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TIRZEPATIDE : DOUBLE TROUBLE FOR DIABESITY

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Abstract:

The growing global burden of obesity and type 2 diabetes mellitus (T2DM), commonly referred to as 'diabesity,' presents profound public health and economic concerns worldwide. Conventional treatment modalities often do not adequately address these intertwined diseases, highlighting the necessity for innovative therapeutic approaches. A recent breakthrough in this area is Tirzepatide, a dual agonist for glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. This paper explores the molecular structure, mechanisms of action, and clinical efficacy of Tirzepatide, particularly its superior performance in glycemic control and weight management compared to existing therapies. Additionally, Tirzepatide shows potential in ameliorating cardiovascular risk factors and metabolic dysfunction-associated steatotic liver disease (MASLD), positioning it as an effective strategy for the holistic management of diabesity

Keywords : Obesity, Diabetes, Tirzepatide, Twincretin, GLP-1 and GIP receptor agonist

Introduction

The global surge in obesity and type 2 diabetes mellitus (T2DM) has reached alarming proportions, posing significant public health and economic challenges. (1) These interconnected conditions not only increase the risk of severe health complications such as cardiovascular diseases, stroke, and various cancers but also contribute to rising morbidity and mortality rates worldwide. The economic burden is equally profound, with escalating healthcare costs and lost productivity placing immense strain on healthcare systems,

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particularly in developing countries.(2) The strong link between obesity and diabetes has given rise to the term “diabesity,” emphasizing the strong pathophysiological link between the two conditions. (3) Even with the latest improvements in treatment approaches, obesity and diabetes still present a significant and closely linked public health issue around the world.

There are numerous advantages to losing weight. A slight reduction in body weight, ranging from 5 to 10%, is associated with betterment in both systolic and diastolic blood pressure, as well as an increase in high-density lipoprotein (HDL) cholesterol levels. For conditions like obstructive sleep apnea (OSA) and non-alcoholic steatohepatitis (NASH), a more significant weight loss of 10% to 15% is often necessary for clinical benefits. Quality of life, including aspects such as depression, mobility, sexual health, and urinary stress incontinence, tends to improve even with modest weight reduction and continues to enhance substantially with further weight loss. In conditions such as polycystic ovarian syndrome and infertility, a modest weight reduction of 2–5% can lead to improvements in menstrual regularities and fertility rates. Moreover, a moderate reduction in weight is also linked to decreased healthcare expenditures.(4)

Traditional therapies often fall short in managing these conditions effectively, highlighting the need for novel treatment approaches. Dual GLP-1 (glucagon-like peptide 1) and GIP (glucose dependant insulinotropic polypeptide) receptor agonists have emerged as promising treatment options in this regard. Among these, tirzepatide, a dual agonist, has shown exceptional efficacy in clinical trials. This article explores the mechanisms, clinical effectiveness, and the side effect profile of tirzepatide in the management of obesity and T2DM.

Molecular structure

Tirzepatide is a synthetic linear peptide made up of 39 amino acids. Its structure is derived from the natural GIP sequence and incorporates a C20 fatty diacid component (eicosanedioic acid), attached through hydrophilic linkers (γ-Glu-2xAdo, gamma glutamate, and bis-aminodiethoxyacetyl) to a lysine residue at the C20 position. The sequence of tirzepatide features two non-standard amino acid residues (Aib, α-amino isobutyric acid) at the 2nd and 13th positions, enhancing its prolonged half-life and strong albumin binding affinity. The peptide’s C-terminus undergoes amidation.(5)

Mechanisms of Action

Tirzepatide uniquely combines dual agonism of GIP and GLP-1 receptors. GIP is secreted by the enteroendocrine K-cells, while GLP-1 is produced by the L-cells. These hormones are central to the incretin effect, which enhances glucose-dependent insulin secretion from pancreatic beta cells following nutrient intake.

GLP-1 has a significant role in promoting satiety and reducing appetite. This effect, along with delayed gastric emptying, contributes to reduced food intake. Moreover, GLP-1 exerts cardioprotective effects, both directly through its receptors present in the cardiovascular system and indirectly by promoting weight loss and improving glycemic control.

GIP complements some of action of actions of GLP-1, but in contrast to GLP-1, it increases the secretion of glucagon and somatostatin, which may counterbalance the hypoglycemic effects of insulin. Additionally, GIP enhances adipose tissue blood flow postprandially, a process often impaired in individuals with obesity or type 2 diabetes, thereby supporting lipid

storage in adipose tissue and potentially mitigating ectopic fat deposition associated with insulin resistance.

Structurally, tirzepatide has an affinity for GIP receptors similar to that of native GIP, while its binding to GLP-1 receptors is approximately five times weaker than that of native GLP-1. Tirzepatide's pharmacokinetics allow for a half-life of around five days, making it suitable for once-weekly subcutaneous administration. (5–7)

Clinical Efficacy

Glycemic Efficacy

Tirzepatide has shown superiority in glycemic control as compared to placebo and other glucose-lowering medications. The SURPASS trials evaluated the safety and efficacy of tirzepatide in individuals with T2DM, ranging from its use as a monotherapy to its addition to other glucose lowering agents in global populations. Additionally, two of these trials were specifically focused on Japanese populations

In individuals with early T2DM managed only with diet and exercise (SURPASS-1), tirzepatide doses of 5, 10 and 15 mg resulted in HbA1c improvements of 1.87%, 1.89% and 2.07% respectively, in contrast to a 0.04% increase in the placebo group.(8) In the SURPASS-2 trial, individuals with established T2DM who were treated with tirzepatide at doses of 5 to 15 mg for 40 weeks achieved HbA1c reductions ranging from 2.09% to 2.46%, compared to a 1.86% reduction with semaglutide 1 mg.(9) In the SURPASS-3 trial, treatment with tirzepatide at doses of 5 to 15 mg for 52 weeks resulted in HbA1c reductions ranging from 1.93% to 2.37%, compared to a 1.34% decrease achieved with insulin degludec.(10) In individuals with advanced T2DM (over 10 years) and elevated cardiovascular risk (SURPASS-4), tirzepatide doses ranging from 5 to 15 mg reduced HbA1c by 2.24% to 2.58%, whereas insulin glargine resulted in a 1.44% HbA1c reduction after 52 weeks. (11)

In the SURPASS-5 trial, adding tirzepatide to a regimen of insulin glargine in individuals resulted in a 2.23% to 2.59% reduction in HbA1c, compared to a 0.93% reduction with placebo. This improvement in glycemic control was also accompanied by a decrease in insulin use.(12)

In a meta-analysis by Karagiannis et al, data from seven trials encompassing a total of 6609 participants was analysed. The participants had a mean baseline HbA1c of 8.2%, a mean body weight of 91.5 kg, and a mean age of 58 years. Compared to placebo, tirzepatide significantly reduced HbA1c levels, with reductions ranging from 1.62% at a 5 mg dose to 2.06% at a 15 mg dose. All doses of tirzepatide outperformed placebo in achieving HbA1c targets of $<7.0\%$, $\leq 6.5\%$ and $<5.7\%$. When compared to GLP-1 receptor agonists, tirzepatide 5 mg, 10 mg, and 15 mg lowered HbA1c levels by 0.29%, 0.65% and 0.92% respectively. Furthermore, tirzepatide was more effective than basal insulin in reducing HbA1c, with mean differences ranging from 0.70% at 5 mg to 1.09% at 15 mg.(13)

Weight outcomes

Clinical trials have demonstrated that tirzepatide induces substantial weight loss. In the SURPASS-1 trial involving individuals with early-onset T2DM, 40 weeks of treatment with tirzepatide at doses 5, 10 and 15 mg resulted in weight loss of 7, 7.8 and 9.5 kg respectively, compared to a 0.7 kg weight loss with placebo.(8) In the SURPASS-2 trial, individuals with established T2DM experienced greater weight loss with tirzepatide at doses of 5, 10, and 15

mg (–7.8 kg, –10.3 kg, and –12.4 kg, respectively) compared to a 6.2 kg weight loss with semaglutide 1 mg.(9) In the SURPASS-3 trial, while insulin degludec caused a weight gain of 2.3 kg after 52 weeks, tirzepatide at doses ranging from 5 to 15 mg resulted in a weight loss of 7.5 to 12.9 kg.(10) In the SURPASS-4 trial, individuals with advanced T2DM on other glucose-lowering medications gained 1.9 kg with insulin glargine over 52 weeks, whereas they lost 7.1 to 11.7 kg with tirzepatide.(11) Similarly, in the SURPASS-5 trial, participants on basal insulin glargine achieved a weight loss of 6.2 to 10.9 kg with tirzepatide, compared to a 1.7 kg weight gain with placebo.(12)

A meta-analysis of 12 randomized controlled trials involving 11,758 patients with and without diabetes demonstrated that tirzepatide significantly reduced BMI, waist circumference, and body weight compared to glucagon-like peptide-1 receptor agonists (GLP-1 RAs), placebo, and insulin groups. Specifically, BMI reductions were MD = −1.71 (95% CI: −2.46, −0.95), MD = −3.99 (95% CI: −3.69, −2.45), and MD = −4.02 (95% CI: −4.72, −3.31). Waist circumference reductions were MD = −4.08 (95% CI: −5.77, −2.39), MD = −7.71 (95% CI: −10.17, −5.25), and MD = −9.15 (95% CI: −10.02, −8.29). Weight reductions were MD = −5.65 (95% CI: −7.47, −3.82), MD = −10.06 (95% CI: −12.86, −7.25), and MD = −10.63 (95% CI: −12.42, −8.84), respectively. Tirzepatide also showed a significant advantage in achieving weight loss of ≥20% and ≥25% compared to placebo, with RR = 30.43 (95% CI: 19.56, 47.33) and RR = 37.25 (95% CI: 26.03, 53.30). Subgroup analysis indicated a dose-dependent therapeutic effect.(14) In a meta-analysis of tirzepatide in indivduals with obesity but without diabetes, the percentage change in body weight was higher with tirzepatide than with placebo (MD -19.44%; 95% confidence interval [CI]: -22.48 to -16.41; p<0.00001). Tirzepatide also had a higher absolute reduction in body weight (MD: -17.55 kg; 95% CI: -32.15 to -2.95; p<0.00001). Higher percentages of people on tirzepatide had a weight reduction of ≥5%, ≥10%, ≥15%, ≥20% and ≥25% compared with placebo. (15)

In a real-world study of 8945 Arab patients with type 2 diabetes, tirzepatide significantly reduced HbA1c and weight over 40 weeks, with greater effects in GLP-RA-naïve patients and those with previous bariatric surgery. Tirzepatide was well tolerated, with 7.8% discontinuing due to adverse effects, mainly gastrointestinal.(16).

Heise et al evaluated the effects of tirzepatide on body composition. At week 28, both tirzepatide and semaglutide led to significant reductions in fat mass and fat-free mass compared to baseline, unlike the placebo. Tirzepatide showed a larger decrease in fat mass compared to placebo (-9.6 kg) and semaglutide (-3.8 kg), with significant differences (P < 0.001 and P = 0.002, respectively). The percentage of fat mass loss was also greater with tirzepatide (-7.1%) compared to semaglutide (-4.0%), with a significant difference (-3.1%; P = 0.001). Additionally, fat-free mass reductions were more pronounced with tirzepatide compared to both placebo (-1.5 kg; P < 0.001) and semaglutide (-0.8 kg; P = 0.018). The weight loss from tirzepatide was mainly attributed to the reduction in fat mass.(17)

Cardiovascular and Metabolic Benefits

Beyond glycemic control and weight loss, tirzepatide offers additional benefits, including improvements in cardiovascular risk factors. Clinical data indicate significant reductions in systolic and diastolic blood pressure and improvement in lipid profile. These effects are crucial, given the high cardiovascular risk associated with obesity and T2DM. Kanbay et al analysed the effects of tirzepatide on blood pressure and ipid profile from seven randomized controlled trials. Tirzepatide significantly reduced systolic blood pressure by a median of -4.20 mmHg (95% CI: -5.17 to -3.23) at a 5 mg dose, -5.34 mmHg (95% CI: -6.31 to -4.37) at a 10 mg dose, and -5.77 mmHg (95% CI: -6.73 to -4.81) at a 15 mg dose. Additionally,

tirzepatide significantly decreased total cholesterol levels by a median of -3.76% (95% CI: -5.20% to -2.31%) for 5 mg, -4.63% (95% CI: -6.07% to -3.19%) for 10 mg, and -5.93% (95% CI: -7.36% to -4.49%) for 15 mg. Furthermore, tirzepatide increased high-density lipoprotein (HDL) cholesterol levels and decreased low-density lipoprotein (LDL) cholesterol and triglyceride levels across all three doses.(18)

The SURPASS-4 trial specifically assessed the cardiovascular safety of tirzepatide in patients with T2DM and high cardiovascular risk. The results showed a favorable cardiovascular safety profile, with no increased risk of major adverse cardiovascular events (MACE) compared to insulin glargine.(11) The ongoing SURPASS-CVOT trial is evaluating tirzepatide in a randomized, double-blind, active-controlled cardiovascular outcomes trial in people with T2DM and established atherosclerotic cardiovascular disease, comparing its effects on MACE against dulaglutide, with a primary focus on noninferiority and potential superiority.(19)

Impact on MASLD

Metabolic dysfunction-associated steatotic liver disease (MASLD) is now the most prevalent chronic liver disease and a significant cause of cirrhosis and hepatocellular carcinoma, with strong links to T2DM and obesity.(20)Tirzepatide has demonstrated promising results in reducing liver fat content, potentially mitigating the progression of MASLD.

Tirzepatide was evaluated in a subpopulation of the SURPASS-3 study to assess changes in liver fat content (LFC), visceral adipose tissue (VAT), and abdominal subcutaneous adipose tissue (ASAT) compared to insulin degludec. The study found that tirzepatide significantly reduced LFC, VAT, and ASAT volumes, demonstrating notable metabolic benefits for patients with T2DM.(21) In another phase 2 trial, tirzepatide significantly improved the resolution of MASLD without worsening fibrosis compared to placebo in patients with moderate or severe fibrosis.(22) These findings are significant, considering the limited treatment options currently available for MASLD.

Renal outcomes

In the SURPASS-4 trial, which involved participants with T2DM and high cardiovascular risk, tirzepatide reduced albuminuria and slowed the decline in estimated glomerular filtration rate (eGFR) compared to insulin glargine. Specifically, the trial noted a significant reduction in a composite kidney endpoint that included eGFR decline, renal death, kidney failure, and new-onset macroalbuminuria. The hazard ratio for these outcomes was 0.59, indicating a 41% reduction in risk compared to insulin glargine. This benefit was particularly driven by a reduction in new-onset macroalbuminuria.(11)

Tirzepatide's protective effects on the kidneys were observed even in patients without baseline chronic kidney disease (CKD), and the benefits were consistent regardless of concomitant use of sodium-glucose co-transporter 2 (SGLT2) inhibitors. The drug also demonstrated a favorable impact on eGFR slopes, indicating a slower progression of kidney function decline. Additionally, tirzepatide caused an initial, reversible dip in eGFR, likely reflecting a reduction in hyperfiltration, which is a common protective mechanism seen with other kidney-protective therapies. Unfortunately, after discontinuing tirzepatide, UACR increased by 34%, although it still remained lower than the values observed in the glargine group.(11)

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The ongoing SURPASS-CVOT trial, which compares tirzepatide to dulaglutide in T2DM patients, includes secondary endpoints of UACR and new or worsening nephropathy. These endpoints could provide valuable insights for developing CKD-focused trials.

Obstructive Sleep Apnea

Two phase 3 trials evaluated tirzepatide in adults with moderate-to-severe OSA and obesity. Participants not on positive airway pressure (PAP) therapy and those on PAP were studied separately. Tirzepatide significantly reduced the apnea-hypopnea index (AHI) and improved secondary outcomes such as body weight, hypoxic burden, hsCRP levels, and systolic blood pressure. The treatment was well-tolerated, with mild to moderate gastrointestinal side effects being the most common. The results suggest tirzepatide as a promising treatment for OSA in obese patients.(23)

Safety and Tolerability

Gastrointestinal (GI) Adverse Events: Gastrointestinal adverse events were the most commonly reported with tirzepatide, showing a dose-dependent increase in incidence. For the 5 mg dose, 39% of patients experienced GI adverse events, while this increased to 46% for the 10 mg dose and 49% for the 15 mg dose. Among the GI adverse events, nausea was notably frequent, affecting 13.27% of patients on the 5 mg dose, 17.89% on the 10 mg dose, and 24.08% on the 15 mg dose. Diarrhea was similarly prevalent, with incidence rates of 13.19%, 17.22%, and 20.79% for the 5 mg, 10 mg, and 15 mg doses, respectively. Vomiting was reported in 5.67% of patients on the 5 mg dose, 8.32% on the 10 mg dose, and 13.98% on the 15 mg dose. Dyspepsia affected 5.97% of patients on the 5 mg dose, 8.52% on the 10 mg dose, and 6.79% on the 15 mg dose. Constipation was most frequent with the 10 mg dose, affecting 8.86% of patients, while abdominal distension was highest with the 15 mg dose at 16.29%.(24)

Gallbladder and Pancreatic Adverse Events: The incidence of gallbladder and pancreatic adverse events was relatively low across all doses of tirzepatide. Cholelithiasis was reported in 0.95% of patients on the 5 mg dose, 0.53% on the 10 mg dose, and 0.52% on the 15 mg dose. Cholecystitis occurred in 0.01% of patients on the 5 mg dose, 0.55% on the 10 mg dose, and 0.24% on the 15 mg dose. Acute pancreatitis was rare, with incidence rates of 0.39% for the 5 mg dose, 0.36% for the 10 mg dose, and 0.32% for the 15 mg dose. Increased lipase levels were noted, with 3.58% of patients on the 5 mg dose, 3.88% on the 10 mg dose, and 6.86% on the 15 mg dose.(24)

Hypoglycemia: Hypoglycemic events were also reported, with varying incidence based on the severity of hypoglycemia. Blood glucose levels ≤ 70 mg/dL were observed in 17.39% of patients on the 5 mg dose, 22.6% on the 10 mg dose, and 20.99% on the 15 mg dose. Blood glucose levels ≤ 54 mg/dL were reported in 3.64% of patients on the 5 mg dose, 3.29% on the 10 mg dose, and 3.49% on the 15 mg dose. Severe hypoglycemia, defined as requiring assistance for treatment, was less common, occurring in 0.25% of patients on the 5 mg dose, 0.17% on the 10 mg dose, and 0.54% on the 15 mg dose.(24)

Other Adverse Events: Injection site reactions were noted in 1.89% of patients on the 5 mg dose, 2.44% on the 10 mg dose, and 3.11% on the 15 mg dose. Hypersensitivity reactions were reported at similar rates across doses, with 3.23% for the 5 mg dose, 3.03% for the 10 mg dose, and 2.42% for the 15 mg dose. Respiratory adverse events, such as nasopharyngitis, occurred in approximately 6.05% of patients on the 5 mg dose, 5.07% on the 10 mg dose, and

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6.42% on the 15 mg dose. Headache incidence increased with higher doses, affecting 4% of patients on the 5 mg dose, 5.16% on the 10 mg dose, and 10.71% on the 15 mg dose. Less common adverse events included hypertension, diabetic retinopathy, major adverse cardiovascular events (MACE), and malignant neoplasms, reported in three or fewer studies without significant association to tirzepatide dose.(24)

Conclusion

Tirzepatide represents a significant advancement in the treatment of diabesity, addressing both glycemic control and obesity, which are critical components of this complex condition. Clinical trials have consistently demonstrated Tirzepatide's superiority over traditional therapies in reducing HbA1c levels and inducing substantial weight loss. Moreover, Tirzepatide has shown potential benefits in cardiovascular health, liver function, and renal outcomes, indicating its role beyond glycemic management. Its dual mechanism targeting both GLP-1 and GIP receptors offers a unique and effective approach to tackling the interlinked issues of obesity and T2DM. However, the clinical adoption and patient outcomes will depend on long-term safety profiles, tolerability, and accessibility of this promising therapeutic agent

Statements and Declarations

All the authors have no competing interests to declare

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