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# TIRZEPATIDE: Trending ‘Weight loss’ Drug– Potential Influence in Tackling Obesity Epidemic

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## Abstract:

Obesity is a chronic disease that is associated with severe complications. A lifestyle involving an increased appetite and reduced energy expenditure promotes weight gain. A better understanding of the endocrine regulation of appetite has led to the development of newer medications for the treatment of obesity. Among these medications is an incretin-based drug named tirzepatide. Many studies have been conducted in obese, insulin-resistant, and lipid-diet-fed mice to evaluate the effect of tirzepatide and its combination of GIP and GLP-1 agonism demonstrated higher anorectic activity by increasing satiety and satiation, decreasing liking for high-fat diets and decreasing sweet taste reference as compared to the effects of semaglutide. Adverse effects of mild gastrointestinal events and decreased appetite were reported with tirzepatide (which reduced after some time) than with placebo. In phase 3 SURPASS clinical trial optimized dose escalation scheme was adopted to improve gastrointestinal tolerability with an initial low dose of tirzepatide. The results of the SURPASS-1 trial showed significant improvement in glycemic control and durable bodyweight reductions with all the doses (3 doses) of tirzepatide compared to placebo in type 2 diabetic patients along with diet and exercise. Weight loss occurred regardless of whether participants reported any gastrointestinal adverse events and did not elevate over the period.

**Keywords:** Tirzepatide, diabetes, GIP (Glucose-dependent insulinotropic peptide), GLP-(Glucagon-like peptide-1), weight loss.



## 1. Introduction

According to W.H.O. obesity is defined as abnormal or excessive buildup of fat that poses a health concern. A body mass index (BMI) of 18.5-24.9 kg/m<sup>2</sup> is considered a healthy body weight and a BMI of 25 -29.9 kg/m<sup>2</sup> is considered 'overweight'. Obesity is defined by a BMI greater than 30kg/m<sup>2</sup> and it has rapidly propagated around the world with millions of cases per year. Obesity is a multifaceted metabolic illness of energy homeostasis that involves both central and peripheral processes. {1} Obesity is correlated to conditions like cerebrovascular diseases, type 2 diabetes mellitus, chronic kidney disease, hypertension, non-alcoholic steatohepatitis, obstructive sleep apnea osteoarthritis, etc. {7,18,21,22} Due to excess adipose tissue, mechanical loading on joints may increase which can lead to osteoarthritis. {10} Excess adiposity can also lead to gastro-esophageal reflux disease by increasing intra-abdominal pressure {23}. Obesity is frequently a co-morbidity of type 2 diabetes and more than 85.2 percent of patients with type 2 diabetes mellitus are overweight or obese. Therefore, to prevent severe complications, it is crucial to encourage weight loss. Some authors give this condition a unique term i.e., diabetes, which must be treated as a single condition to maximize the effect of therapies on patients receiving the same {12}. It's a multi-factorial condition including genetic factors (smaller effect), social and environmental factors like too little physical activity, poor diet, and sleep, behavioral characteristics, etc. influence weight gain {23}. As the pathophysiology of obesity is intricate, drug therapies that target multiple mechanisms should be adopted as they are more efficient than single-targeting agents as the latter shows lesser efficacy.

Among the drugs approved for the long-term management of obesity, incretins (a category of metabolic hormones that lead to the fall in blood glucose levels) represent attractive targets for inducing weight loss and preventing metabolic disorders. Incretins are released from the entero-endocrine cells in the form of peptides. There are two main incretin hormones namely: Glucose-dependent insulinotropic polypeptide (GIP) and Glucagon-like peptide-1 (GLP-1) from the upper and lower gut respectively. {15} In patients with type 2 diabetes mellitus, the incretin effect of insulin secretory response to oral glucose administration is diminished or no longer present. This is due to the significantly reduced effectiveness of GIP in mediating the incretin effect. However, in type 2 diabetics, the insulinotropic and glucagonostatic effects of 'GLP-1' are preserved. Thus, this is why GLP-1 is regarded as the parent compound of incretin-based glucose-lowering medicines. The drug "Tirzepatide" (LY3298176), which is this review's focus, is a once-weekly subcutaneous injectable peptide (approved by the Food and Drug Administration [FDA] for the treatment of type 2 diabetes mellitus). It was engineered from the native GIP sequence and exhibits agonistic activity at both the GIP and GLP-1 receptors. {3} Excitement about extraordinary weight loss associated with tirzepatide and updated anti-obesity recommendations resulted in this year's trending clinical topic. In May 2022, Tirzepatide was approved by US FDA for type 2 diabetic patients. In October, the FDA granted 'fast track' status for its use of an 'anti-obesity drug'.

## 2. Obesity Epidemic: Causes and Context

Obesity is a growing public health crisis across the globe. The World Health Organization (WHO) has observed a significantly increasing number of obese and overweight people and now attention is being given to the global implications associated with this drift. This global burden of obesity has tripled since 1945. {13} According to an analysis, obesity and being overweight were among the top 10 causes of global mortality and burden of disease. The U.S. General released a report in 2001, raising concerns about the growing epidemic of obesity and it was the first study to imply that obesity and problems associated with obesity may soon surpass smoking as the country's most common preventable cause of death. Recent data indicates that the prevalence of obesity is rapidly rising in low- and middle-income nations including China, Brazil, Mexico, South Africa, India, Pakistan, and Russia, and countries like Samoa, Kiribati, and Tonga are affected by more than 75% of prevalence. Most of the countries in different parts of the globe- North America, South America, and the majority of Western and Eastern Europe report that at least 40% of the population between the ages of 45 and 59 years are obese or overweight. And there are comparatively lower rates of obesity in East Asian countries. Currently, in the United States, 60% of adults are either overweight or obese. The rise in obesity among children is more concerning than in the case of adults. Rates



of type 2 diabetes and dyslipidemia in children have also increased simultaneously with a rise in the prevalence of obesity which has tripled over the last 30 years in the United States.

Individuals who are obese have a seven-fold increased chance of developing diabetes than the ones with healthy weight. In racial and ethnic groups such as non-Hispanic blacks in the United States, obesity has reached half of the adult population. A similar distribution of obesity is seen in children (aged 2 to 19 years) regarding race; the prevalence of obesity in non-Hispanic African American children (18.8%) and Mexican American children (22.7%) is higher than in non-Hispanic white children (13.9%). Due to genetics, adipose percentage, and cultural and ethnic variations in fat distribution, the use of BMI measurements is still challenging. {8}

Causes of obesity mainly are large portion size; unhealthy eating habits such as consuming fast food, fructose, and trans fats and a sedentary lifestyle are the potential contributing factors in the obesity epidemic. One in five fatalities worldwide is associated with poor diet, according to the Global Burden of Disease study tracking trends in food consumption (between 1990 and 2017 in 195 countries). There is less need to cook at home because of the increasing variety of fast-food establishments. Food industries are producing highly processed foods and marketing them through advertising and providing a misleading perspective on nutritional value, which is a cause of growing child obesity. Based on Framingham's study, soft drink intake has been correlated with cardiovascular risk and metabolic syndrome. During the last 30 years, the number of calories in sodas and fruit juices has increased substantially. Reducing the intake of sugar-sweetened beverages is likely to help reverse the obesity epidemic, according to a recent systemic assessment of prospective studies. Fructose has been associated with obesity as well. It comes from three sources: fruit, sucrose, and high fructose corn syrup (HFCS). {4} It adds excess calories to a person's diet and it has also been linked to central adiposity, hyperlipidemia, and gout. Numerous more studies have concluded and validated these findings.

### 3. Regulation of Body Weight

Body weight regulation is commonly understood to be the result of a balance between calories burned and calories absorbed, but there are other environmental and physiological variables as well that contribute to the epidemic of obesity by affecting the mechanisms regulating energy intake and its expenditure. Additionally, humans' genetic and epigenetic backgrounds are reprogrammed, predisposing subsequent generations to obesity and weight gain. The obesity epidemic can also be influenced by the surroundings where we live and how we adapt to them as the environmental pressure for survival has doubtlessly involved the need to maintain body fat. Peripheral and central processes work within a limited range to maintain body weight to guard against disorders such as chronic overfeeding and starvation. Both hunger and the body energy metabolism are controlled by the brain and the process is termed a 'gut-brain relationship'. A complex neuro endocrine system controls hunger and satiety by continuous signal assimilation and bidirectional crosstalk between important feeding centers in the brain and the periphery. The gastrointestinal tract, liver, pancreas, and adipose tissue secrete various food intake-regulating hormones i.e., amylin, insulin, and ghrelin which act jointly particularly on the hypothalamus part of the brain to modulate appetite and satiety. {16}

To determine whether the body fat (which constitutes the major energy stored in the body and hence is often related to body weight) is increased or decreased, the balance between energy intake and energy expenditure must be assessed. To understand the imbalance that occurs between energy intake and expenditure, which leads to changing body weight, the following equation makes the concept easy.

$$\text{Rate of change of energy stores} = \text{Rate of energy intake} - \text{Rate of energy expenditure} \quad (1)$$

The above equation is reasonably accurate as it explains that with a small initial positive energy balance from increased energy intake, the energy stores will increase and cause an increase in energy expenditure which will hence balance the increased energy intake. After that, the person will be in energy balance once more, but this time,



their energy intake, energy expenditure, and energy reserves will all be higher, which will eventually cause them to gain weight. Also, weight gain cannot be viewed only as the consequence of an initial positive energy balance but also as the process by which the energy balance is eventually re-established. Therefore, this shows the non-linear relationship between the 'changes in energy fluxes' and the 'changes in energy stores'.

Breaking down the energy balance equation into its constituent macronutrients can yield more useful insights into how energy intake is matched against energy expenditure i.e., to go in-depth and try to understand the concepts of protein balance, fat balance, alcohol balance, and carbohydrate balance in the body. And to learn whether each of these nutrients is oxidized or stored in its compartment or does it gets converted into another compartment for its storage.

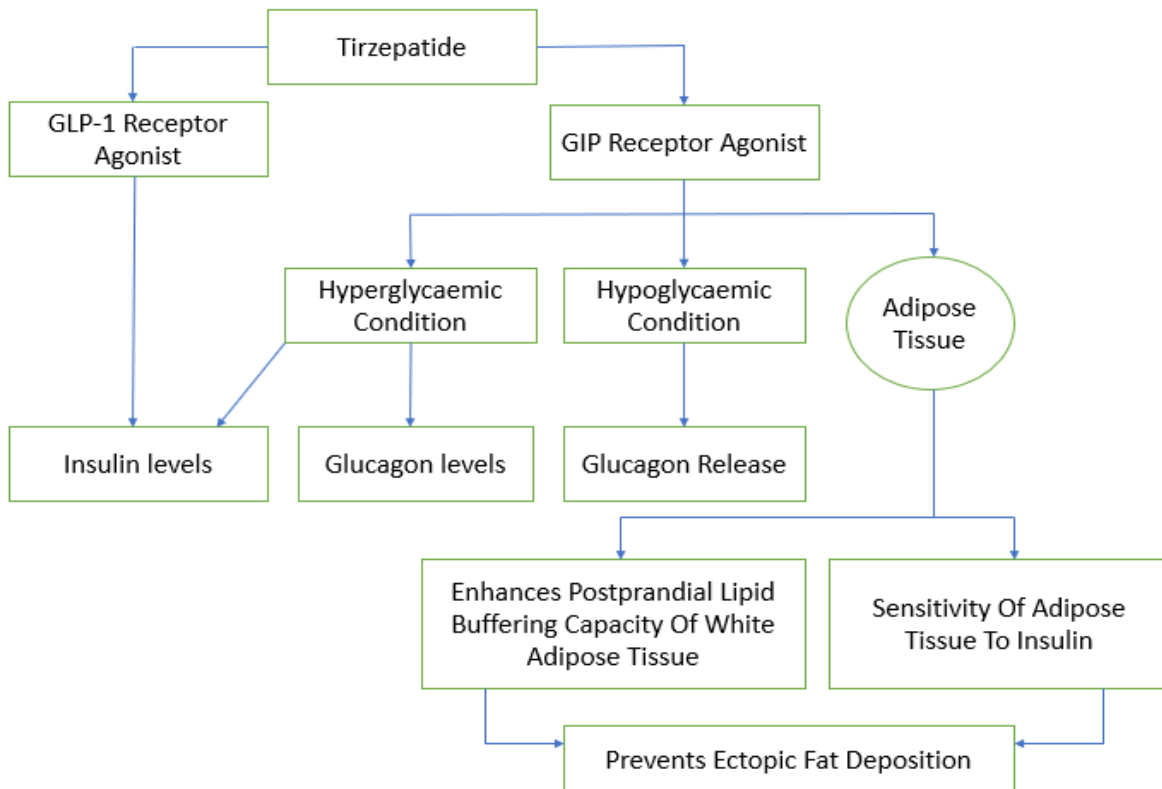
#### 4. Mechanism of Tirzepatide for Weight Loss (Based on Clinical Trial Data)

Preclinical data demonstrated higher weight loss in mice was possible with GIP activation than with GLP-1 receptor mono agonism, suggesting that the two mechanisms worked in combination..{3} In phase 2 studies tirzepatide produced clinically significant weight loss in persons with type 2 diabetes, indicating the need for more research in the treatment of obesity.{9} Based on these results, phase 3 studies with tirzepatide were designed, and the SURPASS study was developed, which includes the following randomized controlled clinical trials: SURPASS-1, tirzepatide monotherapy; SURPASS-2, tirzepatide versus semaglutide; SURPASS-3, tirzepatide versus degludec; SURPASS-4, tirzepatide versus glargine in established CV disease; SURPASS-5, tirzepatide as a basal insulin add-on; SURPASS-6, tirzepatide versus insulin lispro in patients inadequately controlled on insulin glargine; and SURPASS J-mono, tirzepatide versus dulaglutide.{19} Additional details on other ongoing trials with tirzepatide in patients with T2DM can be found at <http://clinicaltrials.gov>.

The primary incretin hormone responsible for the majority of the insulinotropic incretin effect in healthy persons is the glucose-dependent insulinotropic polypeptide (GIP). It inhibits glucagon secretion during hyperglycemia and stimulates the secretion of the same in case of hypoglycemia. GIP receptors are richer in adipose tissue than the GLP-1 and GIP exerts an abundant effect beyond its incretin effect. The Glucagon-like peptide 1 (GLP-1) is also a hormone that binds at GLP-1 receptors which are located at the pancreatic beta-cells to increase glucose-induced insulin secretion. GLP-1 decreases food intake through CNS mechanisms that involve direct activation of afferent fibers of the vagus nerve that project to the nucleus solitaries (NTS) of the hindbrain or area postrema (AP) of the brainstem.

GLP-1 receptor agonists also modulate food intake by acting on the dopaminergic reward system of the brain in the ventral tegmental area. GLP-1 agonists reach the hindbrain via circulation or through vagal afferents, depending on the route of administration and the drug molecule. OXM (oxyntomodulin) hormone exerts its anorexigenic action initially through binding to the GLP-1 receptor and binds to the glucagon receptor (GCGR). Body weight is decreased by multiple mechanisms of glucagon which include augmentation of energy expenditure during lipolysis, etc. The liver-vagus-hypothalamus axis mediates glucagon suppression of food intake. The regulation of energy metabolism by GIP is yet unclear as both stimulation and inhibiting of GIP receptors show a decrease in body weight.

In the case of GLP-1-related drug candidates, their parenteral administration resulted in increased drug concentrations in blood which led to enhanced glycemic control as well as enhanced appreciation for the inherent weight loss properties of GLP-1 receptor agonists. Their specific mechanism of action is associated with the brain, gut, and systemic improvements in insulin sensitivity, each contributing a finite fraction to the total efficacy. In the case of GIP-related drug candidates, preclinical evidence reveals that long-acting GIPR agonists decrease weight in wild-type and GLP-1 knockout mice. Let us reflect upon clinical studies which have been conducted to test the 'efficiency of tirzepatide'. Tirzepatide is a 39 amino acid synthetic peptide that acts as an agonist at both GIP and GLP-1 receptors (as shown in Figure 1).{14} It has a half-life of 5 days which makes the subcutaneous administration of tirzepatide (once weekly) possible. {12}



**Figure 1:** General Mechanism of Tirzepatide

Many studies have been conducted in obese, insulin-resistant, and lipid-diet-fed mice to evaluate the effect of tirzepatide compared to the effects of semaglutide, its combination of GIP and GLP-1 agonism demonstrated higher anorectic action by improving satiety and satiation, decreasing choice for high-fat diets, and lowering preference for sweet tastes..{17} In another phase 2B clinical trial study of 26 weeks which compared the effects of tirzepatide with placebo, dulaglutide, and with or without metformin; it was observed that tirzepatide significantly reduced glycated hemoglobin and body weight as compared to the agents mentioned above.{20} Adverse effects of mild gastrointestinal events and decreased appetite were reported with tirzepatide (which reduced after some time) than with placebo. In phase 3 SURPASS clinical trial optimized dose escalation scheme was adopted to improve gastrointestinal tolerability with an initial low dose of tirzepatide.{6} The results of the SURPASS-1 trial showed significant improvement in glycemic control and major bodyweight reductions with all the3 doses of tirzepatide compared to placebo in type 2 diabetic patients along with diet and exercise alone. Participants lost weight regardless of whether they experienced any gastrointestinal side effects, and the weight did not increase with time.{20}

Inference of the above evidence was that the once-weekly administration of tirzepatide provides a beneficial response in type-2 diabetic patients who were not responding comparatively well to metformin with or without an SGLT2 inhibitor.{14}The wider benefits of tirzepatide for metabolism along with glycemic control include improvements in the body weight, blood pressure, and lipid profile of the patient. Patients, who require



intensification of therapy with an injectable medication due to inadequate glycemic control with oral antihyperglycemic medicine, should be monitored carefully as there is a low risk of clinically relevant hypoglycemia with this algorithm of treatment with tirzepatide. When viewed as a whole, the aforementioned trials demonstrate the potential of tirzepatide as a safe and efficient treatment for glycemic management and weight loss in individuals with obesity and type 2 diabetes mellitus. {5}

### 5. Adverse Effects and Safety

Tirzepatide is a once-weekly subcutaneous injectable medication. 36%-55% mild to moderate adverse effects and around 1%- 16% severe adverse effects have been reported. The serious adverse effects include acute pancreatitis, diabetic retinopathy, cardiac symptoms like sinus tachycardia, hepatobiliary symptoms like biliary tract cholelithiasis and cholecystitis, and kidney disorders like acute kidney injury caused by dehydration. Moreover, a transient spike in mean pulse rate and hypersensitivity reactions are also some of the reported adverse events of tirzepatide. In people with pre-existing diabetic retinopathy, their eyes may be affected even if their glycemic control improves quickly.

Tirzepatide has a dose-dependent safety profile like GLP-1 RAs except in the case of hypoglycemia. Tirzepatide has a dose-dependent risk of hypoglycemia which is comparatively more than the other GLP-1 RAs. Though the incidence of hypoglycemia is small among patients, it should still be paid attention to, especially in the case of higher doses. In the trials for SURPASS 1-5 and SURMOUNT 1 program, gastrointestinal adverse events were majorly reported and were mild to moderate in severity. According to a meta-analysis, all three tirzepatide dosages were linked to dose-dependently higher risks of nausea, vomiting, and diarrhea as compared to basal insulin. {11} The most common effects other than nausea, and vomiting were abdominal cramps, hypertension, indigestion, nasopharyngitis, and decreased appetite that occurred during the dose escalation period. Other gastric effects reported were acid reflux, diarrhea, delayed gastric emptying, and constipation. {2}

### 6. Conclusion

Tirzepatide is a prospective treatment regimen for weight loss in patients with overweight and obesity. Still, we need to be vigilant about its gastrointestinal and other reactions although the incidence of serious adverse effects reported was lower. In various clinical trials, tirzepatide has shown dose-dependent superiority in body weight reduction and glycemic control without the increased risk of hypoglycemia. Tirzepatide can also target various components of metabolic syndrome, making it a promising candidate for weight loss therapy.

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### CRedit authorship contribution statement

Ravjit Kaur: Conceptualization, Writing – original draft & editing. Dr. Hem Raj: Review & editing. Dr. Paras Monga: Supervision, Writing – review & editing.

### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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