Therapeutics, Pharmacology and Clinical Toxicology

Review

Ther Pharmacol Clin Toxicol
Volume: 24, Issue: 2, April–June 2026

Received: 19 February 2026
Accepted: 7 May 2026

Incretin-based therapy for obesity, part 2: effects on obesity complications

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Abstract

The article reviews the effects of incretin-based therapies on obesity complications, focusing on semaglutide and tirzepatide. Obesity is a prevalent chronic condition linked to serious health issues such as cardiovascular disease, diabetes, and metabolic syndrome. The increasing global obesity rates necessitate effective long-term management strategies. Incretin-based therapies have emerged as promising anti-obesity medications, demonstrating significant benefits in weight loss and metabolic health. Clinical trials, including the STEP and SURPASS programs, reveal that both semaglutide and tirzepatide lead to substantial improvements in metabolic risk factors, such as glycemic control, insulin resistance, blood pressure, and lipid profiles. In terms of specific obesity-related complications, semaglutide demonstrated a significant reduction of major cardiovascular events in patients with established cardiovascular disease and overweight or obesity. Both therapies have notably improved heart failure outcomes, especially in patients with preserved ejection fraction. Emerging data also suggest positive effects on metabolic dysfunction-associated steatotic liver disease (MASLD) and comorbidities like obstructive sleep apnea and knee osteoarthritis, highlighting their multifaceted benefits. As incretin-based therapies continue to evolve, selecting the appropriate treatment is crucial in the presence of obesity complications. Current clinical guidelines recommend semaglutide for patients with cardiovascular disease and either semaglutide or tirzepatide for those with heart failure. This article emphasizes the need for informed decision-making in choosing anti-obesity medications, as they hold potential not only for weight management but also for improving associated health outcomes. Overall, incretin-based therapies represent a significant advancement in tackling obesity and its complications effectively.

Keywords: incretin-based therapies, semaglutide, tirzepatide, obesity, weight loss

Introduction

Obesity is a chronic disease that has emerged as a significant burden on public health, with over 1 billion people estimated to be living with a body mass index (BMI) of ≥30 kg/m^2 in 2025. In 2019, 41 million deaths were due to non-communicable chronic diseases: cardiovascular (CV) disease, cancer, chronic lung diseases, and diabetes, of which 5 million could be directly attributed to high BMI [1]. Over 200 complications of obesity are now recognized as contributors to impaired quality of life, low productivity, absenteeism, and early mortality rates in people living with obesity worldwide [2].

The rising prevalence of obesity is attributed to complex mechanisms and numerous genetic, environmental, and behavioural factors, leading to

an urgent need for effective long-term management strategies also capable of tackling obesity complications.

Since the discovery of incretin-based therapies and their effects on body weight, new anti-obesity medications (AOMs) have become an important therapeutic option for weight loss and weight maintenance, improving metabolic health and reducing the risk or progression of obesity-related complications [2].

This article aims to provide a review of the current evidence, mainly from randomized-controlled studies (RCTs) on the benefits of weekly incretin-based therapies, namely semaglutide, a GLP-1 receptor agonist, and tirzepatide, a dual GLP-1/GIP receptor agonist, in patients with established obesity complications. Through this exploration, we hope to highlight the importance of informed decision-making when choosing the best AOM option in a large category of patients living with obesity complications.

Metabolic effects of weekly incretin-based therapies in obesity

Obesity is closely related to a cluster of metabolic disorders, including diabetes, dyslipidemia, insulin resistance, and hypertension. Incretin-based therapies, particularly semaglutide and tirzepatide, have demonstrated solid metabolic benefits in people with overweight and obesity, with or without type 2 diabetes. Their effects extend beyond weight loss reduction, leading to significant improvements in metabolic risk factors. The Semaglutide Treatment Effect in People with obesity (STEP) and Study of Tirzepatide And SURpass Progress in type-2 diabetes (SURPASS)/SURMOUNT randomized control trials programs demonstrate that both semaglutide and tirzepatide substantially improve multiple metabolic complications of obesity. Tirzepatide (with dual GIP/GLP-1 receptor agonism) generally provides greater improvements in glycemia, insulin resistance, blood pressure, lipid profiles, and metabolic syndrome prevalence compared with the selective GLP-1 receptor agonist semaglutide at the studied doses.

Glycemic control and insulin resistance

Glycemic control is a class effect of incretin-based therapy, with substantial improvements in fasting blood glucose and glycated hemoglobin reported with semaglutide and tirzepatide.

In STEP-2 trial, once-weekly semaglutide 2.4 mg significantly reduced glycated hemoglobin HbA1c (1.6% reduction from baseline at 68 weeks) compared with placebo (0.4% reduction) in subjects with overweight or obesity and type 2 diabetes. The proportion of patients achieving an HbA1c target <7.0% was 78.5% with semaglutide 2.4 mg *vs.* 26.5% with placebo [3]. In an exploratory analysis of STEP-1 and STEP-4 trials, once-weekly semaglutide 2.4 mg significantly reduced fasting plasma glucose (FPG) *versus* placebo in adults with overweight/obesity without diabetes [4]. Although absolute values vary by baseline category, semaglutide consistently lowered FPG beyond weight loss groups *vs.* placebo.

Across SURPASS trials, tirzepatide consistently produced greater reductions in glycated hemoglobin than comparators. In SURPASS-2, tirzepatide lowered HbA1c in a dose-dependent manner over 40 weeks (5 mg: 2.01% reduction, 10 mg: 2.24%, 15 mg: 2.30%) *vs.* Semaglutide 1 mg: 1.86% reduction [5]. Both semaglutide and tirzepatide decreased fasting insulin and improved HOMA-IR *versus* placebo.

Strong data support the potential use of semaglutide 2.4 mg as a treatment option for individuals with obesity and prediabetes to achieve reversion to normoglycaemia. In STEP-10 trial, 81% of participants with prediabetes reverted to normoglycaemia at week 52 with semaglutide 2.4 mg *vs.* 14% in placebo group [6]. The findings from SURMONT-1 trial showed that three years of treatment with tirzepatide in persons with obesity and prediabetes resulted in substantial and sustained weight reduction and a markedly lower risk of progression to type 2 diabetes than that with placebo (93% reduction of type 2 diabetes risk after 176 weeks) [7].

Blood pressure control

Hypertension is a frequent and subsequent metabolic complication in people with obesity. Both semaglutide and tirzepatide are associated with reductions in systolic and diastolic blood pressure in clinical studies, although mechanisms are multifactorial and may be partly mediated by weight loss. Semaglutide led to robust reductions in systolic (-5.1mm Hg) and diastolic blood pressure (-2.4 mmHg) *versus* placebo [8]. Tirzepatide 10 mg and 15 mg produced mean systolic blood pressure changes *vs.* placebo of approximately -6.3 mmHg *vs.* -1.2 mmHg at 72 weeks (combined doses) [9].

Lipid control

Incretin-based therapy has favorable effects on lipid metabolism, often in parallel with weight loss. Tirzepatide has been shown to significantly reduce triglycerides (-20.3%), total cholesterol (-3.1%), and LDL-C fractions (-4.2%) while increasing HDL-C levels (in overweight or obese populations) [7]. Semaglutide was also associated

with favorable changes in triglycerides, HDL-C, and non-HDL cholesterol *vs.* placebo among STEP program participants, reflecting cardiometabolic improvement [3, 4].

Atherosclerotic cardiovascular disease and major acute cardiovascular events (MACE)

CV morbidity and mortality are recognized as the most significant impact of obesity on health outcomes. Studies using older AOMs failed to prove any cardiovascular benefit, and there is an unparalleled interest in whether incretin-based therapies used to treat obesity also have significant CV benefits.

It was already demonstrated that in patients with type 2 diabetes and established CV disease or at high CV risk, semaglutide was associated with significant risk reduction in MACE components (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death) compared to placebo [10].

Semaglutide effects in patients with preexisting cardiovascular disease and overweight or obesity (mean body mass index ≥27 kg/m^2), without diabetes, were investigated in the SELECT trial, a randomized, double-blind, placebo-controlled, and event-driven superiority study. A total of 17604 patients with previous myocardial infarction, stroke or peripheral arterial disease were enrolled, and 8803 patients were assigned to receive treatment with once-weekly subcutaneous semaglutide at a dose of 2.4 mg. After a mean follow-up of over 39 months, treatment with semaglutide was superior to placebo in reducing the primary cardiovascular end-point composite consisting of previously mentioned MACE. A significant relative risk reduction of 20% in the primary cardiovascular end-point composite was found in the group of patients treated with semaglutide (6.5%) compared to placebo group (8%) (hazard ratio, 0.80; p<0.001) [11].

The real-world SCORE study included 9321 participants from a United States database, diagnosed with atherosclerotic cardiovascular disease, overweight or obesity, without diabetes, and treated with once-weekly subcutaneous semaglutide 2.4 mg. The study reported a 45% significantly lower risk of MACEs in patients treated with semaglutide compared to their peers without semaglutide treatment over a mean follow-up of 200 days [12]. Data provided by real-world evidence complement the findings reported in the SELECT trial, suggesting that cardiovascular benefits of once-weekly semaglutide treatment in obesity could be translated in the clinical practice.

Recently, SURMOUNT-MMO trial was designed to investigate the effect of once-weekly tirzepatide (doses 2.5 mg up to 15 mg) on morbidity and mortality in adults without diabetes, with overweight or obesity, with established cardiovascular disease or with multiple risk factors for cardiovascular disease. This randomized, double-blind, placebo-controlled and event-driven trial will enroll 15000 participants with body mass index ≥27 kg/m^2 and will have the primary end-point of time to first occurrence of the composite outcome of five components: nonfatal myocardial infarction, nonfatal stroke, heart failure events, coronary revascularization, and death from any cause. Thus, SURMOUNT-MNO will be the first outcome trial assessing the effect of tirzepatide in primary and secondary cardiovascular prevention in patients with obesity, without diabetes [13, 14].

Heart failure

Obesity increases the risk of heart failure with preserved ejection fraction (HFpEF). Addressing increased body mass index has become a key therapeutic focus in the clinical management of heart failure since increasing evidence supports obesity management for improving heart failure outcomes [15].

Heart failure with preserved ejection fraction

A total of 529 patients with obesity and HFpEF were randomly assigned to administer once-weekly semaglutide at a dose of 2.4 mg or placebo for a duration of 52 weeks in the STEP-HFpEF trial. The mean change in Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS) indicated a significant improvement in symptoms and limitations, and in exercise function in the group treated with semaglutide [16].

In the SUMMIT trial, patients with obesity and HFpEF (n=364) treated with tirzepatide once-weekly at a dose starting from 2.5 mg up to 15 mg displayed a significantly lower risk of worsening heart failure (8%) compared to placebo (14.2%), resulting in a 46% relative risk reduction. The KCCQ-CSS indicated a significantly higher value in the tirzepatide group, suggesting a better quality of life compared to placebo group. Also, the composite of death from cardiovascular disease and worsening heart failure was significantly lower in the group treated with tirzepatide after a median duration of follow-up of 104 weeks [17]. An expanded secondary analysis of the data from SUMMIT trial confirmed the improvement in the quality of life and reduction in the need for medication for heart failure in patients treated with tirzepatide [18]. The cardio magnetic resonance sub-study of the SUMMIT trial described

positive physiological changes in left ventricular mass related to tirzepatide treatment [19]. Thus, the inclusion of heart failure end-point in the SURMOUNT-MMO trial is supported by the data collectively reported in the SUMMIT trial. Participants from the SURMOUNT-MMO trial will be treated with tirzepatide or placebo and will be assessed for time to first occurrence of heart failure events that will result in hospitalization or urgent visits, as part of both primary and secondary end-points [13, 14].

Heart failure with reduced ejection fraction

Data regarding the effect of once-weekly semaglutide and tirzepatide in patients with heart failure with reduced ejection fraction (HFrEF) are sparse and uncertain. An "obesity paradox" has been previously described, suggesting that increased body mass index is associated with a higher risk of heart failure, but better heart failure outcomes [20]. Interestingly, the authors of the SELECT trial concluded that semaglutide could benefit both patients with HFpEF and HFrEF, although different pathophysiology is involved in the two subtypes: HFpEF is linked to diseases such as obesity, while HFrEF is related to myocardial injury [21]. Results from a retrospective cohort study indicated that semaglutide in patients with obesity and HFrEF (n=2043) was significantly associated with lower 1-year mortality [22].

Tirzepatide treatment in patients with obesity or overweight with ventricular tachycardia and heart failure with reduced ejection fraction (n=1071) was linked to significantly lower 1-year mortality, reduction in heart failure exacerbation and fewer hospitalizations in a retrospective study [23].

Although positive outcomes were reported with the use of once-weekly semaglutide and tirzepatide in heart failure with reduced ejection fraction in retrospective studies, the cardioprotective safety and efficacy should be validated in prospective trials.

Metabolic dysfunction-associated steatotic liver disease

Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD), formerly non-alcoholic fatty-liver disease (NAFLD), is closely linked to obesity, with 70–90% of individuals with obesity having the condition. Obesity triggers insulin resistance, chronic inflammation, and visceral fat accumulation, which drive liver fat storage, inflammation, and fibrosis. Losing 5% to 10% of body weight can significantly reduce liver fat and improve, or even reverse, MASLD. Conversely, lack of intervention is associated with risk of Metabolic Dysfunction-Associated Steatohepatitis (MASH) and fibrosis, cirrhosis and hepatic failure [24].

Data on the effects of incretin-based therapies in MASLD start to accumulate. The ESSENCE phase 3 RCT enrolled 1197 patients with biopsy-defined MASH and fibrosis stage 2 or 3 to receive once-weekly 2.4 mg semaglutide or placebo for 240 weeks. The results of a planned interim analysis conducted at week 72 showed that resolution of steatohepatitis without worsening of fibrosis occurred in 62.9% of semaglutide-treated subjects *vs.* 34.3% in the placebo group; a reduction in liver fibrosis without worsening of steatohepatitis was reported in 36.8% of the patients in the semaglutide group and in 22.4% of those in the placebo group [25]. In a smaller, phase 2, dose-finding RCT using tirzepatide as investigational product *vs.* placebo, which included 190 subjects with biopsy-confirmed MASH and stage F2 or F3 fibrosis it was shown that resolution of MASH without worsening of fibrosis was 10% in the placebo group *vs.* 44%, 56%, and 62% in the three tirzepatide arms (5, 10, 15 mg). Improvement of at least one fibrosis stage without worsening of MASH was 30% in the placebo group, and 55%, 51% and 51% in the tirzepatide arms [26].

Incretin-based therapies for obesity: effects on obstructive sleep apnea and knee osteoarthritis

Incretin-based agents have revolutionized weight management with robust effects on body weight, and an increasing research focus on comorbidity outcomes such as obstructive sleep apnea (OSA) and knee osteoarthritis (KOA).

Obstructive sleep apnea (OSA)

The SURMOUNT-OSA phase III RCT has been conducted in adults with moderate-to-severe OSA and obesity [27]. Participants were randomized to weekly tirzepatide (10–15 mg) *versus* placebo over 52 weeks. Apnea–Hypopnea Index (AHI), the primary measure of OSA severity, was significantly reduced with tirzepatide *versus* placebo in both continuous positive airway pressure (CPAP)-naïve and CPAP-treated cohorts. In participants who were not receiving CPAP, the mean AHI reduction at week 52 was 25.3 events/hour on tirzepatide and 5.3 events/hour with placebo (P<0.001). Similarly, in those who were receiving CPAP therapy, mean AHI reduction reached 29 events/hour on tirzepatide *vs.* 5 events/hour on placebo (p<0.001). Most of the OSA benefits appear mediated by substantial weight loss and reductions in adipose

burden around the upper airway, although some cardiometabolic improvements (*e.g.*, hsCRP) also correlate with better sleep outcomes.

A recent meta-analysis of incretin-based RCTs that include tirzepatide (2 trials) and once-daily GLP-1 agonist liraglutide (3 trials), demonstrate a significant reduction in AHI overall (pooled mean change −11.6 events/hour *vs.* control), consistent with improvements in weight and respiratory parameters [28].

Semaglutide does not yet have a comparable large Phase 3 OSA RCT with AHI as the primary endpoint available; evidence is currently small or ongoing.

Knee osteoarthritis (KOA)

The STEP-9 phase III RCT randomized adults with obesity and symptomatic KOA to once-weekly semaglutide 2.4 mg *versus* placebo (over 68 weeks), with outcomes including pain, physical function, and body weight. Patients treated with semaglutide showed greater reductions in KOA-related pain and improved physical function compared with placebo. The mean change in the WOMAC pain score was 41.7 points with semaglutide and 27.5 points with placebo (P<0.001). Participants in the semaglutide group had a greater improvement in SF-36 physical-function score than those in the placebo group (mean change, 12.0 points *vs.* 6.5 points; P<0.001). Effects on structural knee joint integrity (*e.g.*, cartilage loss or radiographic progression) have not been adequately examined. The symptomatic benefits appear largely mediated by weight reduction rather than direct modification of joint disease processes [29].

For both OSA and KOA, body weight reduction is a major mediator of clinical improvements. In OSA, weight loss reduces pharyngeal adiposity and retroglossal collapse risk, while in KOA, decreased mechanical load on the knee joint reduces pain and improves function. Beyond weight loss, anti-inflammatory effects (*e.g.*, reductions in hsCRP) may contribute modestly to symptom improvement in OSA, and anti-inflammatory or metabolic modulatory effects on synovial tissues in KOA are speculative and lack robust RCT evidence.

Clinical implications – selection of pharmacotherapy in the presence of obesity complications

In light of current medical evidence, the pharmacotherapy of obesity should take into consideration the presence of comorbidities. After examining the current evidence, recent clinical guidelines recommend that the choice of a specific anti-obesity molecule be made based on potential effects on the obesity complication.

In the presence of atherosclerotic CV disease, the treatment of choice for obesity should be once-weekly subcutaneous semaglutide 2.4 mg, while in the presence of HFpEF, the treatment of choice should be either once-weekly subcutaneous semaglutide 2.4 mg or tirzepatide up to 15 mg. Both molecules can be used for obesity associated with MASH, although more robust data are available for semaglutide. In OSA, evidence are in favor of the use of tirzepatide, while for ameliorating KOA-related pain, semaglutide has proven effects [30–32].

New studies are underway and will potentially provide data that could add to current evidence-based recommendations. As well, numerous other incretin-based therapies are tested for obesity treatment, some of which are very close to being approved for clinical use. The landscape of AOMs is rapidly evolving in parallel with growing unmet needs for treating massive numbers of people currently living with obesity, and represents an important opportunity to stop one of the most challenging epidemics in global health.

Conclusion

Incretin-based therapies, especially semaglutide and tirzepatide, represent innovative and multivalent therapeutic solutions in the management of obesity and its associated complications. The evidence reviewed here demonstrates that their benefits extend well beyond weight reduction, encompassing meaningful improvements in cardiovascular outcomes, heart failure symptoms and prognosis, hepatic steatohepatitis, obstructive sleep apnea, and musculoskeletal comorbidities such as knee osteoarthritis. These findings underscore the importance of selecting the most appropriate agent based not only on achievable weight loss but on each patient's specific cardio-reno-metabolic risk profile.

Acknowledgments

Conflict of interest

D.M.C. reports honoraria for lectures and other support from Sanofi, AstraZeneca, Medtronic, Boehringer Ingelheim, Sandoz, Eli Lilly, Worwag Pharma and Novo Nordisk. A. F reports honoraria for lectures and other support from Sanofi, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Worwag Pharma and Novo Nordisk. G.V.I. reports honoraria for lectures, advisory board participation, and other supportfrom Novo Nordisk, Boehringer Ingelheim, Astra Zeneca, Eli Lilly, Servier, Viatris, Zentiva, Worwag. C.G.B reports

honoraria for lectures, advisory board participation, and other supportfrom Novo Nordisk, Boehringer Ingelheim, Astra Zeneca, Eli Lilly, Novartis, Amgen, Servier, Viatris, Zentiva, Worwag.

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