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Efficacy and safety of semaglutide and tirzepatide in the therapy of obesity and type 2 diabetes – current state of knowledge

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Abstract

Background. The diabesity epidemic (obesity and type 2 diabetes) requires a shift from a glucocentric to a holistic approach, making weight reduction a clinical goal equal to glycemic control. Incretin-based therapies (semaglutide, tirzepatide) represent a breakthrough due to their pleiotropic effects.

Aim. This study analyzes their efficacy, safety, molecular mechanisms, and cardio/nephroprotection in light of recent trials and guidelines.

Material and methods. PubMed and Google Scholar were searched (2018–2026) using MeSH terms: obesity, type 2 diabetes, GLP-1/GIP agonists. The analysis included phase III trials (STEP, SURPASS, SURMOUNT), meta-analyses, and guidelines of the Polish Diabetes Association (PTD 2026), the Polish Association for the Study of Obesity (PTLO 2024), and the American Diabetes Association (ADA). Case reports and early-phase studies were excluded.

Results. Diabesity is linked to an incretin deficit. GLP-1 and dual GIP/GLP-1 receptor agonists mimic the incretin effect, modulating appetite and enhancing insulin sensitivity. This facilitates sustained weight loss and multi-organ protection. Evidence from STEP and SURPASS trials highlights robust cardioprotection, nephroprotection, and reduced hepatic steatosis in MASLD. By targeting cerebral reward centers, these agents address hedonic hunger, improving long-term metabolic health.

Conclusions. Incretin therapy is revolutionizing treatment. Semaglutide and tirzepatide achieve high weight reduction (>20%) and lower the risk of MACE, renal failure, and hepatic steatosis. Latest PTD (2026) and PTLO (2024) guidelines recommend their early implementation in primary care to combat obesity and its complications.

Key words: semaglutide, tirzepatide, obesity, type 2 diabetes mellitus, diabesity.

1. Introduction

Modern medicine is currently facing an escalating epidemic of obesity and type 2 diabetes which, due to their shared pathophysiological basis, are increasingly recognized under the term “diabesity” [1, 2]. In the view of global experts, obesity is no longer perceived through a purely aesthetic lens. Today, it is defined as a chronic and relapsing disease responsible for the

development of over 200 organ-specific complications, particularly cardiovascular diseases, renal disorders, and other metabolic impairments [3, 4, 5].

Traditional therapeutic approaches in type 2 diabetes have primarily focused on achieving normoglycemia (a glucocentric approach), which was frequently associated with iatrogenic weight gain in treated patients [2, 6]. Current international (ADA/EASD) and Polish national guidelines (PTD, PTLO) emphasize a holistic approach, focusing predominantly on weight management as a goal equivalent to achieving glycemic control [4, 7, 8]. Evidence demonstrates that a 10–15% reduction from baseline body weight is a critical factor capable of inducing type 2 diabetes remission and significantly improving cardiovascular and renal prognosis [4, 9, 10, 11].

The introduction of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and dual GIP/GLP-1 receptor agonists marked a breakthrough in the modern management of diabesity [12, 13]. By exerting systemic effects on the satiety center in the hypothalamus, preserving pancreatic β-cells, and slowing gastric motility [6, 14], these agents demonstrate weight reduction efficacy approaching the outcomes of metabolic surgery – a feat previously unattainable with conservative therapies [1, 13]. Recent landmark trial programs, such as FLOW, SELECT, and STEP-HFpEF, provide groundbreaking evidence that modern incretin-based therapies ensure robust organ protection and improve quality of life, thereby extending substantially beyond traditional metabolic control [9, 10, 15].

The objective of this review is to summarize and critically analyze the current state of knowledge regarding the therapeutic efficacy and safety profile of modern incretin-based therapies – semaglutide and tirzepatide – in the management of patients with type 2 diabetes and obesity (referred to as diabesity) [1, 2]. This paper focuses on evaluating the impact of these agents on weight reduction, glycemic control, and extra-metabolic benefits, with a particular emphasis on renal and cardiovascular protection. The entire analysis is based on the results of the latest Phase III clinical trial programs and current guidelines from scientific societies [4, 8].

2. Research materials and methods

A comprehensive literature search was conducted utilizing the PubMed and Google Scholar databases, with a particular focus on publications indexed between 2018 and 2026. To ensure

a precise search strategy, specific Medical Subject Headings (MeSH) terms and keywords were applied in various combinations using Boolean operators (AND/OR) in both English and Polish, including: “obesity”; “type 2 diabetes”; “glucagon-like peptide-1 receptor agonists”; “semaglutide”; and “tirzepatide”.

The inclusion criteria comprised original research papers presenting the results of Phase III clinical trials (specifically the STEP, SURPASS, and SURMOUNT programs), the most recent clinical guidelines from scientific societies (PTD, PTLO, ADA), meta-analyses, and systematic reviews published in high-impact peer-reviewed journals, as well as publications available in full-text format in either English or Polish. Case reports, early-stage experimental studies (Phase I and II trials) with no immediate impact on current clinical practice, and articles published in languages other than English or Polish were excluded from the analysis.

Titles and abstracts were initially screened, after which selected articles underwent a full-text evaluation assessing their substantive and methodological quality. The primary limitation of this review stems from the rapid and highly dynamic evolution of incretin-based pharmacotherapy. Due to the high volume of novel scientific insights published during the manuscript preparation, the latest findings from Phase II trials (e.g., studies on triple agonists) were addressed primarily as future perspectives.

3. Research results

3.1. Molecular Mechanisms and Physiology of Incretin Hormones

The therapeutic foundation of the discussed molecules relies on exploiting the phenomenon known as the incretin effect [6, 14]. This effect is characterized by a significantly higher insulin secretion by pancreatic β-cells in response to oral glucose administration compared to an isoglycemic intravenous glucose infusion [6, 14]. In healthy individuals, incretin hormones are estimated to account for approximately 50–70% of postprandial insulin secretion [6]. In the course of type 2 diabetes and obesity, a pronounced deficit in this mechanism is observed, primarily mediated by an impaired response of pancreatic β-cells to GIP. This, in turn, leads to escalating postprandial hyperglycemia and the progressive exhaustion of the secretory capacity of pancreatic β-cells [2, 6].

The incretin effect is primarily mediated by two molecules secreted within the gastrointestinal tract:

Glucagon-like peptide-1 (GLP-1): released by L-cells in the distal ileum and colon [12, 14]. It is characterized by a glucose-dependent insulinotropic action, which inherently minimizes the risk of hypoglycemia. Furthermore, GLP-1 suppresses glucagon secretion and exhibits cytoprotective properties by inhibiting apoptosis and stimulating the proliferation of pancreatic islet cells, as demonstrated in preclinical models [6, 14].
Glucose-dependent insulinotropic polypeptide (GIP): secreted by K-cells in the duodenum and proximal jejunum [2, 14]. It plays a pivotal role in the regulation of adipose tissue metabolism and energy homeostasis. Notably, in patients with type 2 diabetes and obesity, its capacity to stimulate insulin secretion is substantially blunted [2, 6].

Modern incretin-based drugs have been engineered to ensure resistance against degradation by dipeptidyl peptidase-4 (DPP-4). Preventing rapid enzymatic breakdown substantially extends the plasma half-life of these molecules, thereby enabling a prolonged therapeutic duration of action [6, 12].
Semaglutide (GLP-1 RA): exhibits high (94%) amino acid sequence homology to native human GLP-1, allowing it to target receptors not only within the pancreas but also within the central nervous system (CNS). By stimulating pro-opiomelanocortin/cocaine- and amphetamine-regulated transcript (POMC/CART) neurons located in the arcuate nucleus of the hypothalamus and the area postrema, semaglutide enhances satiety while concurrently suppressing appetite centers [12, 14]. Furthermore, this agent modulates gastrointestinal motility by transiently delaying gastric emptying (an effect that becomes attenuated during chronic administration), which blunts postprandial glycemic fluctuations [1, 6].
Tirzepatide (GIP/GLP-1 RA): represents a single-peptide dual receptor agonist (frequently termed a "twincretin"). Both components act synergistically to reduce appetite and energy intake. Notably, the GIP receptor agonist component additionally enhances insulin sensitivity and lipid buffering capacity within white adipose tissue, thereby optimizing its metabolic function [2, 13]. This synergistic, dual-receptor mechanism accounts for the exceptionally high clinical efficacy in body weight reduction documented across clinical trial programs [13, 16].

3.2. Clinical Efficacy in Body Weight Reduction and Glycemic Control

The primary evidence supporting the efficacy of semaglutide therapy at therapeutic doses is derived from the results of the Phase III clinical trial program designated as STEP (Semaglutide Treatment Effect in People with obesity) [17]. Prior to this milestone, the molecule's

glucoregulatory and metabolic efficacy had been established in the SUSTAIN 1–7 trial series [18]. A pooled analysis of the SUSTAIN program confirmed that once-weekly semaglutide more effectively reduces HbA1c levels and body weight compared to previously established antidiabetic agents, including other GLP-1 receptor agonists [18].

The landmark STEP 1 trial [17], conducted in a population of patients with overweight or obesity but without type 2 diabetes, demonstrated a significant superiority of semaglutide over placebo regarding body weight reduction. Secondary endpoint analyses confirmed that a substantial proportion of patients achieved clinically meaningful weight loss thresholds recognized as critical for improving cardiovascular risk profiles and overall health status [17].

In the STEP 2 trial [19], which evaluated a patient population with comorbid type 2 diabetes, semaglutide demonstrated the feasibility of simultaneously achieving both glycemic and weight-reduction targets. Although the magnitude of weight reduction in patients with diabetes was less pronounced than in the general population investigated in the STEP 1 program, the treatment was accompanied by a marked improvement in glycemic control, with the majority of study participants achieving stringent target glycated hemoglobin (HbA1c) values [19].

The SURPASS and SURMOUNT trial programs demonstrated the synergistic effects of tirzepatide as the first-in-class dual GIP/GLP-1 receptor agonist [13, 20, 21]. In the SURPASS-1 trial [21], tirzepatide monotherapy demonstrated robust glucose-lowering efficacy in patients with type 2 diabetes inadequately controlled by diet and exercise alone. A head-to-head comparison of tirzepatide and semaglutide in the SURPASS-2 trial [16] confirmed the superior therapeutic efficacy of the dual agonist. In the primary analysis utilizing the treatment-regimen estimand, which reflects the effects across all randomized patients, tirzepatide proved more effective in both reducing glycated hemoglobin and lowering body weight. These findings unequivocally underscore the advantage of the dual mechanism of action in the intensive management of diabesity [16].

Evidence supporting the superiority of tirzepatide extends beyond comparisons with GLP-1 receptor agonists. The SURPASS-3 [20] and SURPASS-4 [22] trials demonstrated its superior clinical efficacy compared to basal insulins (insulin degludec and insulin glargine, respectively). Further evidence of the molecule's weight-reduction potential was provided by the SURMOUNT-1 trial [13], conducted in a population of individuals with obesity without comorbid type 2 diabetes. It demonstrated a mean body weight reduction of a magnitude comparable to surgical interventions. Notably, more than half of the participants in the highest-

dose cohort achieved the most stringent weight-loss thresholds specified in the study's secondary endpoints [13].

Table 1. Comparison of the clinical efficacy of semaglutide and tirzepatide in selected populations.

Trial [Ref.]	Drug and dose	Population	Duration (weeks)	Body weight: % change (≥ 20%*)	Δ HbA_{1c} (percentage points)
STEP 1 [17]	Sema 2,4 mg	Obesity	68	–14,9% (32%)	n/a
STEP 2 [19]	Sema 2,4 mg	Obesity + T2DM	68	–9,6% (13,1%)	–1,6
SURMOUNT-1 [13]	Tirz 15 mg	Obesity	72	–20,9% (57,0%)	n/a
SURPASS-1 [21]	Tirz 15 mg	T2DM (monotherapy)	40	–11,0% (n/a)	–2,07
SURPASS-2 [16]	Tirz 15 mg	T2DM (vs Sema 1)	40	–12,0% (n/a)	– 2,30
SURPASS-3 [20]	Tirz 15 mg	T2DM (vs Degl)	52	–12,9% (n/a)	–2,37
SURPASS-4 [22]	Tirz 15 mg	T2DM (vs Glar)	52	–11,7% (n/a)	–2,43

Abbreviations: Sema – semaglutide; Tirz – tirzepatide; Δ HbA_{1c} – change in glycated hemoglobin; T2DM – type 2 diabetes mellitus; n/a – not applicable / not evaluated; * - percentage of patients achieving a body weight reduction of ≥ 20%; vs Sema 1 – comparator: semaglutide 1mg; vs Degl – comparator: insulin degludec; vs Glar – comparator: insulin glargine

Note: The percentage value for the SURPASS-2 trial was calculated based on the mean body weight change expressed in kilograms relative to the baseline weight reported in the primary publication [16].

3.3. Organ-Protective Benefits and Pleiotropic Effects of Incretin-Based Therapies

Modern incretin-based pharmacotherapy offers substantial organ-protective benefits that extend far beyond traditional glycemic control and body weight reduction. The pleiotropic effects of these molecules manifest as robust, multi-organ protection, targeting predominantly the cardiovascular system, the kidneys, and the liver.

The SELECT trial [10] represented a landmark milestone in cardiology, demonstrating that semaglutide significantly reduces major adverse cardiovascular events (MACE) in individuals with overweight or obesity without comorbid type 2 diabetes. These findings establish that the cardioprotective effects of incretin-based therapies are independent of their glucose-lowering action [10]. In the STEP-HFpEF program [15], which evaluated a population of patients with heart failure with preserved ejection fraction (HFpEF) and comorbid obesity, substantial clinical benefits were observed in the semaglutide cohort. This treatment led to a significant improvement in quality of life—assessed using the Kansas City Cardiomyopathy Questionnaire clinical summary score (KCCQ-CSS)—and exercise capacity [15]. Furthermore, the Polish Cardiac Society (PTK) underscores the rationale for the early initiation of GLP-1 receptor agonist therapy in patients with atherosclerotic cardiovascular disease (ASCVD), highlighting its vasculoprotective properties irrespective of the degree of metabolic control [23].

Incretin-based therapies exert potent nephroprotective effects, a finding robustly confirmed in meta-analyses of key clinical trials [11]. The landmark FLOW trial [9] demonstrated that semaglutide significantly reduces the risk of kidney disease progression, as well as death from renal or cardiovascular causes, in patients with type 2 diabetes and chronic kidney disease. Furthermore, findings from the SURPASS-4 trial [24] demonstrated the superiority of tirzepatide over basal insulin therapy in slowing the decline of the estimated glomerular filtration rate (eGFR). These cumulative data establish modern incretin-based agents as a cornerstone in the contemporary management of diabetic kidney disease (DKD).

Another critical dimension of the organ-protective profile of incretin-based therapies is the reduction of hepatic steatosis [2, 25]. In a sub-analysis of the SURPASS-3 MRI trial [25], tirzepatide demonstrated robust efficacy in lowering liver fat content (LFC) and reducing visceral adipose tissue (VAT) volume. This metabolic effect was substantially more pronounced than that achieved with insulin degludec therapy, thereby opening entirely new

horizons in the contemporary management of patients with metabolic dysfunction-associated steatotic liver disease (MASLD) [2, 25].

Table 2. Summary of key organ-protective benefits in selected clinical trials.

Domain of benefit	Trial [Ref.]	Drug	Primary organ-protective effect
Cardiology (MACE)	SELECT [10]	Sema	Reduction in the risk of CV death, myocardial infarction, and stroke in individuals without diabetes.
Heart failure	STEP-HFpEF [15]	Sema	Reduction in HFpEF symptoms and improvement in exercise capacity (6-minute walk test).
Nephrology (eGFR)	FLOW [9]	Sema	Slowing the decline of eGFR and reduction in the risk of kidney failure.
Nephrology (eGFR)	SURPASS-4 analysis [24]	Tirz	Renal benefits compared to insulin glargine in patients with increased CV risk.
Hepatology (LFC)	Subanaliza SURPASS-3 [25]	Tirz	Significant reduction in liver fat content (evaluated via MRI-PDFF).
Overall CV	Meta-analysis by Kristensen et al. [11]	GLP-1 RA	12% reduction in MACE and an 11–12% reduction in all-cause mortality.

Abbreviations: MACE – major adverse cardiovascular events; Sema – semaglutide; CV – cardiovascular; HFpEF – heart failure with preserved ejection fraction; eGFR – estimated glomerular filtration rate; Tirz – tirzepatide; GLP-1 RA – glucagon-like peptide-1 receptor agonists; LFC – liver fat content

3.4. Safety Profile and Tolerability of Long-Term Incretin-Based Therapy

While incretin-based therapies exhibit remarkable clinical efficacy, their administration requires a thorough understanding of their safety profile and potential adverse effects. Proficiency in managing symptoms typical of the initial titration phase is critical to ensuring that the therapy is conducted safely and effectively, thereby maximizing patient comfort and treatment adherence.

The most frequently reported adverse effects associated with semaglutide and tirzepatide therapies are gastrointestinal symptoms, including nausea, vomiting, and diarrhea [17, 18, 19]. According to the findings of the meta-analysis by Kristensen et al. [11], these symptoms are typically mild-to-moderate in severity and are characteristically dependent on the rate of dose escalation. Although these effects are predominantly transient and diminish over the course of treatment, they represent the primary driver of therapy discontinuation observed across clinical trials [11, 23].

The potential risk of acute pancreatitis and thyroid malignancies remains a frequently debated topic in contemporary incretin-based pharmacotherapy. However, data from the landmark meta-analysis by Kristensen et al. [11], which evaluated clinical outcomes from over 56,000 patients, provide robust reassurance regarding these safety concerns:

Acute pancreatitis: No increased risk for the occurrence of this complication was observed in the incretin-treated cohorts compared to control groups (OR: 0.90; 95% CI: 0.73–1.12; $p = 0.34$) [11].

Thyroid malignancies: No statistically significant association was demonstrated between the utilization of GLP-1 receptor agonists and the incidence of thyroid cancer (OR: 0.77; 95% CI: 0.45–1.32) [11].

A landmark 2024 study by Wang et al. [26] addressed pressing concerns regarding the impact of semaglutide on mental health. This analysis, based on real-world evidence (RWE) and encompassing the medical records of over 1.8 million patients, demonstrated that semaglutide therapy is associated with a significantly lower risk of suicidal ideation—both incident and recurrent—compared to those receiving non-GLP-1 receptor agonist antidiabetic or anti-obesity medications [26]. These findings provide compelling evidence supporting the neuropsychiatric safety of this drug class.

Effective anti-obesity pharmacotherapy must incorporate the patient's psychological well-being as an integral component of the therapeutic process. Olszanecka-Glinianowicz et al. [5] emphasize the necessity of evaluating patients for underlying eating disorders, such as binge eating disorder (BED) or night eating syndrome (NES), prior to the initiation of therapy. Modern incretin-based medications facilitate appetite control not only by enhancing homeostatic satiety but also by modulating the activity of the reward system, thereby mitigating hedonic hunger [2, 5]. Importantly, in patients with severe behavioral disturbances, pharmacotherapy should complement comprehensive psychological and dietary care rather than serve as a standalone solution. Such an integrated, multidisciplinary approach is critical for achieving sustainable therapeutic outcomes and preventing weight cycling (the "yo-yo effect") following treatment discontinuation [5].

3.5. The Place of Incretin-Based Therapies in Current Therapeutic Standards and the Polish Healthcare System

The integration of modern incretin-based therapies into routine clinical practice has fundamentally reshaped contemporary therapeutic algorithms. The latest guidelines place a paramount emphasis on treatment personalization and a comprehensive, patient-centered approach, wherein the selection of pharmacotherapy is guided not merely by the degree of metabolic control, but crucially by the presence of comorbidities and organ complications [3, 7].

According to the joint consensus statement of the ADA and EASD [7] and the ADA Standards of Care in Diabetes [3], the management of type 2 diabetes must adopt a holistic, person-centered approach. Within this framework, GLP-1 receptor agonists with proven cardiovascular and renal benefits are strongly recommended as first-line therapy—independent of baseline HbA1c levels—in patients with established atherosclerotic cardiovascular disease (ASCVD) or indicators of high cardiovascular risk. Furthermore, in the context of chronic kidney disease (CKD), these agents represent a vital alternative or adjunctive option to SGLT2 inhibitors [3, 7, 9].

The latest guidelines of the Polish Diabetes Association (PTD 2026) fully integrate these principles into the Polish clinical setting [8]. Experts emphasize that in patients with type 2 diabetes and concomitant obesity, clinical priority should be given to the initiation of

medications with robust efficacy in body weight reduction [4, 8]. Semaglutide and tirzepatide are highlighted as frontline agents that enable patients to achieve strict metabolic targets while simultaneously optimizing their cardiovascular and renal risk profiles [7, 8, 22]. Furthermore, the PTD underscores the necessity of rigorous monitoring for renal complications, against which these modern molecules exhibit a potent, evidence-backed protective effect [9, 24].

The guidelines of the Polish Society for the Treatment of Obesity (PTLO 2024) define the disease of obesity as a chronic condition with no tendency for spontaneous resolution [4]. It requires a comprehensive, multimodal management approach encompassing lifestyle modifications, pharmacotherapy, and, when indicated, bariatric surgery. Currently, semaglutide and tirzepatide therapies represent the cornerstone of highly effective anti-obesity pharmacotherapy [13, 17, 21]. Within this framework, primary care physicians (PCPs) occupy a pivotal role in both the diagnostic and therapeutic pathways. Mamcarz et al. [27] recommend the prompt implementation of coordinated care for patients with diabesity, emphasizing that the early initiation of incretin-based therapy can effectively halt the progression of complications and prevent the future need for insulin therapy intensification. Crucially, evidence demonstrates that a robust body weight reduction of ≥10–15% can induce type 2 diabetes remission in a substantial subset of patients [4, 27].

4. Conclusions

The management of type 2 diabetes has fundamentally evolved from a glucocentric approach toward a comprehensive care strategy, wherein body weight reduction and organ protection represent therapeutic goals equivalent to metabolic control [3, 7, 8]. Consequently, next-generation incretin-based therapies, such as semaglutide and tirzepatide, are rapidly becoming the cornerstone of modern diabesity management [4, 8].

Results from the landmark SURPASS and SURMOUNT clinical trial programs demonstrate that the synergistic co-agonism of tirzepatide on both GIP and GLP-1 receptors enables body weight reduction comparable to the outcomes of bariatric surgery, while simultaneously achieving robust, dose-dependent improvements in glycemic parameters [13, 16, 20, 22].

Proven cardiovascular (SELECT [10]), nephroprotective (FLOW [9]), and hepatoprotective (SURPASS-3 MRI [25]) benefits establish these innovative agents as the therapy of choice for

patients at high risk of macrovascular and microvascular complications, irrespective of their baseline metabolic control [7, 10, 11].

The overall safety and tolerability profile of incretin-based therapies remains highly favorable, with recent real-world evidence successfully ruling out adverse impacts on mental health [26]. Nevertheless, the early detection of underlying eating disorders and the integration of comprehensive psychological and dietary support remain critical to ensuring the long-term sustainability of the therapeutic effect [5].

Within the context of the Polish healthcare system, the implementation of coordinated care in primary settings provides a vital opportunity for the early initiation of these modern therapies. This proactive approach represents the most effective strategy to prevent long-term disability and mitigate the clinical and economic burden of diabesity complications [4, 27].

Disclossure

AI.

The authors utilized artificial intelligence tools for language optimization, stylistic editing, and support in the translation and interpretation of English-language source literature. AI was also employed to prepare the English version of the Abstract and to format the bibliography in accordance with the Vancouver style. Following the use of these tools, the authors conducted a thorough substantive verification of all generated content, ensuring the accuracy of citations and the consistency of numerical data with the original source publications. The authors assume full responsibility for the entire content of the manuscript and confirm that AI did not serve as a co-author of this work.

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