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Review

A Scoping Review on Recent Advances in Antidiabetic Medications: From GLP-1 Receptor Agonists to Dual and Triple Agonists

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Abstract

The management of type 2 diabetes mellitus (T2DM) has evolved substantially with the development of incretin-based therapies targeting the glucagon-like peptide-1 receptor (GLP-1R), glucose-dependent insulinotropic polypeptide (GIP) receptor, and glucagon receptor. This review provides a comprehensive overview of the mechanisms, clinical efficacy, and therapeutic relevance of GLP-1 receptor agonists (GLP-1 RAs), dual GLP-1/GIP receptor agonists, and emerging triple agonists targeting GLP-1, GIP, and glucagon receptors. GLP-1 RAs, now well-established in clinical practice, offer robust glycemic control, weight reduction, and proven cardiovascular and renal benefits through glucose-dependent insulinotropic effects, appetite suppression, and cardiometabolic protection. Dual agonists, such as tirzepatide, expand upon these benefits by simultaneously activating the GIP receptor, yielding superior glycemic efficacy and unprecedented weight loss, alongside potential insulin-sensitizing effects. The latest innovation, triple agonists like retatrutide, incorporate glucagon receptor activation to further enhance energy expenditure, fat loss, and metabolic flexibility, with promising early results in obesity, diabetes, and nonalcoholic fatty liver disease. Together, these agents represent a significant therapeutic advancement in T2DM, with increasing potential for comprehensive cardiometabolic disease management. This review summarizes current evidence from clinical trials and mechanistic studies, discusses comparative benefits, and highlights future directions for optimizing their clinical use.

Keywords

GLP-1 receptor agonists, Dual GLP-1/GIP receptor agonists, Triple GLP-1/GIP and glucagon agonists, Type 2 diabetes mellitus, Management, Cardiometabolic protection

Article History

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1. Introduction

Type 2 diabetes mellitus (T2DM) represents a multifaceted metabolic condition which produces long-term elevated blood sugar levels due to insulin resistance and continuous pancreatic β-cell damage. The worldwide increase of this condition shows no signs of stopping since there were 537 million diagnosed patients in 2021 while experts estimate the number will reach 783 million by 2045 Healthcare systems face significant strain because of the disease's microvascular and macrovascular consequences [1]. While traditional glucose lowering therapies such as metformin, sulfonylureas, and insulin have been the mainstay of T2DM management for many years, they have not directly addressed prevention of weight gain, cardiovascular outcomes, or long-term β-cell health, leading to innovation and new treatment types.

In the last two decades, glucagon-like peptide-1 receptor agonists have developed into the most significant incretin-based therapeutic class with efficacy on glycemic control, as well as benefit on weight loss and cardiovascular outcomes [2]. Recently, multi-receptor agonists have been introduced, specifically and most notably, dual incretin agonists targeting GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) like tirzepatide, or triple agonists incorporating glucagon receptor activity as well [3,4]. These drugs have provided a promising paradigm shift in the pharmacotherapy of T2DM, which aim to partly mimic the pleiotropic effects of endogenous gut hormones, and have shown better overall metabolic profiles than GLP-1 monotherapy.

This review will provide an overview of the mechanistic basis, clinical effectiveness, and safety of recently announced and emerging medications with antidiabetic properties, highlight GLP-1 RAs, review the literature on emerging dual incretin agonists, and introduce the newly emerging triple agonists. We aim to summarize the current data from clinical studies and real-world data to demonstrate how these agents are changing the treatment paradigm for T2DM, with concomitant implications for weight management and cardiometabolic health.

2. GLP-1 Receptor Agonists: Mechanisms and Clinical Impact

GLP-1 receptor agonists (RAs) mimic endogenous GLP-1, binding with β-cell GLP-1 receptors and stimulating insulin secretion as well as disengaging glucagon secretion in a glucose-dependent manner via cyclic AMP (cAMP), PI3K, and MAPK signaling pathways. GLP-1 RAs also allow for β-cell survival, replication, and inhibition of apoptosis [5-8]. GLP-1 RAs also slow gastric emptying and increase feelings of fullness using both central and peripheral GLP-1 receptors. This action may ultimately result in decreased values for caloric intake and body mass. Cardiovascular and vascular mechanisms of GLP-1 RA action is supported by many pathways. GLP-1 RAs act supramolecularly by different methods to also have direct effects on the cardiovascular system by increasing NO via eNOS, reducing oxidative stress and inflammation in endothelial cells, increasing mitochondrial biogenesis and function, and providing benefits of antithrombotic properties secondary to decreased platelet activation (GLP-1RA stimulation elevates intracellular cAMP, activating PKA, which inhibits platelet activation pathways. Moreover, GLP-1RAs reduce ADP-, thrombin-, and collagen-induced platelet aggregation) [5,7,9]. GLP-1 RAs also have direct implications for natriuresis; the potential for reduced oxidative stress and inflammation in proximal tubules, and stabilizing renal hemodynamic state via pathways such intrarenal sodium-hydrogen exchanger 3 (NHE3) inhibition [6,10,11]. Across numerous randomized controlled trials and meta-analyses, GLP-1 RAs reduce HbA1c (~0.8–1.5%) and yield significant weight loss via appetite suppression [7,12]. Authors assessed 15 studied with 180000 diabetic subjects in a meta-analysis and revealed that GLP-1Ras were associated with reduced risks of major adverse cardiac events, stroke and myocardial infarction [7].

Agents like liraglutide, semaglutide, dulaglutide, and albiglutide have reported a statistically significant reduction in major adverse cardiovascular events (12-20% reducing major adverse cardiac events) compared to placebo in major clinical studies published to date [13-16]. Their cardioprotective effects have been confirmed with real world data [17-19]. The potential cardiovascular benefits can be due to several mechanisms including improved endothelial function, reduced inflammatory responses, elevated myocardial glucose uptake, decreased cardiomyocyte cell death, reduced epicardial fat, vasodilation, and antithrombotic/anti-platelet aggregation [6,10,11,17,20].

There is real-world evidence of the therapeutic benefits of these medications. Observations and meta-analysis assessments have shown reductions in endothelial and systemic inflammatory biomarkers, carotid intima/media thickness and scored reduced cardiovascular risks after long-term use of GLP-1 RA therapy [21-31]. Tumor necrosis factor -α, IL-6, IL-1β, MCP-1, VCAM-1, IFN-γ are reduced by GLP-1RAs in animal/in vitro models [32]. Moreover, C-reactive protein, interleukin-6, tumor necrosis factor-α, and interleukin-1β are reduced post-treatment in clinical trials (e.g., liraglutide, exenatide) [33]. A systematic review and meta-analysis studied the cardiovascular benefits in 60080 patients with type 2 diabetes and revealed that hospital admission for heart failure, and worsening kidney function, major adverse cardiac events and all-cause mortality were significantly reduced in subjects receiving GLP-1 receptor agonist treatment [22]. Kristensen et al studied data of 56004 diabetic patients on GLP-1 receptor agonist and reported that these drugs were associated with reduced cardiac mortality and improved renal outcomes [23]. In a clinical trial, authors randomized 3183 diabetic subjects into semaglutide or placebo groups and they showed that death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, death from any cause were not higher in semaglutide group compared to controls [30].

Current American Diabetes Association (ADA), European Society of Cardiology (ESC) and American College of Cardiology (ACC) guidelines recommend considering GLP1RA or for T2DM patients with established atherosclerotic cardiovascular disease (ASCVD) or high cardiovascular risk regardless of glycemic control [21,34,35].

These medications have also shown protection on the renal side as well. The GLP-1 RAs reduce new-onset macroalbuminuria (by ~20-30%), slow the decline of estimated Glomerular Filtration Rate (eGFR) and reduce composite renal endpoints in T2DM individuals with chronic kidney disease [22,23,36,37]. There are data from FLOW and post-hoc analyses of LEADER and SUSTAIN-6 indicating that these therapies slow the deterioration of renal function and decrease albuminuria. There are also stated meta-analysis that report 16-22% reduced risk for kidney failure and what are termed major renal outcomes [38,39]. Liraglutide also improves renal outcomes by reducing albuminuria [40].

The side effects of these medications are primarily (but not exclusively) tolerated gastrointestinal effects including nausea, diarrhea and vomiting). Drug related pancreatitis and gallbladder disease are uncommon. Theoretically, thyroid C-cell tumors have been observed in rodent studies, but thankfully not in humans. There are slight reductions in blood pressure and small increases in heart rate [8]. Most GLP-1RAs raise resting HR by ~2–4 beats/min on average. Meta-analyses and program-level safety reviews consistently show a small but persistent increase [41]. In broad T2DM populations, this small HR increase has not negated the CV benefits of several GLP-1RAs (reduced MACE in outcome trials [42]. A mechanistic study showed that GLP-1R have direct chronotropic effects via PKA-dependent Ca^{2+}-cycling ("calcium clock") in pacemaker cells in human/primate sinoatrial node [43].

Table 1 summarizes some of the GLP-1RA drugs and evidence of their renal and cardiovascular beneficial effects.

Table 1. Characteristics and cardiovascular/ renal benefits of GLP-1RA drugs.

Drug	Mechanism / Half life	Cardiovascular benefits	Renal Benefits
Liraglutide	Acylated, 13-h half-life. Decreases gastric emptying, increases insulin, decreases glucagon	LEADER: Decrease major adverse cardiac events; reduction in macroalbuminuria [13].	Reduce albuminuria [44].
Semaglutide	Long-acting, weekly injection/oral. Weight, appetite, β-cell effects	SUSTAIN-6: Decrease major adverse cardiac events [14]. SELECT: Decrease cardiovascular events in non-diabetics [45].	SUSTAIN-6: decreased albuminuria [14]. FLOW: slowing in chronic kidney disease (CKD) progression [46].
Dulaglutide	Weekly dosing; similar glycemic and satiety effects	REWIND: Decreases cardiovascular events [15].	Benefits on albuminuria and slows decrement in eGFR

Indeed, GLP-1 receptor agonists have emerged as one of the most significant therapeutic advancements for T2DM in the past two decades. Unlike traditional glucose-lowering therapies such as sulfonylureas or insulin, which often carry a risk of hypoglycemia and weight gain, GLP-1 RAs offer a glucose-dependent mechanism of action, resulting in potent glycemic control with added benefits of weight loss and cardiometabolic protection [47]. GLP-1 RAs exert multiple beneficial effects such as stimulation of insulin secretion in a glucose-dependent manner, suppression of glucagon secretion during hyperglycemia, delay in gastric emptying, and enhancement in satiety and reduction in appetite. They also promote β-cell preservation by reducing apoptosis and improving insulin biosynthesis. Glycemic efficacy of the GLP-1RA drugs are well established. They successfully reduce HbA1c and promote weight loss. They can also improve insulin sensitivity, which is an effect independent of weight loss. One of the most compelling reasons for the widespread use of GLP-1 RAs in T2DM is their cardiovascular and renal protection effects. As discussed above, many clinical trials and meta-analyses confirmed their benefits in cardiovascular and renal outcomes of diabetic subjects.

It is obvious that the GLP-1 RA class of drugs has changed the standard for diabetes management. They provide robust glycemic control, significant weight loss, and clear cardiovascular and renal effects through multimodal mechanisms. Future studies ought to evaluate long-term safety in more representative populations. Head-to-head comparisons with SGLT2 inhibitors, efficacy in CKD stages 4–5 and non-diabetic populations, and next-gen agents targeting cerebrovascular, hepatic, and neuroprotective outcomes should also be the topic of future studies.

GLP-1 receptor agonists are now central to modern T2DM treatment strategies, offering benefits far beyond glucose control. Their ability to improve weight, cardiovascular, and renal outcomes, while maintaining a favorable safety profile, makes them an essential therapeutic option. Continued research will likely expand their indications and refine their role in precision diabetes and obesity care.

3. Molecular Mechanisms of Incretin Based Therapies

Possible molecular mechanisms of incretin based therapies on cardiovascular benefits include endothelial protection and nitric oxide bioavailability, anti-inflammatory and anti-oxidative signaling, anti-atherosclerotic effects and plaque stability, direct myocardial and microvascular actions, cardio-renal axis, hemodynamic effects via natriuresis and blood pressure, and cardiometabolic risk-factor modification, which is an indirect CV benefit.

Activation of GLP-1R stimulates cAMP and PKA/CREB (and sometimes PI3K/Akt/AMPK) in vascular cells and immune cells, inhibits NF-κB, lowers ICAM-1/VCAM-1, and boosts eNOS activity/NO, which all together improves vasodilation and reduces leukocyte adhesion [48-50]. These effects result in better endothelial function, less oxidative stress (low NADPH oxidase/ROS), and improved coronary microvascular perfusion [51,52].

GLP-1RAs reduce reactive oxygen species (ROS) and blunt pro-inflammatory cytokine production (such as; TNF-α and IL-6) through PKA-mediated NF-κB inhibition and Nrf2-linked antioxidant responses [51,53].

Preclinical/clinical data indicate reduced vascular smooth muscle proliferation, enhanced plaque stability, and preserved endothelial integrity with GLP-1RAs [52,54]. Moreover, GLP-1 signaling promotes natriuresis/diuresis (proximal tubule NHE3 modulation; gut–kidney cross-talk). In rodents, atrial GLP-1R stimulates atrial natriuretic protein (ANP) secretion which links to vasodilation and BP lowering; in humans, natriuresis occurs without consistent ANP rises, suggesting parallel renal mechanisms [55-57]. GLP-1RAs further improve coronary microvascular function and myocardial perfusion, reduce cardiomyocyte apoptosis, and support mitochondrial efficiency in experimental models and small clinical studies [58].

GLP-1RAs lower weight, blood pressure, triglycerides and improve lipoprotein profile; risk-factor shifts that mediate part of the MACE reduction seen in trials [59]. This class of drugs show renal-protective signals (albuminuria reduction; slowed CKD progression in trials), which likely feeds back to CV risk reduction. Mechanistically, natriuresis, anti-inflammation, and improved renal hemodynamics are likely to cause cardiovascular benefits [60].

4. Dual Incretin Agonists: GLP-1/GIP Receptor Agonists

The incretin system, consisting of GLP-1 and GIP, is central to glucose homeostasis. GLP-1 facilitates insulin secretion and reduces glucagon under conditions of high glucose, and GIP primarily activates insulin at lower glucose levels but can also increase fat storage and glucagon in some conditions [47,61-65]. In a "twincretin" form, the goal is to mimic physiological incretin signaling more closely, with the potential to contribute to improved metabolic outcomes.

Tirzepatide is a fatty-acylated 39-amino acid peptide based on the GIP sequence that has GLP-1 activity, created for weekly injection with a half-life of about 5 days [66,67]. Tirzepatide is a strong agonist of cAMP signaling at lower receptor levels with limited β-arrestin signaling, supporting sustained β-cell insulin secretion [66]. Therefore, it is a biased agonist. Tirzepatide improves β-cell function, insulin sensitivity, and glucagon suppression beyond weight loss alone [62,68,69].

Tirzepatide has consistently been associated with HbA1c reductions approaching 2%, and around 11 kg (~11%) of weight loss with the highest doses in 26-week RCTs of T2DM individuals [70-75]. Meta analyses indicated tirzepatide was superior to semaglutide, insulin degludec, and insulin glargine as selective GLP-1 RAs [64,76-78]. Dual agonists favorably induce reductions in both fat and lean mass; of the total weight loss about 25% is comprised of lean mass loss (about 30% in lifestyle induces weight loss).

In addition to glycemic control, tirzepatide also improves insulin resistance, adiponectin levels, and α-cell function in the pancreas [79]. There are encouraging early cardiovascular safety signals, and subsequent meta-analyses confirm cardiac safety [80-82]. Combination activation modulates glucagon; while GLP-1 suppresses postprandial glucagon secretion, GIP allows flexibility in a fasting state, which adds to the overall metabolic control [47]. Overall side effects for dual agonist medications are identical to GLP-1 RA's. Gastrointestinal (GI) side effects; typically mild to moderate (nausea and diarrhea), typically during periods of dose titration, have been reported with tirzepatide treatment [69]. Tirzepatide may confer less GI side effects than compared to GLP-1 monotreatment alone; likely due to the unbalanced agonism physiologically favoring GIP [66]. The risk of hypoglycemia remains very low unless used with other insulin induced medications [65]. Theoretical risk of thyroid C-cell tumors (based on rodent studies) and acute pancreatitis (warning labels) warnings exist with GLP-1 RA's and dual agonist therapy; both are absolute contraindications for patients with a personal or family history of medullary thyroid carcinoma or MEN2 [69].

Most data has come from tirzepatide; there have been few trials with other dual agonists, limiting overall power of meta-analysis. Trial duration (generally ≤40 weeks) likely did not assess long term outcomes (≥1 year) or very rare safety signals/side effects [64]. The absence of direct head-to-head studies of dual agonists comparative to triple agonists, or compared to other preferred therapies selective for obesity, limits therapeutic guidance.

Dual agonists represent an excellent option for patients with obesity with T2DM with considerable glycemic and weight loss needs [65]. Until more data from cardiovascular outcome studies are available, the current standard of care for patients with T2DM and comorbid atherosclerotic cardiovascular disease (ASCVD) remains established GLP-1 receptor agonists (RAs); however, for some the unique benefit of dual agonists (GIP-GLP-1 receptor agonists) will be a consideration in some patients with a major interest in weight management. Ultimately, efficacy will remain dependent on patient reported outcomes: patients hoping for superior weight loss (dual agonists), cardiovascular protection (GLP-1 RAs with known cardiovascular outcome trial benefit), or those tugging at both of these as evidence continues to emerge.

With tirzepatide being the first dual GLP-1/GIP receptor agonist on the market, dual agonists signal a logical next step in incretin-based therapy for T2DM; with the potential for not only effective HbA1c reduction and significant weight loss, but also promising cardiovascular and glucagon axis effects. Key cardiovascular outcome trials are underway, as are head-to-head studies, which will better inform providers of the utility of dual agonists in patient-centered care for diabetes. Safety will continue to be closely monitored; especially long-term safety; to determine if clinical practice guidelines will include their use. Figure 1 provides an overview of the overall effects of dual agonists.

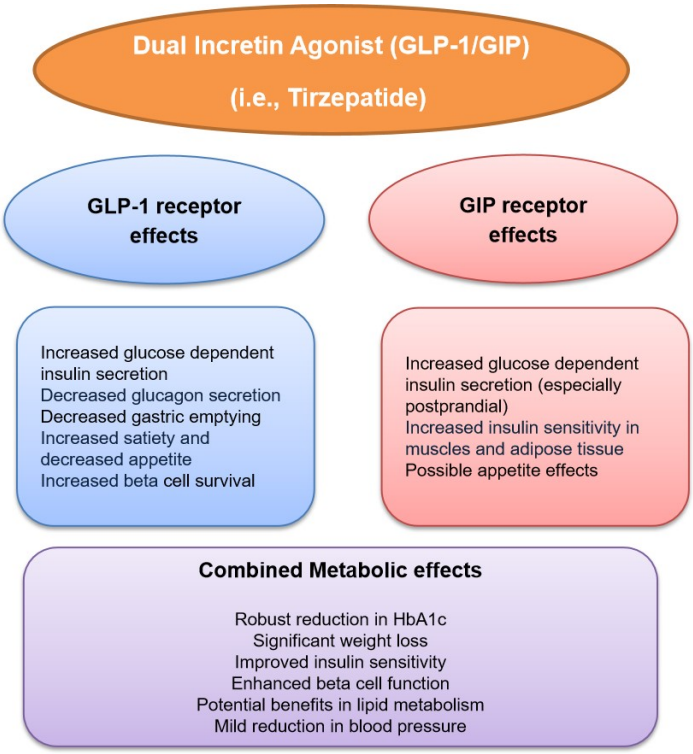

Figure 1. Effects of dual GLP-1 and GIP agonists.

Dual agonists, such as tirzepatide, simultaneously target GLP-1 receptors and GIP receptors. Via GLP-1 receptors they enhance glucose-dependent insulin secretion, suppress glucagon, slow gastric emptying, and reduce appetite. Besides, via GIP receptors, they further augment insulin secretion, improve insulin sensitivity, and may contribute to weight loss. This dual action provides synergistic effects on glucose regulation and weight management. Dual agonists demonstrate superior glycemic control compared to GLP-1 receptor agonists alone, with HbA1c reductions. Significant body weight reductions of 10–15% have been noted, exceeding results with GLP-1 RAs. They also improve insulin sensitivity. Improvements in insulin sensitivity beyond weight loss have been observed with tirzepatide. They have also various cardiac benefits. Tirzepatide has shown favorable effects on blood pressure, lipid profiles, and inflammatory markers (suggesting cardiometabolic benefit). In clinical practice, dual agonists like tirzepatide are now recommended for patients with T2DM and obesity seeking both glycemic control and weight reduction, for those who have inadequate glycemic control on GLP-1 RAs alone. A potential future use could be in obese patients without diabetes and metabolic dysfunction-associated steatotic liver disease (MASLD). Dual GLP-1/GIP receptor agonists represent a major advancement in T2DM therapy by delivering superior glycemic efficacy and unprecedented weight loss compared to existing treatments, while also addressing key cardiometabolic risk factors.

5. Triple Agonists: GLP-1/GIP/Glucagon Receptor Agonists

Triple agonists combine the insulinotropic and anorectic effects of GLP-1 and GIP with glucagon's energy increase. General findings from preclinical studies indicate that these components collectively provide synergistic effects: both GLP-1 and GIP reduce appetite, and promote insulin secretion, while glucagon promotes lipolysis, fatty-acid oxidation, and enhances energy expenditure. Together these effects provide better outcomes than mono and dual agonists for weight and metabolic control [4,83-88].

LY3437943, known as Retatrutide, is a peptide that has balanced agonism with high GIP affinity, and moderate GLP-1/glucagon activity. It is taken via once weekly doses (about 6-day half-life) [85,89]. Preclinical studies showed that it had greater weight loss in obese mice as compared to tirzepatide due to increased energy spending due to glucagon activity [85,87,90,91]. Additional candidates are HM15211 (Efocipegtrutide) and SAR441255 that showed strong weight reductions and increased metabolic outcomes in early studies [92,93]. Authors investigated LY3437943 in a 12-week phase 1b trial of T2DM patients with a proof of concept (expand testing in more populations) and showed dosed-dependent reductions in fasting plasma glucose (est. ~–3 mmol/L), HbA1c (est. ~–1.2 to –1.6%), and body weight loss

(est. at a max ~–9 kg) [4]. It was well tolerated with expected GI reported side effects and appropriate for once weekly dosing [4]. In phase 2 studies, retatrutide has been explored for obesity. In individuals without diabetes, it demonstrated up to 24.2% mean weight loss at 48 weeks [85]. Results from different studies with meta-analysis showed reductions in weight (–14.3%), BMI (on average –5.4 kg/m²) HbA1c (-~0.91%), fasting glucose, and blood pressure (systolic -~9.9 mmHg) in the absence of more adverse events [86]. The MASLD sub study showed >80% relative reduction in liver fat and normalization > 90% of participants at higher doses which could offer significant promise as a potential therapy for NASH [94]. Triple agonists have similar side effects profiles with dual and GLP-1 agonists. GI side effects (nausea, vomiting, and diarrhea) were most subsequently reported and transient or easily dealt with at dosing escalation. There were no signals of major safety concerns, and pancreatitis and thyroid complications were comparable to drugs more classically thought to cause these problems like GLP-1 RAs [91]. The potential for transient heart rate increase can be readily addressed with monitoring. Data continues to emerge; long-term confirmatory trials are pending that will allow claims of beneficial cardiovascular and renal outcomes. Phase 3 trials of retatrutide are ongoing. Comparative data with other established agents, e.g., semaglutide or tirzepatide, are limited. Preclinical models show significant efficacy in animals, but the relationship between dosage-response in humans and what the optimal receptor affinity ratios for agonist therapy should be need further exploration [84].

Triple agonists will provide exceptionally positive reductions in weight and achieve normoglycemia; that might be substantially greater than contemporary GLP-1/GIP dual agonists can provide for treatment of obesity and T2DM, additionally they reduce markers of hepatic steatosis and fibrosis in the treatment of MASLD. Particularly retatrutide show particular promise in this arena in a phase 2 trial [94]. Nonetheless, their potential capacities in terms of cardiometabolic risk reduction and nephroprotection are being assessed.

Triple agonists present a significant advancement in incretin-based therapy, creating a combined effect with the energy expenditure benefits of glucagon to the effects of GLP-1/GIP. It appears early evidence depicts completely unprecedented weight loss (up to 24%), strong glycaemic effects (HbA1c ~1 - 1.6%) and remarkable effects concerning MASLD. Safety appears to be manageable although longer-term outcomes and relative efficacy requires confirmatory phase 3 data. In time, and as investigations unfold, these therapeutics may redefine how we consider management in obesity, diabetes, and metabolic disease. Effects of triple GLP-1/GIP/Glucagon agonists are summarized in Figure 2.

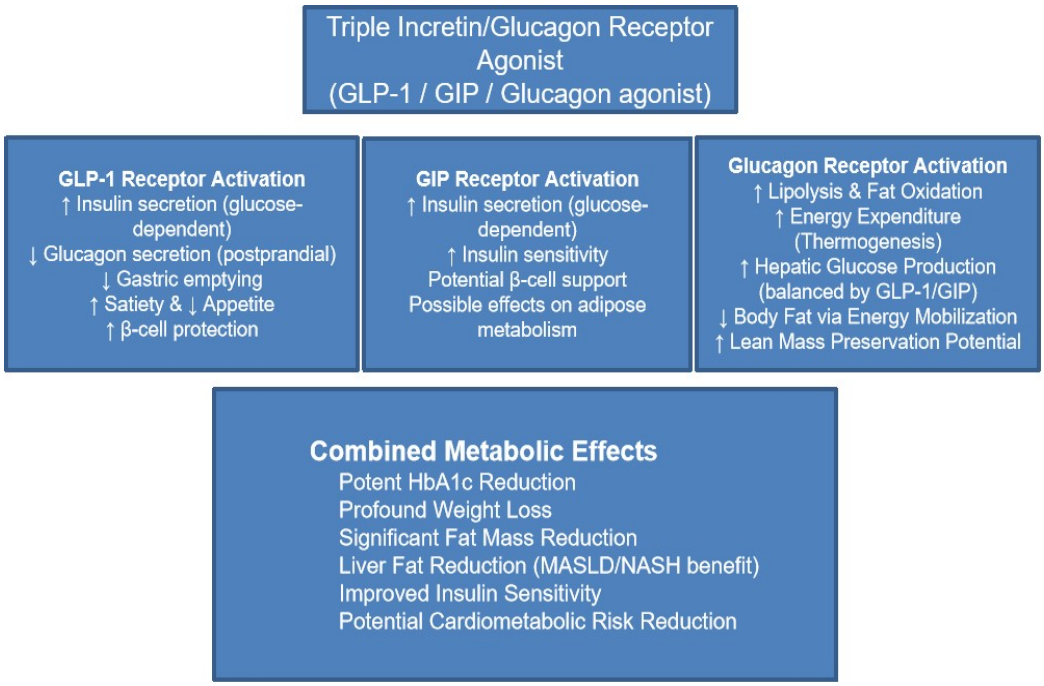

Figure 2. Effects of triple GLP-1/GIP/Glucagon agonists.

6. Conclusions

Recent advances in incretin-based therapies have markedly transformed the management of obesity and type 2 diabetes mellitus. GLP-1 receptor agonists remain the cornerstone of this class, providing robust glycaemic control, clinically meaningful weight loss, and well-established cardiovascular and renal benefits. Their multi-faceted mechanisms—including stimulation of glucose-dependent insulin secretion, suppression of glucagon release, delayed gastric emptying, and appetite reductio—offer a therapeutic effect that extends beyond glucose regulation alone.

Building on this foundation, dual incretin agonists targeting both GLP-1 and GIP (e.g., tirzepatide) have demonstrated superior efficacy in glycaemic control and weight reduction compared with GLP-1 receptor agonists. These benefits are attributed to enhanced β-cell responsiveness and improved metabolic flexibility through the complementary actions of GLP-1 and GIP, with emerging signals of cognitive safety.

Next-generation incretin therapies that also engage the glucagon receptor are showing unprecedented reductions in body weight and liver fat content, along with improved glycaemic outcomes. Triple agonists targeting GLP-1, GIP, and glucagon hold promise not only for type 2 diabetes and obesity but also for broader metabolic disorders, including MASLD.

Although long-term safety and cardiovascular outcome data are still evolving, early results are highly encouraging. Collectively, incretin-based therapies are progressing from GLP-1 receptor agonists to dual and potentially triple agonists, representing a paradigm shift toward treatments that are more potent, durable, and pleiotropic. This evolution signals a move beyond glycaemic control toward comprehensive cardiometabolic health. Future research should focus on long-term outcomes, patient selection strategies, and integration of these therapies into routine clinical practice, ensuring their optimal and safe use in populations most likely to benefit.

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No data generated in preparation of this work.

Conflict of Interest

Nothing to declare.

Generative AI Statement

No Gen AI used in this manuscript.

Abbreviations

ACC: American College of Cardiology

ADA: American Diabetes Association

ANP: atrial natriuretic protein

ASCVD: atherosclerotic cardiovascular disease

cAMP: cyclic AMP

CKD: chronic kidney disease

eGFR: estimated Glomerular Filtration Rate

ESC: European Society of Cardiology

GI: Gastrointestinal

GIP: glucose-dependent insulinotropic polypeptide

GLP: glucagon like peptide

GLP-1 RAs: glucagon like peptide-1 receptor agonists

HbA1c: glycated hemoglobin

MASLD: metabolic dysfunction associated steatotic liver disease

NHE3: Sodium-hydrogen exchanger 3

NO: nitric oxide

RAs: receptor agonists

T2DM: type 2 diabetes mellitus

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