REVIEW PAPER

The Role of GLP-1 Receptor Agonists in Obesity Management: Evidence from Glycemic and Non-Glycemic Populations

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Abstract

Obesity is a Multifactorial, Chronic illness that is typified by an excess adiposity and is accompanied by metabolic, cardiovascular, and systemic complications. It is increasingly becoming common all over the world, which accentuates the necessity of efficient and long- lasting therapeutic methods. The typical management strategies, such as lifestyle change, pharmacotherapy, and bariatric surgery, are usually limited either by low levels of long- term compliance, limited effectiveness or low availability. Here, incretin hormone glucagon-like peptide-1 (GLP-1) that plays a role in the regulation of glucose levels and appetite has become an important therapeutic target.

GLP- 1 receptor agonists (GLP- 1RAs) emulate the endogenous GLP- 1 activity and have a pleiotropic effect, such as stimulating glucose- dependent insulin release, inhibiting glucagon release, slowing gastric emptying, and reducing central appetite. All these mechanisms play a role in the enhancement of glycemic control and considerable weight loss. It has been shown in clinical trials that GLP- 1RAs, including liraglutide and semaglutide, can result in significant weight loss and body weight reduction in patients with type 2 diabetes, as well as significant weight loss advantages in non-diabetic groups. New dual and triple incretin agonists, such as tirzepatide and retatrutide, also increase the therapeutic effect, showing a better response in weight loss and metabolism.

Although they have positive efficacy, GLP-1RAs have gastrointestinal adverse effects that are usually temporary and can be controlled. Altogether, incretin-based therapies are a revolutionary breakthrough in obesity treatment, which can be doubly beneficial in terms of weight loss and metabolic well-being. The review identifies the mechanistic foundations, clinical effectiveness, and the emerging therapeutic potential of GLP-1-based interventions, as a means of dealing with the worldwide obesity crisis.

Keywords: Obesity, GLP-1 receptor agonists, Incretin therapy, Weight loss, Type 2 diabetes mellitus, Appetite regulation, Metabolic disorders

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Introduction

The WHO describes obesity as a chronic, multifactorial illness, which is excess or abnormal fat accumulation, and which is associated with a high risk of health. It has a strong linkage with an augmented rate of non-communicable diseases, such as type 2 diabetes mellitus, cardiovascular disorders, and some types of cancer. Moreover, being overweight has a negative impact on musculoskeletal strength, its reproductive, and general well-being, which frequently worsens the quality of sleep and physical mobility [1].

Most commonly, overweight and obesity are assessed by measuring the Body Mass Index (BMI) which is defined as weight in kilograms divided by height in meters squared (kg/m 2). Although the use of BMI in screening is popular, it is known to be an indirect measure of adiposity. Therefore, other anthropometric measures, including waist circumference and waist-to-hip ratio, are suggested to give a more accurate assessment of the fat distribution in the middle and risk of metabolism [1].

Recent discoveries have pointed obesity as a chronic condition that is physiologically regulated to maintain a high body-weight set point, despite lifestyle changes. Obesity rates in the United States of generalized, extreme, and central obesity are on the increase in all age groups, reaching a high prevalence in midlife and significant sex, race, and ethnicity differences, especially among Black women and Hispanics. The rising prevalence among children and adolescents is an urgent societal health issue, which has led to the obesity epidemic worldwide, increased health-care expenditures, and health-system burdens. To overcome this dilemma, it is necessary to tackle this issue through innovative social and economic approaches that are geared towards prevention [2].

The endogenous incretin hormone glucagon-like peptide-1 (GLP-1) is produced by special endocrine cells of the small intestine and colon known as enteroendocrine L-cells. It has a central influence in the control of the postprandial glucose metabolism by combining signals that increase the release of insulin in response to glucose, inhibit the secretion of inappropriate glucagon, slow the emptying of the gastric sac, and alter the sensation of appetite via the central pathways. Taken together, these measures help to optimize the processing of nutrients and the balance of energy following the consumption of food [3].

GLP-1 receptor agonists and DPP-4 inhibitors that either replicate or extend endogenous GLP-1 stimulation have become the mainstay therapy in the treatment of type 2 diabetes mellitus and are finding greater application in the pharmacotherapy of obesity. Moreover, more resistant analogs of this peptide with longer half-life and increased receptor specificity are also being developed in clinical trials, highlighting the broadening translational potential of this peptide in metabolic health, disease prevention, and therapeutic discovery [3,4].

The problem of obesity, which is characterized by the excessive accumulation of adipose tissue and is associated with a high level of risk in metabolic and cardiovascular disorders, has become a worldwide health concern.

The current review will outline the mechanistic foundations of GLP-1 physiology, discuss the role of GLP-1 in the pathophysiology of obesity and metabolic disease, and summarize the existing data on the use of GLP-1 in therapy, thus giving a more inclusive view of its clinical and translational relevance.

Pharmacological agents like orlistat, naltrexone-bupropion and phentermine-topiramate and more recently, GLP-1 receptor agonists are also additionally advantageous but not equally effective, safe and accessible. The shortcomings of these treatments and the general requirement of better and more sustainable, patient-friendly therapies bring about the potential benefits of

GLP-1 receptor agonists in managing obesity in both glycemic and non-glycemic groups [5].

Current Management Approaches

Management of obesity traditionally relies on a multifactorial approach encompassing lifestyle interventions, pharmacotherapy, and surgical options:

- ***Lifestyle Modification*:** Calorie-restricted diets, increased physical activity, and behavioral interventions remain the cornerstone of obesity treatment. Despite initial effectiveness, long-term adherence is challenging, and weight regain is common [6].
- ***Pharmacological Therapy*:** Currently approved medications include orlistat, naltrexone-bupropion, phentermine-topiramate, and glucagon-like peptide-1 receptor agonists (GLP-1 RAs) such as Liraglutide and Semaglutide. These agents offer modest to substantial weight loss but vary in efficacy, safety profile, and tolerability. Accessibility and cost continue to be barriers in many regions [7].
- ***Bariatric and Metabolic Surgery*:** Surgical procedures such as Roux-en-Y gastric bypass and sleeve gastrectomy provide the most significant and sustained weight reduction. They also improve obesity-related comorbidities, including T2DM remission. However, surgery is invasive, costly, and not universally accessible, with risks of long-term nutritional deficiencies [8].

Need for Improved Therapies

The shortcomings of lifestyle change, small effectiveness of available pharmacological therapies, and limited access to bariatric surgery underscore the clinical gap of safer, more effective, and broadly available treatment modalities. GLP-1 receptor agonists, in this regard, have not only been noted to have glycemic potential in diabetes, but also have been found to have strong and sustained weight-loss potential in diabetic and non-diabetic populations.

Role of GLP-1 Receptor Agonists in Obesity Treatment

The Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RA) is a groundbreaking type of therapeutic agent in the treatment of obesity, largely because of their multidimensional effects on the body besides controlling glycemic levels, which involves the control of energy balance and body fat [9,10]. These agents regulate appetite and satiety, resulting in a lowering of caloric intake and consequently weight loss of both individuals with and without type 2 diabetes mellitus [11,12]. Their effectiveness in encouraging substantial weight loss has been observed in a wide range of groups, such as pediatric groups which highlights their universal usage [13,14]. In addition to appetite control, GLP-1 RAs have pleiotropic effects through improved mitochondrial activity, anti-inflammatory, and overall metabolic control [15]. This makes GLP-1 RAs an attractive drug treatment of obesity that can be used in the future, instead of conventional methods of weight loss, to treat dysregulations in physiology [14].

Glycemic vs. Non-Glycemic Populations: A Comparative Analysis

Here, the detailed efficacy and safety profiles of GLP-1 RAs in these different patient groups will be explored and the differences in weight loss, metabolic benefits, and incidence of adverse events analyzed. In particular, the impact of GLP-1 RAs on glucose homeostasis and body weight in diabetic and normal subjects will also be brought into the limelight with recognition of their pleiotropic actions, not limited to glucose regulation but also to cardiometabolic well-being and renal safeguards [16]. Moreover, the role of the described agents and their effects on appetite and satiety in regulating the total energy consumption and leading to sustainable weight loss in a wide range of patient phenotypes will also be examined [17,18]. Knowledge of these differences is important in maximizing treatment plans and the prescription of GLP-1 RA to meet the needs of different patients with comorbid conditions [20]. Considering the proven efficacy of GLP-1 RAs in both glycaemic and non-glycaemic groups, with their significant effects on weight loss, the analysis of their therapeutic

opportunities and drawbacks should be performed thoroughly [21,22]. In particular, the long-term studies have confirmed the maintained weight loss with GLP-1 RAs, including semaglutide and liraglutide, in randomized controlled trials over a duration that can be longer than 40 weeks with a positive safety profile mainly comprised of gastrointestinal side effects [23]. Recent multi-target agents, including retatrutide, are even more effective in weight loss and still have tolerable levels, broadening the therapeutic index in the treatment of obesity [24]. The new semaglutide and tirzepatide, which are approved by the FDA, have further cemented the role of GLP-1 RAs in the management of obesity, with tirzepatide showing better results in weight loss outcomes than semaglutide, especially in people with type 2 diabetes [25]. The clinical effectiveness of GLP-1RAs, such as liraglutide, semaglutide, and tirzepatide, to achieve significant weight loss in patients with obesity, is further supported by real-world data [26]. Furthermore, the therapeutic benefit of GLP-1 RAs does not only include weight loss but also major changes in cardiovascular risk factors, fatty liver disease markers, and renal functions [27].

Mechanisms of Action of GLP-1 Receptor Agonists

GLP-1 Receptor Activation and Signaling Pathways

GLP-1 RAs are analogs of the endogenous incretin hormone GLP-1, which binds to its G-protein coupled receptors to activate intracellular signaling cascades that control glucose-dependent insulin secretion, glucagon suppressions, and gastric emptying [28]. The result of this activation of mechanisms is a complicated metabolic, cardiovascular, inflammatory, and neurohormonal process, thus affecting the total energy homeostasis and delivering systemic therapeutic effects [29]. These agonists also alleviate ectopic fat build-up in hepatic and muscular tissues, thus boosting insulin sensitivity and altering lipid profiles [30].

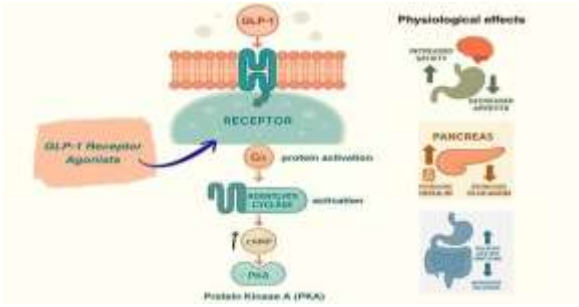

Fig.01: GLP-1 Receptor Activation and Signaling Pathways

Effects on Appetite Regulation and Satiety

The agonists regulate the central nervous system and pathways that control hunger and reward, and in doing so, reduce caloric intake and stimulate a sense of fullness [31]. This process occurs via both direct and indirect routes that influence regions of the brain like the hypothalamus and brainstem, which play a significant role in energy balance. In addition to central actions, GLP-1 RAs also slow down gastric emptying, an action that further promotes long-term satiety and decreased postprandial glucose excursions. This complex intervention on central and peripheral physiological mechanisms highlights their efficacy in inducing considerable and long-term weight reduction in various populations [32-35].

In fact, recent studies have shown that GLP-1RA such as Semaglutide has a considerable anti-obesity effect in lowering the body mass index and waist circumference in non-diabetic overweight and obese patients. This effectiveness extends to the enhancement of many metabolism parameters making GLP-1 RAs an important therapeutic tool in the overall management of obesity [36,37].

Additionally, GLP-1 RAs like Liraglutide, semaglutide and tirzepatide have proven to be highly effective in weight-loss, with regards to their tolerability and risk factors. The main mechanisms in which these agents act are: to reduce weight by regulating hypothalamic hunger and satiety centers which suppress appetite, and also by slowing down

gastric emptying and increasing insulin secretions. Not only does this dual action help in reducing weight but also enhances glycemic regulation making GLP-1 RAs appealing agents in the management of obesity especially in people with concomitant type 2 diabetes [38-41].

Impact on Gastric Emptying and Nutrient Absorption

The postponement of gastric emptying caused by GLP-1 RAs helps in controlling postprandial glucose and increasing satiety, which in turn helps in supporting their weight management effects. This physiological process slows down the digestion process hence extending the feeling of fullness and thus lowering total caloric intake. Pharmacological experiments have further demarcated that this gastric slowing is majorly in the first post-prandial hour indicating that there are other mechanisms besides generalized gastric stasis that contribute to the weight loss mediated by GLP-1RA [42,43]. Moreover, GLP-1RAs have been demonstrated to decrease energy consumption and elevate satiety, some of which have shown this effect occurs through both peripheral and central mechanisms. This overall energy balance and metabolic regulation highlights the potential of GLP-1RAs in treating obesity in various patient groups [44,45].

Influence on Insulin Secretion and Glucose Metabolism

GLP-1RAs enhance insulin secretion in a glucose-dependent manner and suppress glucagon secretion, thereby lowering blood glucose levels. This glucose-dependent mechanism minimizes the risk of hypoglycemia while effectively improving glycemic control in patients with type 2 diabetes. Beyond their glycemic effects, GLP-1RAs also demonstrate direct protective effects on pancreatic beta cells, including enhancing beta-cell proliferation and inhibiting apoptosis. These actions collectively contribute to improved pancreatic function and glucose homeostasis, underscoring their utility beyond mere glycemic reduction. In addition to glucose regulation, GLP-1 RAs are known to enhance β-cell function and stress resistance, which may contribute to slowing the progression of diabetes [46-49].

Efficacy of GLP-1 Receptor Agonists in Glycemic Populations

Clinical Trials in Type 2 Diabetes Patients with Obesity

Particularly, GLP-1RAs enhance glycemic regulation through increased insulin release in response to glucose, decreased glucagon release, and increased peripheral insulin sensitivity, which jointly result in significant improvements in the levels of HbA1c. Moreover, these agents also exhibit a noteworthy enhancement in postprandial hyperglycemia, by decelerating gastric transit, thereby regulating nutrient absorption and alleviating salient glucose surges after meals. This long-term glycemic control is usually supported by a clinically significant reduction in weight, a vital advantage considering the high rate of obesity in people with type 2 diabetes. The mechanism that contributes to the weight-reducing effects of GLP-1RAs, e.g. semaglutide, liraglutide, tirzepatide, is their capacity to enhance the feeling of satiety and decrease caloric intake by the central and peripheral pathways [50-54].

A number of randomized controlled trials have established that GLP-1RAs result in a significantly larger weight loss than placebo or other glucose-lowering medications, as a single agent and an adjunct agent. This effectiveness is carried over to cardiovascular outcomes and renal protection, which further confirms their application in the overall management of diabetes. In addition to glycemic and weight effects, GLP-1RAs have also shown pleiotropic effects, such as the reduction in blood pressure and lipid profile, which further alleviates cardiovascular risk factors that are often related to type 2 diabetes and obesity. These larger metabolic benefits highlight their usefulness in controlling the complicated interaction of diabetes, obesity and cardiovascular disease [54-59].

Weight Loss Outcomes and Glycemic Control

An example is the case of GLP-1 receptor agonists that decrease the HbA1c by 1.5-1.8% and body weight by 4.5-6.4 kg in individuals with type 2 diabetes. These drugs produce substantial improvements in HbA1c and body weight, 12.0 to 17.5 mmol/mol and up to 12.4 percent body weight loss, respectively, in type 2 diabetic people. Although

weight loss is a major factor in long term glycemic benefit with GLP-1 RAs, especially with long actuities, patients who lose weight insignificantly might not gain major benefits in glycemic control [60,61].

As an example, dulaglutide specifically works well in the management of the type 2 diabetes, which can be used in both primary and secondary prevention of major adverse cardiovascular events. These agents can also provide a lesser risk of hypoglycemia than insulin, further increasing their therapeutic benefit in controlling type 2 diabetes. In people with type 2 diabetes, tirzepatide has been shown to result in superior changes in HbA1c and bigger weight reduction after 40 weeks of treatment with tirzepatide versus semaglutide 1 mg, a single time weekly. In addition, semaglutide has been demonstrated to be statistically better than other GLP-1 RAs in glycemic control and weight loss. Predictors of response to GLP-1 RAs however, might differ between agents, although higher levels of HbA1c at baseline of treatment correlate with greater activity, despite the fact that body weight and disease duration does not appear to influence their activity [62-65].

Clinical Evidence of GLP-1 Receptor Agonists in Obese Individuals Diabetes: Weight Loss and Metabolic Outcomes

In a variety of clinical trials, GLP-1 receptor agonists and dual incretin therapies have been demonstrated to significantly decrease body weight and enhance glycaemic control in individuals with type 2 diabetes and obesity. In the STEP-2 trial, semaglutide 1 mg once a week led to a body weight reduction of 9.6% and a HbA1c reduction of 1.6% over 68 weeks, as Shown in Table 1. In the SUSTAIN-7 trial, semaglutide decreased HbA1c by 1.5-1.8% at 40 weeks and resulted in 5-6 kg reduction in weight. Liraglutide 3 mg was found to reduce weight (6%), and HbA1c (1.3) in the 56-week SCALE Diabetes trial. Weight reduction of 4-5 kg and HbA1c of 1.6-1.9% in 56 weeks were found with dulaglutide in AWARD-11. Tirzepatide was the most effective drug in the SURPASS-2 trial, leading to a weight loss of 7-9.5 kg and a 2.0-2.3% decrease in HbA1c in 40 weeks [66-70].

These findings are in line with the two-fold advantage of GLP-1-based therapy to treat obesity and diabetes because they demonstrate the effective response of GLP-1-based therapy to weight management as well as glycaemic control in diabetic groups.

Adverse Effects and Tolerability in Glycemic Populations

GLP-1 receptor agonists and tirzepatide are usually well-tolerated in patients with type 2 diabetes, but the most commonly reported adverse events are gastrointestinal. Nausea, vomiting, and diarrhoea are typically acute, dose-related and most noticeable on initiation of treatment. There have also been reports of mild constipation and injection-site reactions. The safety profile of glycaemic populations is good generally since there are no severe adverse events and the discontinuation rates due to adverse events are not high [66-70].

Drug	Clinical Trial	Population	Duration	HbA1c Reduction	Weight Change	Reference
Semaglutide 1 mg	STEP-2	T2DM + overweight/obesity	68 weeks	−1.6%	−9.6% body weight	66
Semaglutide	SUSTAIN-7	T2DM	40 weeks	−1.5% to −1.8%	−5–6 kg	67
Liraglutide 3 mg	SCALE Diabetes	T2DM + obesity	56 weeks	−1.3%	−6.0% body weight	68
Dulaglutide	AWARD-11	T2DM	56 weeks	−1.6% to −1.9%	−4–5 kg	69
Tirzepatide	SURPASS-2	T2DM	40 weeks	−2.0% to −2.3%	−7–9.5 kg	70

Table 1: Efficacy of GLP-1 Receptor Agonists in Weight Loss with Diabetic Populations

The table recaps in the STEP-2 and SUSTAIN-7 trials, semaglutide showed substantial changes in glycemic control with a decrease in HbA1c by an average of 1.5-1.8% and an observed weight loss. The SCALE Diabetes trial demonstrated a moderate weight loss and a large HbA1c decrease (~1.3) with liraglutide in patients with T2DM and obesity. Dulaglutide also showed a slight weight loss and HbA1c of 1.6-1.9 in AWARD-11 trial. Remarkably, the greatest Glycemic improvement was observed in the SURPASS-2 trial with the dual incretin agonist tirzepatide, which resulted in significant weight loss (7-9.5 kg) and HbA1c (reduction) of up to.
2.3%.

Comparative Efficacy of Tirzepatide and Semaglutide in Diabetic Populations: -

Direct treatment comparisons show that tirzepatide is superior to semaglutide 2 mg in weight reduction in type 2 diabetes patients over a span of 40 weeks, in the SURPASS and SUSTAIN FORTE trials. Tirzepatide 5 mg and semaglutide 2 mg had similar weight loss outcomes, whereas tirzepatide 10 mg and 15 mg led to additional weight loss of about 3.15 kg and 5.15 kg, respectively [71].
These findings corroborate the established glycemic advantages of tirzepatide and suggest a dose-dependent effect in decreasing weight in diabetic populations compared to semaglutide.

Drug	Clinical Trial	Population	Duration	Weight Change
Tirzepatide 5 mg	Indirect treatment comparison (SURPASS trials vs SUSTAIN FORTE)	Type 2 diabetes patients	40 weeks	Similar to semaglutide 2 mg
Tirzepatide 10 mg	Indirect treatment comparison (SURPASS trials vs SUSTAIN FORTE)	Type 2 diabetes patients	40 weeks	−3.15 kg greater weight loss vs semaglutide 2 mg
Tirzepatide 15 mg	Indirect treatment comparison (SURPASS trials vs SUSTAIN FORTE)	Type 2 diabetes patients	40 weeks	−5.15 kg greater weight loss vs semaglutide 2 mg
Semaglutide 2 mg	Indirect treatment comparison (SURPASS trials vs SUSTAIN FORTE)	Type 2 diabetes patients	40 weeks	Reference comparator

Table 2: Comparing the Effects of Semaglutide and Tirzepatide on Weight Loss in Type 2 Diabetes [71]

This table describes Tirzepatide 10 mg and 15 mg produced Considerably greater body-weight reduction compared with semaglutide 2 mg, with estimated treatment differences of −3.15 kg and −5.15 kg respectively at week 40.

Efficacy of GLP-1 Receptor Agonists in Non-Glycemic Populations

Clinical Evidence of GLP-1 Receptor Agonists in Obese Individuals without Diabetes: Weight Loss and Metabolic Outcomes –

In obese people without diabetes, GLP-1 receptor agonists and dual incretin therapies have shown notable improvements in metabolism and cardiovascular health in addition to weight loss. Semaglutide 2.4 mg in the STEP trials reduced weight by 14.9–17.4%, enhanced insulin sensitivity, and slightly decreased fasting glucose, as Shown in **Table 3 [72-75]**. Liraglutide 3 mg reduced weight by about 8% while improving cardiovascular and glycaemic markers [76]. In the SURMOUNT trials, tirzepatide demonstrated the highest efficacy, reducing weight by 20.9–26%

while also improving blood pressure, lipid profiles, and insulin sensitivity [77].

Overall, these treatments offer the dual advantages of significant weight loss and decreased cardiovascular risk, which supports their growing role in the treatment of obesity.

Adverse Effects and Tolerability in Non-Glycemic Populations

GLP-1 receptor agonists and tirzepatide are generally well tolerated in obese individuals without diabetes but gastrointestinal side effects are most commonly reported. Diarrhoea, nausea and vomiting are generally transient and in dose-dependent fashion, often at the beginning of treatment [72,73,77]. Mild constipation as well as injection-site reactions have been reported. The adverse events are few and rates of discontinuation due to side effects are low indicating a reasonably good tolerability profile in non-glycemic populations.

Drug	Clinical Trial	Population	Duration	Weight Loss	Glycemic Change	Reference
Semaglutide 2.4 mg	STEP-1	Overweight/obesity without diabetes	68 weeks	−14.9% body weight	Fasting glucose ↓ ~5–6 mg/dL	72
Semaglutide 2.4 mg	STEP-3	Obesity + lifestyle therapy	68 weeks	−16.0% body weight	Improved insulin sensitivity	73
Semaglutide 2.4 mg	STEP-4	Obesity without diabetes	68 weeks	−17.4% body weight (continued therapy)	-	74
Semaglutide 2.4 mg	STEP-5	Obesity without diabetes	104 weeks	−15.2% body weight	Improved glycemic markers	75
Liraglutide 3 mg	SCALE Obesity & Prediabetes	Obesity without diabetes	56 weeks	−8.0% body weight	Reduced progression to diabetes	76
Tirzepatide	SURMOUNT-1	Obesity without diabetes	72 weeks	−20.9% body weight	Significant improvement in glucose metabolism	77
Tirzepatide	SURMOUNT-3	Obesity without diabetes + lifestyle intervention	72 weeks	−24–26% body weight	Improved insulin sensitivity	77

Table 3: Efficacy of GLP-1 Receptor Agonists in Weight Loss in Non-Diabetic Populations

In the STEP trials, this table outlines the constant improvement of fasting glucose and insulin sensitivity of semaglutide and a considerable reduction in weight of approximately 14-16 percent after 68-104 weeks. In people with obesity and prediabetes, liraglutide decreased the risk of developing diabetes and caused moderate weight loss (~8%) in the SCALE trial. Interestingly, in the SURMOUNT trials, the dual GIP/GLP-1 agonist tirzepatide exhibited the greatest reduction in weight, up to 24-26 per cent body weight loss in combination with lifestyle changes. These findings show that incretin-based medication is becoming an important clinical approach that is effective in the management of obesity and metabolism.

Comparative Analysis: Glycemic vs. Non-Glycemic Populations

GLP-1 Receptor Agonist	Clinical Trial	Population	Duration	Mean Weight Loss	Reference
Semaglutide 2.4 mg	STEP-1	Obesity without diabetes	68 weeks	−14.9% body weight	72,78
Semaglutide 2.4 mg	STEP-2	Type 2 diabetes + obesity	68 weeks	−9.6% body weight	66
Semaglutide 2.4 mg	STEP-3	Obesity without diabetes + lifestyle therapy	68 weeks	−16.0% body weight	73
Semaglutide 2.4 mg	STEP-4	Obesity without diabetes	68 weeks	−17.4% body weight (continued therapy)	74
Semaglutide 2.4 mg	STEP-5	Obesity without diabetes	104 weeks	−15.2% body weight	75
Liraglutide 3 mg	SCALE Obesity & Prediabetes	Obesity without diabetes	56 weeks	−8.0% body weight	76
Liraglutide 3 mg	SCALE Diabetes	Type 2 diabetes	56 weeks	−6.0% body weight	68
Tirzepatide	SURMOUNT-1	Obesity without diabetes	72 weeks	−20.9% body weight	77
Tirzepatide	SURMOUNT-3	Obesity without diabetes + lifestyle intervention	72 weeks	−24.3% to −26.6% total weight loss	
Tirzepatide	SURPASS-2	Type 2 diabetes	40 weeks	−7 to −9.5 kg	69

Table 4: Comparative Analysis of both Glycemic and non-glycemic population

GLP-1 receptor agonist and dual incretin clinical trials show promising improvements in the treatment of obesity. Semaglutide 2.4 mg has been shown to result in significant weight loss (~15-17) in non-diabetic individuals, and a smaller, but not zero, weight loss in type 2 diabetes patients. These effects have been shown to be sustainable over the long term, but the continued treatment is required to avoid weight regain.

Liraglutide 3 mg is moderate (~68% weight loss) and therefore, not as potent as semaglutide. Conversely, dual GIP/GLP-1 receptor agonist tirzepatide has shown better results, with weight loss of more than 20

percent, especially used in conjunction with lifestyle changes.

These conclusions, in general, outline that incretin-based treatments are a useful and clinically significant intervention to treat obesity and that newer agents have increased efficacy.

Adverse Effects and Tolerability of GLP-1 Agonists in Diabetic and Non-Diabetic Populations

GLP-1 receptor agonists (semaglutide, liraglutide) and dual GIP/GLP-1 agonist tirzepatide are well tolerated by diabetic and non-diabetic populations and gastrointestinal events are the most commonly reported side effects. The constipation is uncommon, diarrhoea is frequent, and nausea and vomiting are frequent in individuals with type 2 diabetes; similar but mostly less common occurrences are observed in non-glycemic obese populations. Although hypoglycemia is not common, but may occur, especially in combination with insulin treatment, injection site reactions are common in both groups

Drug	Adverse Effect	Glycemic Population (Type 2 Diabetes)	Non-Glycemic Population (Obesity/Overweight)	Clinical Implications	References
Semaglutide	Nausea/Vomiting	Frequently reported; higher incidence than placebo	Common (~10–15%)	Dose-related; transient	79,82
	Diarrhea	Common (~10–20%)	Moderate (~5–10%)	Self-limiting	80,83
	Constipation	Occasional	Low to moderate	Dietary management	81,84
	Retinopathy	Slight increased risk	Not reported	Monitor carefully	87
	Injection-site reactions	Common	Common	Proper technique required	88,89
	Hypoglycemia	Rare; higher with insulin	Rare	Adjust therapy	12
Liraglutide	Nausea/Vomiting	Frequent early phase	Common (~10–15%)	Dose-dependent	79,82
	Diarrhea	Moderate	Moderate	Self-limiting	80,83
	Constipation	Reported	Less frequent	Symptomatic treatment	81,84
	Gallbladder disease	Increased risk	Limited data	Monitor	85,14
	Injection-site reactions	Common	Common	Rotate sites	90,91

Tirzepatide	Nausea/Vomiting	Common	Frequent	Dose escalation helps	82,83
	Diarrhea	Frequent	Moderate	Transient	83
	Constipation	Occasional	Occasional	Mild	84
	Gallbladder disease	Emerging evidence	Limited	Further study needed	85,92,93
	Pancreatitis	No consistent increase	Insufficient data	Use caution	86,94,95

Table 5: Adverse Effects and Tolerability of GLP-1 Agonists in Diabetic and Non-Diabetic Population

Other side effects are that semaglutide has a slightly risk of retinopathy increase in diabetic patient groups and emergent gallbladder disease and pancreatitis with liraglutide and tirzepatide, although such events are rare On balance, these therapies possess a good safety profile, and most side effects are dose-dependent and short-lived and can be treated with supportive care or progressive dose increase.

Emerging GLP-1 Receptor Agonists and Combination Therapies

In addition to approved GLP-1RAs, novel therapeutic agents and combinations, including dual GLP-1/GIP agonists, including tirzepatide, and new triple agonists, are under development to further improve metabolic effects and therapeutic coverage. These new-generation treatments are intended to utilize the synergistic effects to obtain greater weight reduction and cardio metabolic benefits, especially in patients not responding to monotherapy [96,97].

Indicatively, semaglutide with cagrilintide is currently in Phase III development, and other non-peptide small molecule GLP-1 agonist (oral) agents that have a higher therapeutic potential because they reduce gastrointestinal adverse events due to a gradual up-titration. This method aims to maximize patient tolerability and maximize efficacy, which is why it is important to overcome the major obstacle to long-term adherence in the treatment of obesity [98,99].

The discovery of multi-agonist therapies, including dual GLP-1/GIP agonists and triple agonists like retatrutide, is a promising development in pharmacological management of obesity, and could potentially be more effective and more tolerable since it activates more than one incretin pathway [100,101].

Additional studies efforts are focused on clarifying the long-term safety outcomes and expanded clinical applicability of these new and combination treatment approaches. This will involve assessing their relative effectiveness to the current GLP-1 RAs and investigating their potential in the various patient groups. Additionally, upcoming studies will evaluate the effects of dual GLP-1/GIP receptor agonists on cardiovascular and all-cause mortality, and cardiovascular safety of oral GLP-1 RAs, among obese individuals. [102-105]

Conclusion

Individuals who do not have type 2 diabetes usually shed a lot of weight compared to those who have the conditions. Newer dual incretin agonists such as tirzepatide (compared to traditional GLP-1 receptor agonists) have a greater weight loss (20-25%). Overall, these results show that incretin-based treatments are important therapeutic options for the treatment of Type 2 Diabetes Mellitus and related obesity because they are very successful in enhancing glycemic control while also promoting weight loss. GLP-1 receptor agonists are considered to be safe and well-tolerated, although this group of medication requires proper patient selection, dosing, and follow-up to minimize the side effects and optimize treatment outcomes.

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