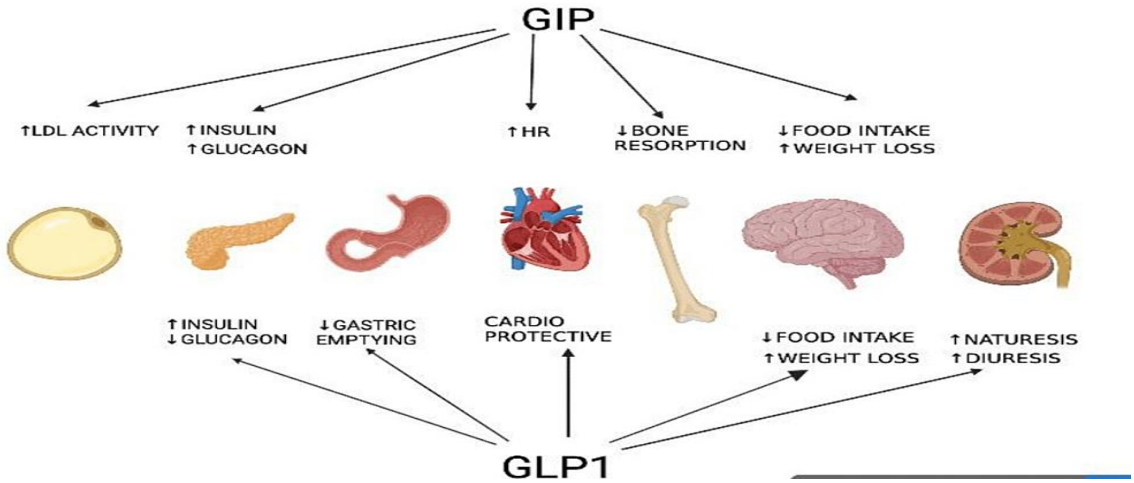

Figure 2: Mechanism of action of tirzepatide.[2]

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3.1. Cellular mechanism of β- cell dysfunction

Beta cell dysfunction in type 2 diabetes results from a combination of environmental triggers and molecular imbalances. Factors such as excessive calorie intake, obesity, high levels of free fatty acids (FFAs), chronic high blood sugar (hyperglycemia), and abnormal lipid levels (hyperlipidemia) contribute to insulin resistance (IR) and persistent inflammation. These conditions place significant stress on beta cells, including metabolic and oxidative stress, endoplasmic reticulum (ER) stress, inflammatory responses, disrupted calcium (Ca2+) signaling, activation of cell death pathways, and amyloid buildup. When combined with genetic vulnerabilities, these stresses can damage islet cell structure and activate unfolded protein response (UPR) pathways, leading to beta cell failure [15].

Elevated saturated FFAs can interfere with ER function by activating inositol 1,4,5-trisphosphate (IP3) receptors or inhibiting sarco/endoplasmic reticulum Ca2+-ATPase (SERCA), disrupting the regulation of ER Ca2+ levels. Persistently high glucose concentrations stimulate the production of islet amyloid polypeptides (IAAP) and proinsulin, causing the accumulation of misfolded insulin and IAAP, while also increasing reactive oxygen species (ROS) levels [16]. These disturbances in calcium balance and protein folding trigger cell death signals, degrade insulin mRNA, and release interleukin (IL)-1β, which draws macrophages to the area and amplifies local inflammation within the islets.

Proper regulation of insulin secretion is essential to meet the body's metabolic needs, and maintaining the structural integrity of pancreatic islets is crucial for this function. However, these pathological processes disrupt islet architecture, impair communication between cells, and interfere with the secretion of insulin and glucagon, leading to worsened hyperglycemia. The failure of beta cells and impaired insulin secretion are core features of type 2 diabetes, often caused by defects in insulin synthesis or release. Reduced expression of glucose transporter-2 (GLUT-2) and improper folding of proinsulin contribute significantly to decreased insulin production and the onset of diabetes[15].

3.2. Incretin hormone

Incretins are hormones released from the intestines in response to nutrient intake, regulating insulin secretion, blood glucose levels, appetite, gut motility, immune function, and lipid metabolism. The two primary incretin hormones are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), which act on G-protein-coupled receptors on pancreatic β-cells [17].

GIP is a 42-amino acid peptide derived from pro-GIP, produced in enteroendocrine K cells of the duodenum and proximal jejunum. Upon nutrient stimulation, GIP is secreted and promotes glucose-dependent insulin release. GIP is also produced in the central nervous system [17]. Neutralizing GIP reduces glucose-stimulated insulin secretion, supporting its role in local insulin regulation . In mice lacking the GCG gene, β-cells produce active GIP, while regulating factor X6 (Rfx6) has been identified as a key regulator of GIP production in K cells [18].

GLP-1 is synthesized from pre-proglucagon in enteroendocrine L cells of the small and large intestines [18]. Active forms include GLP-1 [7-36 amide] and GLP-1 [7-37]. GLP-1 expression is also seen in the CNS and salivary glands. Its release is triggered by nutrients (proteins, fats, carbohydrates) and interleukin-6 (IL-6). Both GIP and GLP-1 are rapidly degraded by dipeptidyl peptidase-4 (DPP-4), with half-lives of 7–8 minutes and 2–5 minutes, respectively. GLP-1 is secreted in two phases after meals: an early peak (10–15 min) due to vagal stimulation and a later peak (30–60 min) from direct nutrient interaction [19]. GLP-1 enhances glucose-dependent insulin secretion, suppresses glucagon release, promotes satiety, and supports weight loss, while GIP stimulates glucagon at lower glucose levels. A study by Gasbjerg et al. showed GIP as the dominant driver of the incretin effect after oral glucose, with GLP-1 playing a lesser role due to its impact on gastric emptying[15]. However, when gastric emptying effects were removed, GLP-1 and GIP contributed more equally to insulin secretion. Incretins influence various organs: in the pancreas, they enhance insulin secretion and suppress glucagon; in the liver, they reduce glucose production; in adipose tissue, they improve insulin sensitivity and lipid metabolism. GLP-1 promotes satiety through hypothalamic pathways, aids in weight regulation, and has neuroprotective effects. It also supports kidney function by promoting natriuresis and diuresis, and its anti-inflammatory effects may benefit conditions like type 2 diabetes[15].

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IV. CHEMISTRY

Tirzepatide's molecular formula is $C_{225}H_{348}N_{48}O_{68}$, with a molecular weight of approximately 4813.5 g/mol. It is a synthetic peptide of 39 amino acids, sharing 19 amino acids with human GIP, and acts as an agonist on both GIP and GLP-1 receptors. Chemically, tirzepatide is a fatty-acid-modified dual incretin receptor agonist, enhancing stability and allowing once-weekly dosing. It mimics native GIP at the GIP receptor (GIPR) but shows a bias toward cyclic AMP signaling at the GLP-1 receptor (GLP-1R), contributing to better glucose control and weight regulation. Tirzepatide adopts an α-helical conformation, with its N-terminal tyrosine (Tyr1Tzp) forming strong interactions with GIPR and weaker ones with GLP-1R. Molecular dynamics reveal more stabale binding with GIPR due to hydrogen bonding with the lipid moiety, while acylation-dependent signal transduction helps maintain high GIPR affinity. In contrast, GLP-1R binding promotes biased signaling and reduces receptor desensitization, contributing to tirzepatide's unique therapeutic profile.

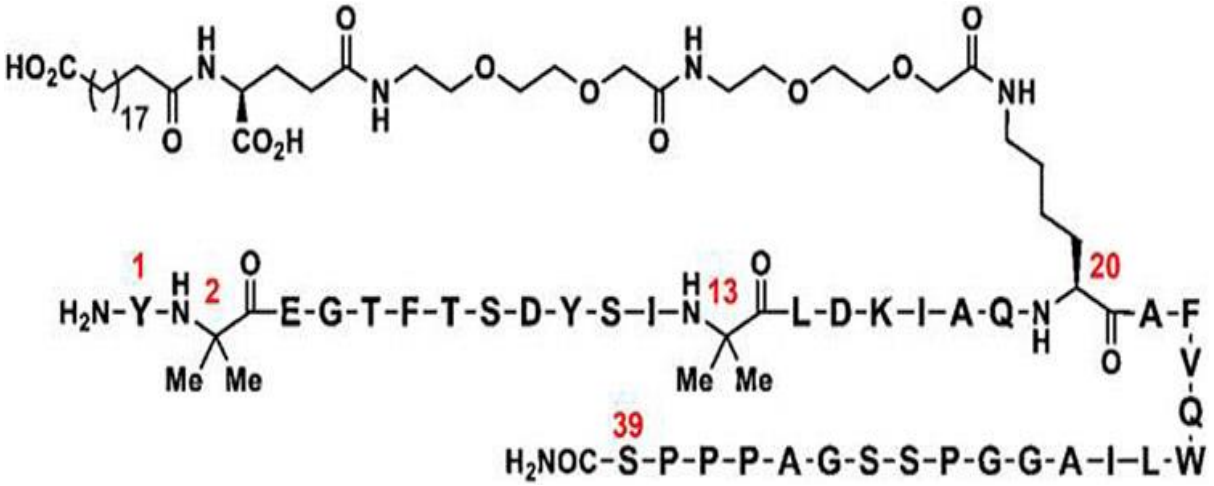

Figure 3: Structure of Tirzepatide.[20]

Tirzepatide's molecular formula is $C_{225}H_{348}N_{48}O_{68}$. It is a synthetic peptide of 39 amino acids that shares 19 amino acids with human GIP and is based on the sequence of natural GIP. Tirzepatide acts as an agonist on both the GIP and GLP-1 receptors. Chemically, tirzepatide (LY3298176) is a fatty-acid-modified, dual incretin receptor agonist. This modification enhances its stability and prolongs its half-life, allowing for once-weekly dosing. It exhibits pharmacology similar to native GIP at the glucose-dependent insulinotropic polypeptide receptor (GIPR) but shows a bias toward cyclic adenosine monophosphate (cAMP) signaling at the glucagon-like peptide-1 receptor (GLP-1R). This pathway bias at the GLP-1R contributes to tirzepatide's efficacy in improving glucose control and body weight regulation in type 2 diabetes mellitus. Structurally, tirzepatide adopts an α-helical conformation with its N-terminus reaching deep within the transmembrane core of both receptors. The N-terminal tyrosine (Tyr1Tzp) shows a weak interaction with the GLP-1R but forms stronger interactions with the GIPR. Molecular dynamics simulations reveal that tirzepatide's lipid moiety forms intermittent hydrogen bonds more frequently with GIPR than GLP-1R, resulting in a more compact tirzepatide–GIPR complex. Additionally, acylation-dependent signal transduction influences tirzepatide's structure-activity relationship, allowing it to maintain high affinity for GIPR despite fatty acid modifications. In contrast, high-affinity binding to the extracellular domain of GLP-1R, along with decreased stability from the lipid moiety, promotes biased signaling and reduces receptor desensitization. These structural and chemical properties contribute to tirzepatide's unique pharmacological profile and therapeutic efficacy[20].

V. CLINICAL DEVELOPMENT

The Phase 1 clinical trials for tirzepatide, lasting 4 weeks followed by an additional 4 weeks of safety assessment, demonstrated a significant reduction in HbA1c levels and postprandial glucose. A subsequent 26-week Phase 2 trial, which also included a dulaglutide group, showed that tirzepatide had superior efficacy compared to dulaglutide. Additionally, participants experienced weight loss and reduced appetite. The SURPASS-1 Phase 3 trials, conducted across six countries, involved patients already on SGLT2 inhibitors like dapagliflozin. When tirzepatide was administered alongside dapagliflozin, it resulted in further reductions in

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HbA1c and weight. In the SURPASS-2 Phase 3 trial, tirzepatide, when combined with metformin, demonstrated more effective results than the selective GLP-1 receptor agonist semaglutide, with a 1 mg weekly dose showing notable benefits. Additional effects of tirzepatide included a decrease in very low-density lipoproteins (VLDL) and triglycerides, improved blood pressure, and an increase in high-density lipoprotein (HDL). Common side effects included nausea, vomiting, and diarrhea, primarily occurring during the dose-escalation phase, with mild to moderate intensity. In a Phase 2 trial involving tirzepatide alongside controlled nutrition and lifestyle modifications, either with or without metformin, the treatment resulted in dose-dependent improvements in HbA1c and weight loss, surpassing the effects of dulaglutide. Moreover, a 12-week Phase 2 trial with a moderate dose-escalation regimen showed better gastrointestinal tolerability when the dose was gradually increased from a lower starting point[4].

VI. PHARMACOKINETIC OF TIRZEPATIDE

Tirzepatide is a novel dual agonist of the GLP-1 and GIP receptors, with pharmacokinetic properties that support its use for once-weekly subcutaneous (SC) administration. Following SC injection, tirzepatide demonstrates an absolute bioavailability of approximately 80%. The time to maximum plasma concentration (Tmax) ranges from 8 to 72 hours, with steady-state plasma concentrations reached after approximately four weeks of consistent weekly dosing. The drug's half-life, which is around 120 hours (5 days), is notably extended due to structural modifications that increase its stability, allowing for infrequent dosing.

The volume of distribution (Vd) of tirzepatide is about 10.3 L, indicating moderate distribution into the body. It is highly bound to plasma albumin (99%), which may influence its clearance. The apparent clearance is 0.061 L/h, and tirzepatide is not detected in urine or feces in its active form. Instead, its metabolites are primarily excreted through feces and urine. Importantly, the pharmacokinetic profile of tirzepatide remains unaffected by renal or hepatic impairment, making it suitable for a broad patient population, including those with varying degrees of renal or hepatic dysfunction.[21][22]

VII. PHARMACODYNAMICS OF TIRZEPATIDE

Tirzepatide exhibits a robust pharmacodynamic profile, particularly in the context of glucose regulation and weight management in patients with Type 2 diabetes (T2DM). The drug effectively lowers both fasting and postprandial glucose levels, contributing to improved overall glycemic control. It enhances insulin secretion in a glucose-dependent manner, boosting both the first and second phases of insulin release. Additionally, tirzepatide significantly reduces glucagon secretion, leading to a 28% reduction in fasting glucagon levels and a 43% reduction in postprandial glucagon AUC after 28 weeks of therapy.

Another key feature of tirzepatide is its ability to reduce food intake, which contributes to its weight loss effects. Studies have demonstrated that tirzepatide's ability to delay gastric emptying (GE) plays a crucial role in managing postprandial glycemia. However, tachyphylaxis to the gastric emptying effect develops over time, particularly at lower doses (5 mg), with a diminishing effect on gastric emptying after several doses. Despite this, tirzepatide's ability to control postprandial glucose levels remains effective, even with repeated dosing. Furthermore, weight reduction effects persist over the long term, with 4.8 kg weight loss at 26 weeks compared to a more modest reduction at earlier time points, underscoring the sustained efficacy of tirzepatide in both glucose control and body weight management.[21][22]

VIII. COMPARISON WITH OTHER DRUGS

Tirzepatide and semaglutide help people manage their weight by promoting the pancreas to produce more insulin and postponing stomach emptying, which prolongs feelings of fullness. Since more than 70% of US individuals are overweight or obese, a substantial number of people could potentially take GLP-1s. Tirzepatide affects two distinct gut hormones, which may make it more successful for weight loss. While tirzepatide mimics GLP-1 and a second hormone known as GIP, semaglutide functions by activating GLP-1 receptors. This systematic review and network meta-analysis included 28 RCTs with 23,622 participants, comparing tirzepatide and semaglutide at various doses. Only two trials directly compared tirzepatide with semaglutide, while others provided indirect comparisons through common comparators. The primary outcomes were changes in HbA1c and body weight, with tirzepatide showing greater reductions in both parameters compared to semaglutide[23][24][25].

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IX. CONCLUSION

Tirzepatide represents a significant advancement in the treatment of T2DM and obesity, offering superior glycemic control and weight reduction through its dual GIP and GLP-1 receptor agonist mechanism. Its approval marks a breakthrough in the management of metabolic disorders, providing an alternative for patients struggling with conventional therapies. Clinical evidence underscores its efficacy and safety, making it a valuable addition to current treatment regimens. Future research should focus on long-term cardiovascular outcomes, broader patient populations, and combination therapies to further establish its role in diabetes and weight management. Overall, Tirzepatide stands as a promising therapeutic innovation with the potential to redefine metabolic disease treatment strategies.

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