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Review Article

The Multifaceted Potential of Tirzepatide in Metabolic and Non-Metabolic Disorders

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ABSTRACT

Tirzepatide is redefining the treatment landscape for metabolic and non-metabolic disorders. By uniquely harnessing two critical hormonal pathways, the review provides comprehensive insights into how Tirzepatide's dual mechanism of action sets it apart from existing therapies. Noteworthy findings from clinical and preclinical studies underscore Tirzepatide's potential in addressing complex conditions Highlighting its role in cardio protection, renal protection, neuroprotection, bone health in osteoporosis, reproductive health, respiratory health, genetic conditions management, cancer-associated weight gain, psychiatric illness and antipsychotic drug-induced obesity, inflammatory conditions, and other conditions. This comprehensive review not only underscores tirzepatide's potential to address unmet clinical needs but also identifies key avenues for future research, aiming to elucidate its broader applicability and optimize patient outcomes. By highlighting these novel insights, this review positions tirzepatide as a transformative agent with the potential to redefine therapeutic paradigms across diverse medical domains.

Keywords: Tirzepatide, T2DM, Obesity, Metabolic Health, Bone Health Cardiovascular health, Reproductive Health, Neurological Health, Renal Health, Respiratory Health, Inflammatory conditions.

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INTRODUCTION

Tirzepatide (TIR) is a novel dual Glucose-dependent Insulinotropic Polypeptide (GIP) and Glucagon-Like Peptide-1 Receptor Agonist (GLP-1 RA) that represents a promising advancement in the treatment of metabolic diseases, particularly obesity and Type 2 Diabetes Mellitus (T2DM). Approved by the FDA in 2022 for the management of T2DM and obesity, TIR operates by acting on both the GLP-1 and GIP receptors, two critical hormonal systems involved in glucose metabolism, appetite regulation, and energy homeostasis. These two pathways have historically been targeted individually by separate classes of medications, but TIR's unique Mechanism of Action (MOA) offers a synergistic approach that enhances its therapeutic effects (Syed, 2022). GLP-1RAs like liraglutide and semaglutide have demonstrated efficacy in improving glycemic control, promoting weight loss, and reducing cardiovascular risk factors. However, TIR's dual-action, leveraging both the GLP-1 and GIP receptors, sets it apart by improving Insulin Sensitivity (IS) and increasing insulin secretion in response to meals, while also reducing appetite and increasing satiety through effects on the central nervous system. The GIP receptor activation is not present in other GLP-1 RAs, it is thought to improve lipid metabolism and further enhance the weight loss effects, potentially making TIR more effective in managing obesity compared to traditional GLP-1 RAs alone. One of the most notable advantages of TIR is its superior efficacy compared to other GLP-1RAs and metabolic drugs (Jensterle, Rizzo, Haluzík, and Janež, 2022). Clinical studies have shown that TIR leads to significantly greater weight loss than other GLP-1RAs like semaglutide, and it also provides superior blood glucose control in patients with T2DM (Mather *et al.*, 2022). TIR's potential extends beyond weight loss and glycemic control, as emerging evidence suggests it also provides protective benefits across several organ systems, making it an exciting candidate for broader therapeutic applications. In this review, we will explore how TIR can influence not only obesity and diabetes but also other important aspects like cardio protection, renal protection, neuroprotection, bone health in osteoporosis, reproductive health, respiratory health, genetic conditions management, cancer-associated weight gain, psychiatric illness and antipsychotic drug-induced obesity, inflammatory conditions, and other conditions. This comprehensive understanding could pave the way for its broader use in clinical practice, offering potential benefits for a wide array of patients suffering from

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diverse health conditions. Figure 1: Multifaceted effects of Tirzepatide as a GLP-1/GIP receptor agonist on metabolic and non-metabolic disorders, highlighting its systemic benefits across various organ systems.

Tirzepatide In Metabolic Health

TIR addresses several key mechanisms contributing to prediabetic conditions, including IR (IR), beta-cell dysfunction, impaired glucose transport, hepatic glucose overproduction, and impairments in the incretin system (involving hormones like GLP-1 and GIP). These dysfunctions lead to chronic hyperglycemia and increased insulin secretion, which, over time, progress to T2DM. (Hankosky *et al.*, 2023) conducted a 72-week clinical study showing that TIR significantly reduces the risk of developing T2DM in individuals with obesity or overweight, regardless of glycemic status. It is also effective for patients with IR, dyslipidemia, and hypertension. Phase 3 trials by (Jastreboff *et al.*, 2024) reported significant reductions in body weight and IR compared to placebo, indicating TIR's potential in preventing T2DM progression. Additionally, TIR has been found safe for children aged 10 and older, presenting a promising pharmacological option for managing pediatric obesity and controlling both glycemia and weight in this vulnerable population (Guan, Li, and Ma, 2023). While TIR shows promise, clinical trials specifically targeting adolescents with T2DM are still needed to assess its safety and effectiveness in this group. However, the increasing number of trials registered in the U.S. Clinical Trials Registry indicates growing interest in its potential for younger populations. A Phase 2 study by (Mather *et al.*, 2022) demonstrated that TIR significantly improves IS compared to semaglutide, with benefits extending beyond weight loss. (Jastreboff *et al.*, 2022) also emphasized that TIR (15 mg) achieved comparable weight-loss outcomes to bariatric surgery, with 36.2% of participants achieving ≥25% body weight reduction, positioning it as a viable, non-surgical alternative for obesity management. This makes TIR a promising treatment option for Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD). Phase 2 clinical trials by (Loomba *et al.*, 2024) showed that TIR outperformed placebo in resolving Metabolic dysfunction-Associated Steatohepatitis (MASH) without exacerbating fibrosis, also improving fibrosis staging outcomes. TIR has also demonstrated significant reductions in hypertriglyceridemia, a key component of metabolic syndrome. In the SURPASS-2 trial, TIR led to greater reductions in serum triglyceride levels compared to semaglutide 1 mg (Nicholls *et al.*, 2024). Furthermore, a meta-analysis by (Zeng *et al.*, 2023) found that TIR was not significantly associated with an increased risk of pancreatitis or gallbladder-related diseases, supporting its general safety in these areas, although further research is needed to confirm these findings.

Tirzepatide in bone health

(Mabilleau G *et al.*, 2014) conducted a meta-analysis on the effects of GLP-1RAs on osteoporosis, identifying 28 eligible studies. Among these, 21 studies reported no fractures, while 7 studies observed at least one fracture in patients receiving GLP-1RA treatment. The analysis suggested a potential protective effect of GLP-1RAs against fractures in placebo-controlled and high-quality studies, although these findings were not statistically significant. The results exhibited variability, with some trials indicating a trend toward reduced fracture risk, while others showed no effect or even an increased risk, particularly in lower-quality studies. Similarly, (Gabe *et al.*, 2022). studied the combined effects of GIP and glucagon-like peptide-2 (GLP-2) RA, finding that their co-administration resulted in an additive reduction in bone resorption, which was more effective than either hormone alone. This indicates that combining GIP and GLP-2RA can synergistically improve bone metabolism, In comparison, TIR, a dual GLP-1/GIP RA, and known to reduce systemic inflammation measured by C-Reactive Protein (CRP) (Borlaug *et al.*, 2024) could potentially reduce osteoporosis through multiple mechanisms, including reducing body weight, anti-inflammatory activity and suppressing osteoclast activity, ultimately improving bone health.

Tirzepatide in reproductive system health

The studies on GIP receptor agonists all investigated the effects of receptor agonists in overweight women with PCOS, focusing on both reproductive and metabolic outcomes. GLP-1RAs, particularly when combined with metformin, significantly improved menstrual cycle regularity, ovulation rates, and androgen levels, enhancing hormonal and reproductive health. These therapies were also more effective than metformin alone in promoting weight loss, particularly reducing abdominal fat, and improving IS and glucose metabolism (Elkind-H *et al.*, 2008). (Nylander *et al.*, 2017) observed reductions in body weight; improvements in markers of hyperandrogenism (e.g., increased Sex Hormone-Binding Globulin (SHBG) and decreased free testosterone, and a modest reduction in ovarian volume, indicating a positive effect on ovarian morphology. (Kahal *et al.*, 2015) further emphasized that GLP-1 analogs contributed to reduced testosterone levels, offering benefits for hyperandrogenism, which is often linked to IR and obesity in PCOS. Additionally, the GIP receptor plays a critical role in improving IS by enhancing glucose-dependent insulin secretion and promoting fat metabolism. This reduction in IR lowers circulating insulin levels, which can decrease testosterone production, a common issue in women with PCOS. Elevated insulin stimulates the ovaries to produce more testosterone, exacerbating hyperandrogenism. By improving IS, GIP receptor agonists help mitigates this hormonal imbalance. These agonists also support weight loss and fat metabolism, further contributing to better overall metabolic and reproductive outcomes. However,

gastrointestinal side effects, such as nausea and constipation, were more frequent in the intervention groups (Samms, Coghlan, and Sloop, 2020). In conclusion, combining GLP-1/GIP receptor agonists may provide a more effective treatment strategy than individual therapies, addressing both metabolic dysfunction and androgen excess in PCOS.

Tirzepatide in cardiovascular health

Tirzepatide has demonstrated significant cardiovascular and metabolic benefits across various high-risk populations, including individuals with type 2 diabetes, obesity-related Heart Failure with preserved Ejection Fraction (HFpEF), moderate-to-severe Obstructive Sleep Apnea (OSA), and dyslipidemia. In a 52-week study, (Borlaug *et al*., 2024) reported reductions in systolic blood pressure (-5 mmHg), estimated blood volume (-0.58 L), and systemic inflammation, evidenced by a 37.2% decrease in CRP levels. Additionally, a significant 10.4% reduction in troponin T levels suggested potential mitigation of cardiac injury. (Frías *et al*., 2021) and (Del Prato *et al*., 2021) further emphasized TIR's lipid-modifying effects, showing improvements in triglycerides, Very-Low-Density Lipoprotein (VLDL), and High-Density Lipoprotein (HDL) cholesterol compared to semaglutide. Similarly, demonstrated dose-dependent reductions in lipid parameters, including serum triglycerides (up to 23%), LDL cholesterol (up to 8%), and non-HDL cholesterol (up to 12%) over a 52-week period compared to insulin glargine (Del Prato *et al*., 2021). The SURPASS trials reinforced these findings by showing consistent reductions in both systolic and diastolic blood pressure, with systolic reductions ranging from -4.7 mmHg to -6.6 mmHg across different trial phases (Forzano *et al*., 2022). In patients with OSA and obesity, (Malhotra *et al*., 2024) observed significant reductions in the Apnea-Hypopnea Index (AHI) by -25.3 events per hour in trial 1 and -29.3 events per hour in trial 2, along with improvements in body weight, hypoxic burden, high-sensitivity CRP, systolic blood pressure, and sleep quality. (Ludvik *et al*., 2021) added to the evidence, demonstrating that TIR provides superior glycaemic control compared to insulin degludec while significantly reducing the incidence of hypoglycaemic events. This dual benefit of enhanced glucose regulation and reduced hypoglycaemia may contribute to cardioprotection by minimizing cardiovascular stress. Overall, TIR demonstrated substantial benefits in reducing sleep apnea severity and improving cardiovascular markers, emphasizing its potential in managing cardiovascular risk and metabolic health in diverse patient populations.

Tirzepatide in renal health

TIR demonstrated significant cardiovascular and renal benefits. Kidney function was assessed using estimated Glomerular Filtration Rate (eGFR)-creatinine and eGFR-cystatin Cat baseline, with values similar for both TIR and insulin glargine. Over a 52-week period, TIR showed a smaller decline in kidney function, with less reduction in both eGFR-creatinine and eGFR-cystatin C compared to insulin glargine. No significant subgroup differences in eGFR changes were observed. Additionally, small but statistically significant correlations were found between changes in HbA1c and eGFR-cystatin C, suggesting a mild association between glycemic control and kidney function (Heerspink *et al*., 2023). Over 104 weeks, TIR continued to demonstrate kidney-protective effects, with a better long-term eGFR slope and sustained benefits even after discontinuation, despite an initial modest eGFR decline. TIR also reduced albuminuria progression, indicating decreased glomerular hypertension, with a greater proportion of participants achieving significant improvements, particularly in those with greater baseline kidney impairment. These renal benefits were dose-dependent and consistent across subgroups (Heerspink *et al*., 2022). In addition to its renal effects, TIR showed cardiovascular advantages, including reductions in systolic blood pressure, pulse pressure, and markers of inflammation like CRP, suggesting improved aortic compliance. Furthermore, TIR improved glycemic control, significantly reduced HbA1c levels, and led to substantial body weight reductions, which are attributed to its unique mechanism of dual GLP-1/GIP receptor agonism (Borlaug *et al*., 2024). (Urva S. *et al*., 2021) conducted a Pharmacokinetic (PK) study to assess TIR exposure in individuals with varying levels of renal impairment. The results showed that TIR exposure was similar across all groups, including those with renal dysfunction and healthy controls. While a slight increase in exposure was noted in the group with moderate renal impairment, it was not deemed clinically significant. Furthermore, no meaningful relationship was found between TIR exposure and kidney function, even in patients with severe renal impairment or end-stage renal disease. Overall, the study concluded that renal impairment does not have a significant impact on TIR pharmacokinetics. It can be effectively used to treat type 2 diabetes, obesity, and other related conditions, even in patients with renal impairment, as its PKs remain largely unaffected by varying degrees of kidney dysfunction. These multifaceted benefits make TIR a promising treatment for individuals with both metabolic and renal complications.

Tirzepatide in neurological health

Obesity is strongly associated with an increase in both the frequency and severity of migraines. Individuals who are severely obese are nearly twice as likely to experience severe headache pain compared to those with a normal weight. As obesity worsens, migraine frequency also rises, with 13.4% of obese individuals and 20.7% of severely obese individuals reporting frequent headaches (10-14 days per month). This increase in migraine frequency and severity is compounded by factors such as sympathetic dysregulation, reduced serotonin levels, and inflammation, which contribute to more frequent and intense headaches. Behavioral factors like low physical activity and conditions such as obstructive sleep apnea further exacerbate migraine outcomes.

Given these challenges, interventions targeting obesity may offer benefits for individuals suffering from both obesity and migraines (Bond, Roth, Nash, and Wing, 2011). In this, TIR has shown promise. Both (Jastreboff AM *et al.*, 2022) and (Heise T *et al.*, 2023) examined the effects of TIR on body weight in individuals with obesity. (Jastreboff AM *et al.*, 2022) conducted a 72-week study and found significant and sustained reductions in body weight with weekly doses of TIR (5 mg, 10 mg, or 15 mg). (Heise *et al.*, 2023) showed that TIR led to greater reductions in body weight and fat mass compared to both placebo and semaglutide. In both studies, TIR was shown to significantly reduce appetite compared to placebo, with no significant differences in appetite scores or energy intake reductions between TIR and semaglutide. It reduces the pro-apoptotic BAX/Bcl-2 ratio, modulates apoptotic markers, and activates the CREB and BDNF signaling pathways to enhance neuronal survival and synaptic activity (Fontanella *et al.*, 2024). (Yang *et al.*, 2024) demonstrated that weekly TIR administration (10 nmol/kg for 8 weeks) in APP/PS1 Alzheimer's disease mice reduced cortical amyloid plaques, Aβ-induced neuronal apoptosis, and astrocytic activation (GFAP), despite a paradoxical decrease in GLP-1R protein expression. Furthermore, TIR improved glucose regulation, upregulated mRNAs linked to glucose metabolism in the hypothalamus (GLP-1R, SACF1, ATF4, Glu2A, Glu2B) and cortex (glucose transporter 1, hexokinase, glucose-6-phosphate dehydrogenase, phosphofructokinase), and mitigated Aβ-induced mitochondrial dysfunction by regulating ROS, stabilizing mitochondrial membrane potential, and ensuring ATP production. These findings suggest that TIR may help reduce both obesity and its associated complications, including migraines, potentially improving the quality of life for individuals affected by both conditions.

(Kalinderi, Papaliagkas, and Fidani, 2024) further highlight TIR's promising neuroprotective mechanisms, emphasizing its ability to reduce inflammation, oxidative stress, and apoptosis while promoting neurogenesis and improving mitochondrial function to prevent dopaminergic neuronal death. Preclinical evidence demonstrates that TIR and related incretin-based therapies protect neurons from toxins such as rotenone, MPTP, and 6-OHDA by enhancing autophagy and reducing neuroinflammation. GLP-1RAs like exendin-4, liraglutide, lixisenatide, and semaglutide have shown efficacy in protecting the nigrostriatal dopaminergic system and mitigating inflammatory and apoptotic pathways. Dual GLP-1/GIP receptor agonists, including DA5-CH and DA-JC1, exhibit superior neuroprotection by reducing α-synuclein aggregation and enhancing dopamine synthesis. Comparative studies reveal that certain dual agonists outperform single agonists like NLY01 and liraglutide in neuroprotection and inflammation suppression. Clinical evidence from trials with exendin-4, liraglutide, and lixisenatide underscores their potential, with improvements in motor and cognitive function and reductions in disability scores. Despite side effects such as nausea and weight loss, the sustained benefits post-treatment highlights their promise. TIR, given its dual-agonist nature and broader metabolic effects, holds great potential for a personalized treatment approach in Alzheimer and Parkinson's disease management.

Tirzeaptide in respiratory health

Obesity, a condition known to impair pulmonary function and exacerbate airway inflammation, was a key focus in the study by (Toki *et al.*, 2023) investigating TIR in polygenic obese TALLYHO Jng/J mice. The drug demonstrated significant metabolic and anti-inflammatory benefits, achieving greater bodyweight reduction, improved glycemic control, and decreased serum leptin levels compared to semaglutide and [D-Ala2]-GIP. It also reduced Th2 cytokines, including IL-5 and IL-33, and eosinophil and lymphocyte counts in Bronchoalveolar Lavage Fluid (BALF), highlighting its potential for alleviating allergic inflammation. However, its effects on certain markers like CCL17 and CCL22 were comparable to semaglutide, and it did not improve airway responsiveness or significantly impact neutrophil-related inflammation. The findings suggest that TIR offers specific advantages but has limitations in its broader anti-inflammatory efficacy combained with weight loss effect of TIR could help improve asthma control and reduce the burden of obstructive sleep apnea and other obesity-related pulmonary issues (Forzano *et al.*, 2022).

Tirzepatide in genetic conditions

The study by (Ganawa, Santhosh, Parry, and Syed, 2022) discusses the use of GLP-1RAs for managing obesity in patients with Bardet-Biedl Syndrome (BBS). The patient in this case report initially received liraglutide, resulting in a significant weight reduction over five months. This was later replaced with semaglutide for convenience, resulting in further weight loss and improved metabolic control. The patient achieved a final BMI of 24.3 kg/m² after 19 months, demonstrating that GLP-1RAs can effectively manage obesity and associated metabolic complications in BBS. TIR may help alleviate some symptoms of Alström syndrome, a rare genetic disorder characterized by obesity, type 2 diabetes, vision and hearing loss, and cardiovascular issues (Ryan, 2021). Its dual mechanism, activating both GLP-1 and GIP receptors, improves IS (Mather *et al.*, 2022), lowers blood sugar, and reduces inflammation, potentially benefiting individuals with IR and metabolic disturbances. TIR also promotes weight loss by reducing appetite and fat accumulation, helping manage obesity (Borlaug *et al.*, 2024). Additionally, it can improve lipid profiles and support heart health, addressing cardiovascular complications (Del Prato *et al.*, 2021). However, it does not treat vision or hearing loss. Even in Wolfram Syndrome, TIR does not address the underlying WFS1 or CISD2 mutations, which lead to Endoplasmic Reticulum (ER) stress, beta-cell apoptosis, and neurodegeneration. However, as a dual GIP and GLP-1RA, it enhances insulin secretion when beta-cell function

is intact, suppresses glucagon release, slows gastric emptying, and reduces postprandial glucose levels. Additionally, GLP-1RAs are known to reduce inflammation, potentially alleviating ER stress, and promote weight loss, while GIP improves IS and supports metabolic regulation. Both pathways exhibit cytoprotective and neuroprotective activities (Boshchenko *et al.*, 2024). Despite these benefits, in Wolfram Syndrome, the beta-cell loss is often severe and irreversible, and TIR does not directly modulate the genetic mutation or fully counteract the progression of neurodegeneration. Nevertheless, a Phase 2 clinical trial (NCT05659368) registered in the U.S. shows promise in exploring TIR's role in managing Wolfram Syndrome, offering hope for improved outcomes or at least better symptom control (Clinicaltrials.gov). In the treatment of hidradenitis suppurativa, (Chan, Kaur, and Kaffenberger, 2024) demonstrated the potential in improving HS with metabolic comorbidities. Administered at 2.5 mg weekly and titrated to 7.5 mg, TIR significantly reduced HS severity (improved DLQI, VAS, and HS-PGA) while decreasing inflammatory lesions. It also achieved substantial metabolic benefits, including HbA1c reduction in half, triglyceride improvement, and 16% weight loss. These outcomes suggest TIR's synergistic impact on HS and metabolic control. TIR also shows promise as a treatment for rare lipodystrophy syndromes, where the loss of subcutaneous fat results in ectopic fat deposition in the liver, muscles, and visceral regions. These abnormal fat accumulations exacerbate IR, hepatic steatosis, and systemic inflammation, contributing to metabolic dysfunction (Zammouri *et al.*, 2022). TIR promotes fat mobilization from ectopic sites, reduces hepatic fat accumulation, improves dyslipidemia, and modulates inflammatory pathways, potentially mitigating organ-specific damage.

Tirzepatide in cancer associated weight loss

Cancers are significantly influenced by obesity, which is a major risk factor for endometrial cancer and atypical hyperplasia; these patients often undergo progestin therapy, but high recurrence rates persist as the underlying cause-obesity-remains unaddressed (Onstad, Schmandt, and Lu, 2016). TIR holds promise as a weight loss agent to improve reproductive and oncological outcomes. In node-positive high-risk early breast cancer patients with obesity or overweight, adding TIR as an adjuvant therapy could enhance outcomes compared to standard therapies alone. The anti-inflammatory properties of GLP-1RAs, including their ability to reduce CRP, TNF-α, IL-6 (Batiha *et al.*, 2023) and Myeloid-Derived Suppressor Cells (MDSCs), contribute to mitigating systemic inflammation, IR, and hyperglycemia-all factors associated with increased MDSC levels and tumor-promoting inflammation (Wang *et al.*, 2021). Obesity-related chronic low-grade inflammation, driven by adipokines and macrophage infiltration, further exacerbates MDSC activity, indirectly addressed by TIR's mechanisms. Drugs like ruxolitinib, used to treat polycythemia vera, often cause weight gain (Krichevsky *et al.*, 2018), and GLP-1RAs like TIR could counteract this while preventing hyperglycemia. Moreover, TIR may support long-term weight and metabolic health (Jastreboff *et al.*, 2024) in cancer survivors at risk of recurrence or secondary cancers due to obesity. Notably, a retrospective study by (L. Wang, *et al.* 2024) demonstrated a significant reduction in pancreatic cancer risk among GLP-1RA users, particularly in obese individuals or those with tobacco use disorder, with even greater risk reduction observed in combination therapies. Furthermore, hormonal therapy in breast and prostate cancer frequently causes

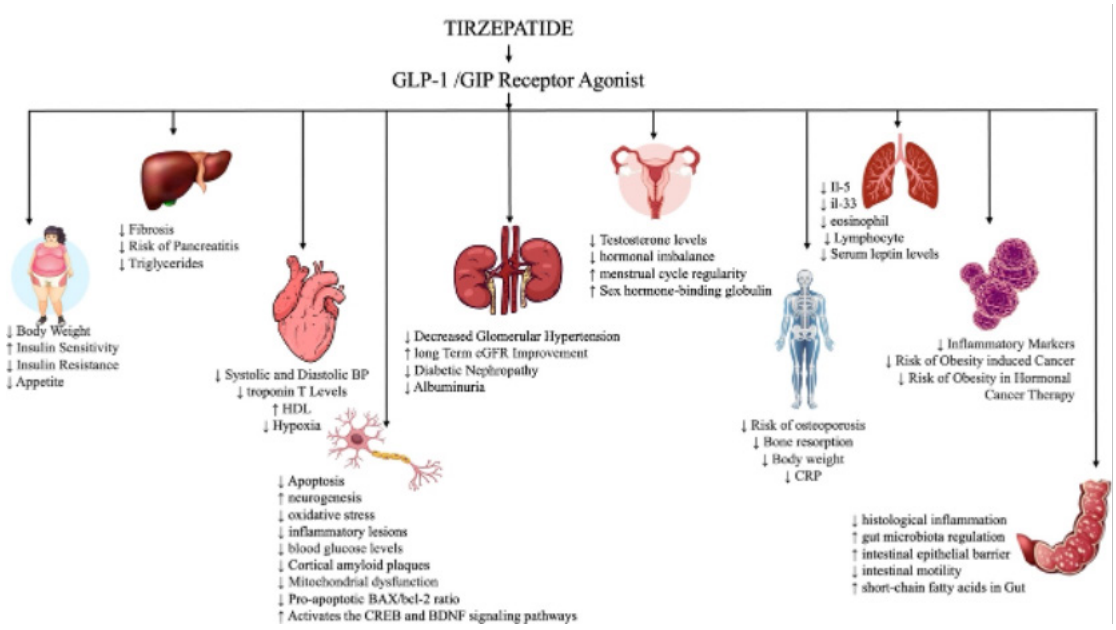

Figure 1: This diagram shows the effects of Tirzepatide, a GLP-1/GIP receptor agonist, on various systems. It highlights benefits like weight loss, improved insulin sensitivity, reduced inflammation, and better heart and kidney health. It also impacts hormones, bone health, and gut function, while lowering the risk of obesity-related cancer.

weight gain (Pati, *et al.*, 2023), which TIR could address through improved metabolic control and appetite regulation, potentially delivering substantial benefits in weight management and overall cancer care (Heise *et al.*, 2023) even Supporting long-term weight and metabolic health in cancer survivors at risk for recurrence or secondary cancers due to obesity.

Trizepatide in psychatric illness

Patients with Binge Eating Disorder (BED) are often obese and require both psychological and pharmacological treatments to manage their symptoms. While many drugs, including antidepressants and antipsychotics, are commonly prescribed, the obesity associated with BED often remains unaddressed. A systematic review by (Aoun *et al.*, 2024) highlighted favorable results in weight management when GLP-1RAs were used alongside standard therapies. TIR, a GLP-1RA, has the potential to manage obesity effectively. This is particularly important given the weight gain commonly caused by chronic use of antipsychotic medications such as olanzapine and clozapine (Dayabandara *et al.*, 2017). TIR's ability to suppress appetite and reduce cravings makes it a promising option for achieving weight reduction in such cases (Heise *et al.*, 2023).

Tirzepatide in inflammatory conditions

Obesity is strongly linked to several autoimmune diseases. By promoting significant weight loss, TIR helps reduce chronic low-grade inflammation and immune dysregulation, key drivers of autoimmune disease progression and severity. Weight reduction achieved through TIR can alleviate disease activity in conditions like rheumatoid arthritis, psoriasis, and systemic lupus erythematosus, while also improving therapeutic responses in Hashimoto's thyroiditis, autoimmune hepatitis, and inflammatory bowel disease. Adolescence-associated obesity that Increase the risk of conditions like multiple sclerosis, TIR's ability to regulate appetite, reduce cravings, and enhance metabolic health can mitigate the impact of obesity, ultimately improving outcomes and reducing the burden of autoimmune diseases particularly it reduces levels of cytokines such as TNF-α, IL-1β, and IL-6 (Chen *et al.*, 2024) which are elevated in Inflammatory Bowel Disease (IBD) and drive intestinal inflammation and enhancing the integrity of the intestinal epithelial barrier, GLP-1 prevents translocation of bacterial endotoxins (Y. Zeng *et al.*, 2024) and also slows gastric emptying and intestinal motility reduces further mechanical stress on inflamed bowel segments and epithelial cell proliferation could repair IBD lesions (Karrar *et al.*, 2023). Additionally, obesity is a known aggravating factor in IBD severity due to its contribution to systemic and gut inflammation. TIR's synergistic effect in enhancing metabolic benefits and lower systematic inflammation contributing to IBD. (Arvanitakis *et al.*, 2023). Reviewed numerous animal studies highlighting the anti-inflammatory potential of GLP-1 RA in the context of IBD, with a particular focus on the cAMP/NF-κB pathway. These studies demonstrated significant reductions in pro-inflammatory cytokines such as TNF-α and IL-1α and a notable downregulation of NF-κB phosphorylation, a key regulator of intestinal immune function. Additionally, GLP-1 RA was shown to improve colitis symptoms in animal models (W. Wang *et al.*, 2023), including enhanced stool consistency, decreased histological inflammation, and attenuation of associated diarrhea. Furthermore, improvements in gut microbiota regulation (Silva-Veiga *et al.*, 2025) and the restoration of GLP-1 production from short-chain fatty acids were observed, suggesting a multifaceted therapeutic potential for GLP-1 RA in managing IBD.

Tirzepaide in other conditions

Post-transplant patients often struggle with obesity due to steroids and metabolic changes due to the glucocorticoicoids alter the activity of AMP-activated protein kinase in the hypothalamus and decrease Uncoupling Protein 1 (UCP-1) and activates endocannabinoid system (Hu *et al.*, 2019; Bowles *et al.*, 2015) all these combine leads to reduced metabolic rates, increase in food intake and decrease in energy expenditure GLP-1/GIP Receptor agonist can be used to decrease the appetite and suppress the food craving and enhance IS (Heise *et al.*, 2023). Even in patient with and Antiretroviral Therapy (ART) often experience metabolic changes and IR is most common in older protease inhibitors and NRTIs contribute to poor glycemic control and dyslipidemia often lead to obesity, inflammation and metabolic dysfunction (Ergin, Inga, Maung, Javed, and Khan, 2020) TIR can be used to treat these metabolic dysregulations with ART.

Future Directions

This review underscores the potential of TIR in addressing a broad spectrum of metabolic and non-metabolic disorders. While current research demonstrates promising short-term efficacy, there remains an urgent need for longitudinal studies to evaluate the safety profile and long-term adverse effects of TIR across diverse patient populations. Understanding the precise mechanisms by which TIR exerts its effects on various organ systems is critical for optimizing its therapeutic application and dosing regimens. The role of TIR in adolescent populations is notably underexplored, necessitating further investigation to assess its safety, efficacy, and outcomes in this demographic. This review highlights the potential of TIR as an adjuvant therapy in combination with other therapeutic agents, which could enhance its clinical efficacy. Rigorous clinical trials are warranted to elucidate the synergistic benefits of such combinatorial approaches. Emerging evidence also suggests that TIR may possess neuroprotective and anti-inflammatory properties, opening new avenues for its application in neurological disorders. Comprehensive studies are required to explore its therapeutic role in these conditions. Additionally, the use of TIR in cancer-related weight management and as an adjunct therapy to improve treatment outcomes in oncology represents an area

of significant clinical interest. Genetic and phenotypic variations among patients may influence their responses to TIR. Future research should prioritize identifying predictive biomarkers to facilitate the development of personalized treatment strategies. Furthermore, robust studies assessing the impact of TIR on patients' quality of life, including psychological and functional well-being, are needed. Real-world evidence, obtained through observational studies, could provide critical insights into the effectiveness and safety of TIR in routine clinical practice. As its therapeutic potential expands, careful consideration of the regulatory, economic, and policy implications of its broader use will be essential. In summary, while TIR shows immense promise in managing a range of disorders, ongoing research must focus on addressing knowledge gaps related to its mechanisms, safety, long-term outcomes, and broader clinical applications.

CONCLUSION

TIR represents a significant advancement in the treatment of obesity, T2DM, and a range of other metabolic and non-metabolic disorders. The evidence gathered from clinical studies demonstrates TIR's superior efficacy in improving glycemic control, promoting weight loss, and offering protective benefits across various organ systems. TIR's unique mechanism of action provides synergistic effects that enhance insulin sensitivity, reduce appetite, and improve lipid metabolism. This multifaceted approach not only addresses the primary symptoms of obesity and T2DM but also offers promising therapeutic potential in areas such as cardiovascular health, renal function, neurological protection, and bone health. The comprehensive analysis of TIR's applications extends beyond metabolic diseases, highlighting its potential in managing reproductive health disorders like PCOS, mitigating cardiovascular risks, supporting renal health, and offering neuroprotection in conditions such as Alzheimer's and Parkinson's disease. Moreover, TIR shows promise in addressing weight-related complications in cancer, psychiatric illnesses, and various inflammatory and genetic conditions. Despite the promising results, further research is essential to fully understand the long-term efficacy and safety of TIR. Future studies should focus on elucidating the underlying mechanisms, exploring its use in pediatric populations, and investigating combination therapies. Additionally, the potential of TIR in personalized medicine and its cost-effectiveness should be evaluated to maximize its clinical utility. Tirzepatide offers a groundbreaking approach to managing a broad spectrum of health conditions, providing hope for improved therapeutic outcomes and enhancing the quality of life for patients with diverse health challenges.

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ABBREVIATIONS

TIR: Tirzepatide; **GLP-1 RA:** Glucagon-like peptide-1 receptor agonist; **GIP RA:** Glucose-dependent insulinotropic polypeptide receptor agonist; **T2DM:** Type 2 diabetes mellitus; **MOA:** Mechanism of action; **GLP-2 RA:** glucagon-like peptide-2 receptor agonist; **PCOS:** Polycystic Ovary Syndrome; **IS:** Insulin sensitivity; **CRP:** C-Reactive Protein; **SHBG:** Sex hormone-binding globulin; **IR:** Insulin Reactive; **OSA:** Obstructive sleep apnea; **VLDL:** Very-low-density lipoprotein; **HDL:** High-density lipoprotein; **LDL:** Low-density lipoprotein; **AHI:** Apnea-hypopnea index; **eGFR:** Estimated Glomerular Filtration Rate; **PK:** pharmacokinetics; **HbA1c:** Glycated hemoglobin; **BAX/Bcl-2:** BCL2-associated X protein/B-cell lymphoma 2; **CREB:** Cyclic AMP response element-binding protein; BDNF: Brain-derived neurotrophic factor; **GFAP:** Glial fibrillary acidic protein; **SACF1:** Spindle and Akt/PKB associated Cofactor 1; **ATF4:** Activating transcription factor 4; **Glu2A:** Glutamate receptor subunit 2A (AMPA receptor subtype); **Glu2B:** Glutamate receptor subunit 2B (AMPA receptor subtype); **ROS:** Reactive oxygen species; **MPTP:** 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; 6; **OHDA:** 6-hydroxydopamine; **DA5-CH:** a 5-carbon hydroxy dopamine analog; **DA-JC1:** Dopamine-JC1; **BALF:** Bronchoalveolar lavage fluid; **CCL17:** Chemokine (C-C motif) ligand 17; **CCL22:** Chemokine (C-C motif) ligand 22; **IL-5:** Interleukin 5; **IL-33:** Interleukin 33; **BMI:** Body Mass Index; **BBS:** Bardet-Biedl syndrome; **WFS1:** Wolfram syndrome 1; **CISD2:** CDGSH iron sulfur domain 2; **ER:** Endoplasmic reticulum; **HS:** Hidradenitis suppurativa; **DLQI:** Dermatology Life Quality Index; **VAS:** Visual Analog Scale; **HS-PGA:** Hidradenitis Suppurativa Physician Global Assessment; **TNF-α:** Tumor Necrosis Factor-alpha; **IL-6:** Interleukin 6; **IL-1β:** Interleukin 1 beta; **MDSC:** Myeloid-Derived Suppressor Cells; **BED:** Binge Eating Disorder; **IBD:** Inflammatory bowel disease; **cAMP:** Cyclic adenosine monophosphate; **NF-κB:** Nuclear Factor kappa-light-chain-enhancer of activated B cells; **UCP-1:** Uncoupling protein 1; **HIV:** Human Immunodeficiency Virus; **ART:** Antiretroviral Therapy; **NRTIs:** Nucleoside Reverse Transcriptase Inhibitors.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

Tirzepatide (TIR), a dual GLP-1/GIP receptor agonist that provides better glycemic control and weight loss, was approved by the FDA in 2022 for the treatment of type 2 diabetes and obesity. By lowering blood pressure, improving lipid profiles, and reducing inflammation, it aids the cardiovascular system while also safeguarding renal function. In terms of neuroprotection, lung health, and reproductive health-specifically in the treatment of PCOS-TIR exhibits promise. It helps control weight gain

from cancer, psychiatric diseases such antipsychotic-induced obesity, and metabolic dysfunction in genetic disorders. It helps autoimmune conditions like rheumatoid arthritis and inflammatory bowel illness because of its anti-inflammatory qualities. Evaluation of its long-term safety and wider clinical uses are the goals of ongoing research.

AUTHOR CONTRIBUTIONS

Thalal Mohamed-data curation, and writing-original draft.

Srimathi Mahadevan-methodology and supervision.

Jayashri Vidya Prabhakaran, Sundari Venkatesan-formal analysis and investigation.

Mohammed Fayaz-conceptualization, data curation, methodology, project administration, validation, and writing-original draft.

Vijayakumar Thangavel Mahalingam-conceptualization, data curation, methodology, project administration, validation, and writing-original draft.

All authors read and approved the final manuscript.

WRITING DISCLOSURE

No writing assistance was utilized in the production.

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