International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Scholarly Publisher
RS Global Sp. z O.O.
ISNI: 0000 0004 8495 2390

Dolna 17, Warsaw,
Poland 00-773
+48 226 0 227 03
editorial_office@rsglobal.pl

ARTICLE TITLE	LATEST ADVANCES IN INJECTABLE AND ORAL MEDICATIONS FOR TYPE 2 DIABETES TREATMENT
DOI	https://doi.org/10.31435/ijitss.3(47).2025.3883
RECEIVED	10 August 2025
ACCEPTED	27 September 2025
PUBLISHED	30 September 2025
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

LATEST ADVANCES IN INJECTABLE AND ORAL MEDICATIONS FOR TYPE 2 DIABETES TREATMENT

Katarzyna Jurkiewicz *(Corresponding Author, Email: kasiaj02@op.pl)*
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0009-6247-0984

Marek Ciechański
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0007-9940-4775

Aleksandra Kasprzyk
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0003-2912-2319

Klaudia Wilk
Andrzej Mielęcki Independent Public Clinical Hospital of the Medical University of Silesia, Katowice, Poland
ORCID ID: 0009-0004-0615-2432

Edyta Witkowska
Brothers Hospitallers of Saint John of God Hospital in Kraków, Kraków, Poland
ORCID ID: 0009-0005-6139-5282

Szymon Cholewiński
4th Clinical University Hospital in Lublin, Lublin, Poland
ORCID ID: 0009-0000-3235-9382

Bernadetta Wilk
Cardinal Stefan Wyszyński Provincial Specialist Hospital in Lublin, Lublin, Poland
ORCID ID: 0009-0009-8488-5232

Piotr Stachura
Cardinal Stefan Wyszyński Provincial Specialist Hospital in Lublin, Lublin, Poland
ORCID ID: 0009-0002-0229-4690

Piotr Rejman
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0004-3869-034X

Katarzyna Pszczoła
Medical University of Lublin, Lublin, Poland
ORCID ID: 0009-0006-1100-5845

ABSTRACT

Introduction: Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by insulin resistance and impaired beta-cell function. Effective management extends beyond glycemic control and includes weight reduction and cardiovascular risk mitigation. In recent years, injectable therapies such as GLP-1 receptor agonists and the novel dual GIP/GLP-1 receptor agonist tirzepatide have shown promising results. These agents offer significant improvements in blood glucose levels, body weight, and cardiometabolic outcomes, positioning them as essential components of modern T2DM treatment strategies.

Materials and Methods: This article presents a comprehensive review of literature derived from the PubMed database, encompassing studies published between 2015 and 2025.

Results: Recent clinical studies confirm the effectiveness of GLP-1 receptor agonists (GLP-1RAs) and the dual GIP/GLP-1 agonist tirzepatide in managing type 2 diabetes. Long-acting GLP-1RAs, especially semaglutide, show superior HbA1c and weight reduction compared to other agents. Tirzepatide demonstrated even greater efficacy than semaglutide in reducing blood glucose and body weight, along with benefits for blood pressure and lipid levels. Both drugs have similar safety profiles, with mild gastrointestinal side effects. The development of oral semaglutide further enhances treatment options, particularly for patients avoiding injections.

Conclusions: Advances in injectable therapies for type 2 diabetes, particularly GLP-1 receptor agonists and the dual GIP/GLP-1 agonist tirzepatide, have significantly improved glycemic control, weight management, and cardiovascular outcomes. Tirzepatide shows greater efficacy than semaglutide in reducing HbA1c and body weight. While safety profiles are favorable, long-term data are still needed. These therapies offer personalized treatment options, supporting better long-term health for people with type 2 diabetes.

KEYWORDS

Type 2 Diabetes Mellitus, GLP-1 Receptor Agonists, Tirzepatide, Semaglutide, Injectable Therapies, Glycemic Control, Weight Loss, Cardiovascular Outcomes, Incretin-Based Therapies, Dual Agonists, DPP-4 Inhibitors, Modern Diabetes Treatment

CITATION

Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła. (2025). Latest Advances in Injectable and Oral Medications for Type 2 Diabetes Treatment. *International Journal of Innovative Technologies in Social Science*, 3(47). doi: 10.31435/ijitss.3(47).2025.3883

1. Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia.It is broadly categorized into two primary types: type 1 and type 2 diabetes mellitus.

Type 1 diabetes is defined by autoimmune-mediated destruction of pancreatic beta cells, resulting in an absolute deficiency of insulin. Conversely, type 2 diabetes is associated with varying degrees of insulin resistance and relative insulin deficiency. According to the World Health Organization (WHO) and American Diabetes Association (ADA) guidelines, the diagnosis of diabetes is established based on one or more of the following criteria: a fasting plasma glucose level equal to or exceeding 7.0 mmol/L (126 mg/dL), a two-hour plasma glucose level equal to or greater than 11.1 mmol/L (200 mg/dL) following a 75-gram oral glucose tolerance test, and/or a hemoglobin A1c (HbA1c) value of 6.5% (48 mmol/mol) or higher, or a random plasma glucose level of ≥200 mg/dL in the presence of classic symptoms of hyperglycemia or a hyperglycemic crisis.If initial results are equivocal, repeat testing is recommended for confirmation [1,2] Type 2 diabetes is a chronic, multifactorial, highly heterogeneous and progressive metabolic disorder, characterized by both genetic and environmental factors contributing to insulin resistance, as well as impairments in both the quality and quantity of insulin secretion. [3] Accurate diagnosis is essential for determining prognosis, identifying the risk of complications, and initiating appropriate therapeutic interventions.In the youth population, accurate diagnosis of type 2 diabetes mellitus (T2DM) requires careful exclusion of other forms of diabetes that may present with similar clinical features. The differential diagnosis should include type 1 diabetes mellitus (T1DM), latent autoimmune diabetes in adults (LADA), and maturity-onset diabetes of the young (MODY). [2]

In recent decades, three novel classes of glucose-lowering drugs: glucagon-like peptide-1 receptor agonists (GLP-1RAs), dipeptidyl peptidase-4 (DPP-4) inhibitors, and sodium-glucose cotransporter-2 (SGLT2) inhibitors- have been developed and are now widely utilized in the management of type 2 diabetes. [4] Beyond improving glycemic control, these therapeutic agents demonstrate protective effects on the heart and kidneys, effectively lowering the risk and severity of diabetic complications. [5] However, an increasing body of evidence suggests that SGLT2 inhibitors may reduce the risk of acute kidney injury (AKI) in individuals with type 2 diabetes. Some studies also indicate that GLP-1 receptor agonists (GLP-1RAs) may exert renoprotective effects; however, a number of postmarketing case reports have linked GLP-1RAs to the onset of AKI. Likewise, the association between DPP-4 inhibitors and AKI remains inconclusive and continues to be a subject of debate. [4]

The purpose of this study is to provide a comprehensive analysis of the latest research on type 2 diabetes mellitus. In addition to identifying the primary causes, risk factors, and symptoms associated with this condition, the study aims to evaluate the diagnostic and therapeutic methods currently in use. Furthermore, the study seeks to raise awareness of this disorder and its complications.

2. Pathophysiology of Type 2 Diabetes Mellitus

Type 2 diabetes mellitus (T2DM) is defined by the presence of both fasting and postprandial hyperglycemia, which constitute major pathophysiological drivers of a broad spectrum of potentially life-threatening complications and metabolic comorbidities. The etiology of hyperglycemia in T2DM is inherently multifactorial, involving a complex interplay between genetic, environmental, and metabolic factors. At its core, however, the condition is underpinned by a progressive decline in peripheral insulin sensitivity—commonly described as insulin resistance—accompanied by a failure of pancreatic β-cells to sustain compensatory insulin secretion, a process referred to as β-cell dysfunction or islet failure. [6] Insulin resistance and β-cell dysfunction represent two fundamental pathophysiological processes. [7] In type 2 diabetes mellitus (T2DM), islet dysfunction involves both a reduction in β-cell mass and impaired β-cell function, along with inappropriate elevation of glucagon secretion. Insulin resistance in T2DM primarily affects skeletal muscle, the liver, and adipose tissue. [6] This results in a dysfunctional feedback mechanism between insulin effectiveness and its secretion, ultimately causing hyperglycemia. [2] It is characterized by decreased glucose uptake in muscle, insufficient suppression of hepatic glucose production, and increased lipolysis and inflammation within adipose tissue. [6] The vicious cycle of hyperglycemia is driven, in part, by unhealthy lifestyle choices and/or metabolic dysfunction syndrome, which contribute to increased levels of triglycerides and non-esterified fatty acids. Excess lipid accumulation in non-adipose tissues disrupts insulin signaling pathways, leading to the development of insulin resistance. This effect is particularly pronounced in the liver, where impaired insulin action enhances hepatic glucose production and reduces glucose uptake. As a result, blood glucose and basal insulin levels rise. The elevated insulin levels further stimulate lipid storage, thereby exacerbating insulin resistance and perpetuating a self-reinforcing cycle. Increased levels of glucose and lipids contribute to glucolipotoxicity, leading to lipid accumulation within the pancreatic islets and exerting toxic effects on β-cells. This results in impaired insulin secretion and a reduction in β-cell mass, which in turn worsens hyperglycemia. [7]

3. Risk Factors for Type 2 Diabetes Mellitus

Diabetes remains a major contributor to serious health complications and ranks among the top ten causes of mortality globally. As there is currently no cure for the disease, preventive strategies are essential to reduce its incidence. [8] Risk factors for type 2 diabetes mellitus can be categorized as modifiable and non-modifiable. Non-modifiable factors include ethnicity and family history or genetic predisposition, while modifiable factors involve obesity, low levels of physical activity, and an unhealthy diet. The development of Type 2 Diabetes Mellitus (T2DM) is driven by a range of risk factors and underlying pathological mechanisms that contribute to the progression of insulin dysfunction. A multifaceted interplay between genetic, metabolic, and environmental influences gives rise to both non-modifiable risk factors such as ethnicity and genetic predisposition/family history and modifiable ones, including obesity, physical inactivity, and an unbalanced diet. These factors disrupt normal cellular processes, giving rise to a complex cascade of interrelated pathophysiological alterations that collectively sustain and worsen insulin resistance and β-cell dysfunction. [9] Robust scientific evidence supports that adopting a healthy lifestyle- characterized by maintaining an appropriate body weight, consuming a balanced diet, engaging in at least 30 minutes of daily physical activity, and avoiding both smoking and excessive alcohol consumption represents one of the most effective and cost-efficient strategies for the prevention and management of type 2 diabetes. [10]

3.1. Obesity

Obesity, defined as a body mass index (BMI) of 30 kg/m² or higher, is the most significant risk factor for type 2 diabetes mellitus and is closely linked to metabolic disturbances that contribute to the development of insulin resistance. [9] Type 2 diabetes mellitus (T2DM) arises from a combination of factors that contribute to insulin resistance and impaired β-cell function. Numerous cross-sectional and longitudinal studies have consistently demonstrated a strong association between obesity and the development of T2DM. Approximately 50% of individuals with T2DM are classified as obese (BMI > 30 kg/m²), and up to 90% are overweight (BMI > 25 kg/m²). As such, even modest weight reduction can lead to significant improvements in glycemic control and disease progression. [11] The strong correlation between obesity and diabetes has given rise to the term "diabesity", emphasizing the fact that most people diagnosed with diabetes are either overweight or obese. [12] The most pronounced link was found between body weight and the development of type 2 diabetes. Individuals who were overweight had a 133% increased risk, while those classified as obese faced a 510% higher risk compared to individuals of normal weight. Although excess body weight emerged as a key contributor to type 2 diabetes risk, its impact on disease incidence was less substantial when considered alone than when combined with other lifestyle-related factors. [10,13] A study on nurses' health, cited by Wild and Byrne, revealed that women with a body mass index (BMI) exceeding 35 had a 49-fold increased risk of developing type 2 diabetes mellitus (T2DM) compared to those with a BMI below 22. Similar trends were observed in men: those with a BMI of 35 or higher had a 42-fold greater likelihood of developing T2DM than men with a BMI under 23, based on data from a U.S. male cohort. Notably, for Asian populations- particularly individuals of Indian descent- the elevated risk of diabetes manifests at lower BMI thresholds, typically between 15 and 20. However, emerging evidence suggests that waist circumference may be a more reliable predictor of T2DM risk than BMI alone. Studies conducted in China, the United States, and Finland have consistently demonstrated that even moderate weight loss can significantly reduce the likelihood of developing T2DM. [11]

3.2 Physical inactivity

A sedentary lifestyle has been identified as a significant risk factor for the development of type 2 diabetes mellitus (T2DM). [9] An individual is classified as physically inactive when they fail to engage in the recommended 30 to 60 minutes of exercise three to four times per week. Physical inactivity contributes to a decline in insulin sensitivity and is associated with the progressive deterioration of pancreatic β-cell function, ultimately resulting in impaired glucose tolerance and the development of type 2 diabetes mellitus (T2DM). Although the independent relationship between physical inactivity and the prevalence of T2DM remains underexplored, one plausible explanation for this association is that a sedentary lifestyle often contributes to the development of obesity- a well-established and significant risk factor for T2DM. [8] Evidence from large-scale cohort studies, such as the Women's Health Study and the Kuopio Ischemic Heart Disease Risk Factor Study, demonstrated a 34% and 56% reduction in T2DM incidence among individuals who engaged in walking for 2-3 hours per week or at least 40 minutes weekly, respectively. [9] Prior research has demonstrated that individuals engaging in high levels of physical activity exhibit a 35% reduced risk of developing type 2 diabetes. [10] Physical activity contributes to delaying the onset of T2DM through several key mechanisms. Firstly, skeletal muscle contractions during exercise increase muscle blood flow, thereby enhancing glucose uptake from the bloodstream. Secondly, physical activity helps reduce visceral (intra-abdominal) fat, a well-established contributor to insulin resistance. Thirdly, moderate-intensity exercise has been shown to enhance glucose uptake by up to 40%. Beyond improving insulin sensitivity and glucose utilization, regular physical activity also has beneficial effects on systemic inflammation and oxidative stress, both of which are involved in the pathogenesis of T2DM. [9] A decline in physical activity levels, limited engagement in exercise training, and prolonged sedentary behavior have been recognized as key contributors linking obesity to type 2 diabetes mellitus (T2DM). These lifestyle factors are strongly associated with elevated markers of chronic low-grade systemic inflammation. Under such conditions, proinflammatory cytokines- including interleukin-6 (IL-6), C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1)- are released both into the circulation and within metabolic tissues, thereby promoting a state of metabolic inflammation. This inflammatory milieu ultimately disrupts pancreatic β-cell function and induces apoptosis, thus impairing insulin secretion and exacerbating glucose dysregulation. [9,12,13]

3.3 Smoking

Cigarette smoking has been associated with a 30–40% increased risk of developing type 2 diabetes. This elevated risk is partly attributed to nicotine-induced reductions in glucose uptake by skeletal muscle, which contributes to the development of insulin resistance. [8] Nevertheless, the American Diabetes Association and the International Diabetes Federation do not officially recognize smoking as a risk factor for the development of type 2 diabetes mellitus. [14] Nicotine has been found to directly disrupt glucose homeostasis, indicating its significant contribution to the pathogenesis of type 2 diabetes. Additionally, cigarette smoking elevates serum concentrations of toxic heavy metals, including lead, arsenic, and cadmium. [15] Substances found in cigarette smoke trigger widespread inflammation in the body, potentially impairing the action of insulin. Additionally, these chemicals can lead to oxidative stress, which damages cells. The combined effects of inflammation and oxidative stress are believed to contribute to an elevated risk of developing diabetes. [14] In individuals with type 2 diabetes (T2D), active smoking has been identified as an independent factor contributing to poorer glycemic control, with studies reporting a dose-dependent increase in HbA1c levels ranging from 0.21% to 1.08% among smokers. Findings from the Japanese Fukuoka Diabetes Registry, which analyzed data from 2,490 men with T2D, revealed a consistent rise in HbA1c values corresponding to the number of cigarettes smoked daily and cumulative smoking exposure (measured in pack-years), when compared to individuals who never smoked. This decline in glycemic control is believed to be primarily related to an increase in insulin resistance. However, the impact of smoking on insulin secretion remains less clear. While some studies have observed no significant differences in markers of β-cell function, others have reported a negative association between smoking and insulin secretory capacity. [16] Literature findings indicate that the link between smoking and diabetes strengthens as the number of cigarettes smoked per day rises. Will et al. examined the influence of gender on this relationship and found that the connection between cigarette smoking and type 2 diabetes is stronger in men than in women. Comparable findings were reported by Jee et al. Additionally, Wannamethee et al. demonstrated that individuals who smoke pipes or cigars have a 2.15-fold higher risk of developing type 2 diabetes, while cigarette smokers have a 1.6-fold increased risk compared to non-smokers. [8] The coexistence of elevated blood glucose levels in individuals with diabetes and active smoking significantly hastens vascular injury, thereby heightening the likelihood of both microvascular and macrovascular complications associated with type 2 diabetes mellitus. Research indicates that quitting smoking markedly reduces the risk of developing these diabetes-related vascular complications. [15]

3.4 Alcohol

Alcohol consumption can influence the risk of developing type 2 diabetes, depending on the amount consumed. Moderate intake appears to have a protective effect, while excessive consumption increases the risk. A comprehensive meta-analysis conducted by Knott et al., which examined data from 38 studies including over 1 million men and more than 800,000 women, found that consuming alcohol in quantities below 63 grams per day was associated with a reduced risk of T2DM. The most significant risk reduction was observed with daily intake between 10 and 14 grams. [11] It was also found that consuming alcohol in moderation (10–14 g per day) was linked to an 18% reduced risk of developing type 2 diabetes compared to those who abstain from drinking. [10,17] However, when alcohol intake exceeded 63 grams per day, the risk of developing type 2 diabetes began to rise, showing a clear positive association. [11] Various biological mechanisms have been suggested to account for the observed reduction in type 2 diabetes risk among moderate alcohol consumers. One theory is the anti-inflammatory effect of alcohol, which may influence the regulation of metabolic inflammatory markers such as adiponectin and interleukin-1β. Another possibility is that alcohol may stimulate the production of high-density lipoprotein (HDL), which plays a protective role in metabolic health. However, the research supporting these mechanisms often faces significant limitations, such as small study populations and short durations of follow-up, making it difficult to draw broad or long-term conclusions. [17]

4. Pharmacological Treatment Options for Type 2 Diabetes Mellitus

Prior to 2018, metformin was recommended as the first-line treatment for type 2 diabetes mellitus according to the ADA and EASD position statement. If patients did not reach their HbA1c goals, additional anti-diabetic medications were added stepwise as second- and third-line therapies. However, this approach has evolved in recent years. [18] The range of treatment options for type 2 diabetes mellitus (T2DM) has expanded as our knowledge of the disease's underlying pathophysiology has grown. Effective management should address multiple aspects of T2DM and adopt a patient-centered strategy that goes beyond simply controlling blood sugar, also focusing on reducing cardiovascular risk. [19] Adults with type 2 diabetes mellitus (T2DM) who have a confirmed or high risk of atherosclerotic cardiovascular disease, heart failure, or chronic kidney disease need treatment plans that include medications proven to lower cardiorenal risks. Effective weight management is essential for improving glucose control in T2DM patients and should be an integral part of any glucose-lowering therapy. [18] Recent treatments such as GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists possess a distinctive capacity to reduce appetite and enhance pancreatic insulin secretion, leading to significant weight loss and improved insulin sensitivity. [20] Sodium-glucose co-transporter 2 (SGLT2) inhibitors have been shown to reduce the incidence of heart failure, cardiovascular complications, and kidney-related events. Glucagon-like peptide-1 (GLP-1) receptor agonists improve glycemic control, support weight loss, and decrease the risk of cardiovascular events. [18] Several clinical trials investigating sodium-glucose cotransporter-2 (SGLT2) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists have provided evidence of cardiovascular benefits, including a reduced risk of major adverse cardiovascular events and hospitalizations due to heart failure, as well as a delay in the progression of diabetic kidney disease. [21] Additionally, newer dual agonists targeting both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors offer enhanced glycemic management and promote greater weight reduction compared to GLP-1 receptor agonists alone. [18]

4.1 SGLT2 Inhibitors

SGLT2 inhibitors (also known as gliflozins) act by competitively binding to SGLT2 transporters located in the S1 segment of the proximal renal tubules. This inhibition reduces the reabsorption of glucose and sodium, resulting in their increased elimination through urine. [18] The majority of SGLT2 inhibitors are highly selective for the SGLT2 transporters located in the renal proximal tubules, exhibiting a selectivity that is 200 to 2500 times higher than for SGLT1, which is expressed in both the kidneys and the gastrointestinal system. [2] Research indicates that individuals with type 2 diabetes mellitus (T2DM) exhibit upregulated SGLT2 expression, which enhances renal glucose reabsorption and contributes to sustained hyperglycemia. Inhibiting SGLT2 reduces this reabsorptive capacity by around 30% to 50%, thereby increasing urinary glucose excretion and helping to lower elevated blood sugar levels. [19] The glucose-lowering action of SGLT2 inhibitors does not depend on insulin, which translates into a lower risk of hypoglycemia. These agents typically lower HbA1c levels by approximately 0.7% to 1.0%, whether used as monotherapy or in combination with other antidiabetic drugs. [18] Clinical trials have repeatedly shown that SGLT2 inhibitors effectively reduce blood glucose, with HbA1c levels decreasing by approximately 0.5% to 0.9% (5–9 mmol/mol) following 12 months of treatment. [2] Additionally, they have been shown to support an average weight reduction of 2–3 kg over a six-month period. Some studies also report modest decreases in blood pressure, with reductions of up to 5 mmHg systolic and 2 mmHg diastolic. [18] Because of their noninsulin-dependent mode of action, SGLT2 inhibitors can be used in combination with any class of glucose-lowering agent and at any stage of disease, including in patients with long-standing T2DM who have minimal insulin secretion. [19] SGLT2 inhibitors are recommended as part of comprehensive treatment strategies, as they not only aid in glycemic control but have also demonstrated benefits in reducing the progression of chronic kidney disease and lowering the risk of cardiovascular complications, and normalizing the lipid profile in various clinical studies. [2,22] Sodium-glucose cotransporter-2 inhibitors (SGLT-2is)- such as canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin- have demonstrated cardiovascular benefits in individuals with both diabetes and heart disease in clinical studies. More recent trials involving dapagliflozin and empagliflozin have further shown their effectiveness in the treatment and prevention of heart failure, not only in patients with diabetes but also in those without the condition. [23] Nevertheless, phlorizin-derived SGLT2 inhibitors have been associated with several significant side effects, such as urinary tract and genital infections, diabetic ketoacidosis, and, in some cases, an elevated risk of bladder cancer with dapagliflozin, as well as increased incidences of amputations and bone fractures with canagliflozin. [22,24]

4.2 GLP-1 Receptor Agonists

Glucagon-like peptide-1 (GLP-1) receptor agonists are recently approved drugs used in the management of both diabetes and obesity. [2]

Short-acting GLP-1 receptor agonists typically lower HbA1c by approximately 0.8% to 1.2%, whereas long-acting agents achieve a greater average reduction of around 1.0% to 1.8%. Weight loss averages between 2 and 4 kg with exenatide (twice daily), lixisenatide (once daily), liraglutide (once daily), and dulaglutide (once weekly). In comparison, oral semaglutide (once daily) and subcutaneous semaglutide (once weekly) are associated with an average weight loss of 4 to 6 kg. [18] Short-acting GLP-1 receptor agonists, such as exenatide (twice daily) and lixisenatide, are less effective in lowering overnight and fasting plasma glucose but retain their ability to slow gastric emptying over long-term use. In contrast, long-acting agents like liraglutide, once-weekly exenatide, dulaglutide, albiglutide, and semaglutide provide stronger reductions in overnight and fasting glucose levels as well as HbA1c, whether used alongside oral antidiabetic medications or in combination with basal insulin. [25] Treatment with GLP-1 receptor agonists reduces appetite, leading to weight loss, which in turn contributes to enhanced quality of life and lowers the risk of cardiovascular and kidney-related complications. [26] GLP-1 receptor agonists consistently lower systolic blood pressure by approximately 2–5 mmHg, while their effect on diastolic pressure is more variable. These agents also promote weight loss and lead to modest reductions in lipoprotein levels, including decreases in LDL cholesterol and triglycerides. [27] GLP-1 affects various tissues and organs beyond the pancreas- it slows gastric emptying in the stomach, provides cardioprotective effects on the heart, enhances glucose uptake in adipose tissue and skeletal muscle, and acts on hypothalamic neurons in the brain to promote a sense of satiety. [2] Although GLP-1RAs are highly effective and offer multiple clinical benefits, their early use was restricted due to the necessity of injectable administration. To overcome this limitation, an oral version of semaglutide was developed by combining it with sodium N-(8-[2-hydroxybenzoyl]amino)caprylate- a well-established transcellular absorption enhancer- resulting in the first GLP-1RA available in oral form. [28]

4.3 DPP-4 Inhibitors

DPP-4 inhibitors are small-molecule, orally administered medications that act quickly and selectively to block the activity of the DPP-4 enzyme. This enzyme is widely distributed in the body, found in the bloodstream and on the surface of many cell types, and is responsible for deactivating the incretin hormones GLP-1 and GIP. By inhibiting DPP-4, these drugs increase the levels of active GLP-1 and GIP after meals by approximately two- to three-fold. All currently approved DPP-4 inhibitors offer comparable glucose-lowering effects, typically leading to a moderate reduction in HbA1c of about 0.5-0.8%. [29] DPP-4 inhibitors contribute to glucose regulation by increasing the effectiveness of the incretin system. [30] Evidence from major clinical trials indicates that treatment with DPP-4 inhibitors leads to improved glycemic control by enhancing insulin secretion from pancreatic islet cells, lowering HbA1c levels, decreasing adipocyte size, and reducing inflammatory responses. [31]

DPP-4 inhibitors are considered weight neutral, as they only modestly increase GLP-1 activity and, unlike GLP-1RAs, have no effect on gastric emptying or weight loss. [29,31] These medications raise GLP-1 levels by approximately two- to three-fold after meals, which is considerably lower than the ten-fold increase seen with GLP-1 receptor agonists. [2] The incretin hormone GLP-1 has minimal impact on stimulating insulin release from pancreatic beta cells when blood glucose levels are not elevated, particularly in the absence of glucose absorbed from the gut. Because of their glucose-dependent mechanism of action through GLP-1, the likelihood of hypoglycemia with DPP-4 inhibitors is low. [29] Although DPP-4 inhibitors offer several advantages, including good tolerability and a low risk of hypoglycemia, their ability to reduce HbA1c is generally weaker when compared to GLP-1 receptor agonists. [2] Lower risk of hypoglycemia is a clear advantage compared to sulfonylureas, which stimulate insulin secretion by closing ATP-sensitive potassium channels- a process that operates independently of blood glucose levels to a significant extent. [32]

4.4 Tirzepatide

Tirzepatide is an innovative drug that activates both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors, leading to better blood sugar regulation and notable weight loss. [33] It binds to the GIP receptor with a strength comparable to the body's natural GIP, while its binding affinity to the GLP-1 receptor is about five times lower than that of natural GLP-1. [34] Moreover, tirzepatide has positive effects on blood pressure, LDL cholesterol, and triglyceride levels, indicating its potential to help lower the risk of complications related to type 2 diabetes. [35] Clinical studies have demonstrated that tirzepatide effectively

reduces appetite and overall food intake by increasing feelings of fullness and decreasing hunger. For instance, in a study involving patients with type 2 diabetes (T2D), a 15 mg dose of tirzepatide resulted in an approximate reduction of 310 kcal in energy consumption during an ad-libitum lunch compared to placebo. [36] Further mechanistic research in individuals with obesity but without diabetes confirmed that tirzepatide significantly lowers food intake compared to placebo. These studies also showed an increase in fat oxidation, without a significant effect on metabolic adaptation. Tirzepatide improves glycemic control in people with T2D by lowering both fasting and post-meal blood glucose levels. This is achieved through several mechanisms, including enhanced beta-cell function, improved insulin sensitivity, reduced glucagon secretion, and delayed gastric emptying, although the effect on gastric emptying tends to decrease over time. [37]

5. Comparative Effectiveness of Semaglutide and Tirzepatide for Weight Reduction in Adults with Overweight or Obesity

Although tirzepatide leads to greater weight loss than semaglutide in individuals with type 2 diabetes, direct comparison studies in patients with overweight or obesity are still lacking. [38] Based on this large cohort study using propensity score matching, it was demonstrated that individuals with overweight or obesity treated with tirzepatide achieved significantly greater and more clinically meaningful weight loss compared to those receiving semaglutide (injectable). Out of 41,222 adults included in the study (32,029 on semaglutide; 9,193 on tirzepatide), 18,386 were matched using propensity scores. The average age was 52 years, with 70.5% female and 52% having type 2 diabetes. The mean baseline weight was 110 kg. Treatment was discontinued by 55.9% of tirzepatide users and 52.5% of semaglutide users. Tirzepatide users were significantly more likely to achieve ≥5%, ≥10%, and ≥15% weight loss, with hazard ratios of 1.76, 2.54, and 3.24, respectively. At 3 months, the average body weight reduction was 5.9% (95% CI: -6.0% to -5.8%) with tirzepatide, compared to 3.6% (95% CI: -3.7% to -3.4%) with semaglutide. At 6 months, the reductions were 10.1% (95% CI: -10.4% to -9.9%) and 5.8% (95% CI: -6.0% to -5.5%), respectively. By 12 months, tirzepatide led to a 15.3% weight loss (95% CI: -16.0% to -14.5%) versus 8.3% (95% CI: -9.0% to -7.6%) for semaglutide. After adjusting for residual confounding factors, the absolute differences in weight reduction between the two treatments were-2.4% (95% CI: -2.5% to -2.2%) at 3 months, -4.3% (95% CI: -4.7% to -4.0%) at 6 months, and -6.9% (95% CI: -7.9% to -5.8%) at 12 months. Weight loss was also greater with tirzepatide at 3, 6, and 12 months. Gastrointestinal side effects occurred at similar rates in both groups. [39]

6. Tirzepatide Versus Placebo: Findings from the Phase 3, Double-Blind, Randomized SURPASS-1 Trial

In 2021, the SURPASS-1 trial- a randomized, double-blind phase 3 study- was conducted to assess the effectiveness of once-weekly subcutaneous tirzepatide versus placebo in individuals with type 2 diabetes inadequately managed through diet and exercise alone. The results showed that all tested doses of tirzepatide led to significantly greater reductions in body weight, fasting glucose, and HbA1c compared to placebo. At week 40, all doses of tirzepatide showed significantly greater improvements compared to placebo in lowering HbA1c, fasting serum glucose, body weight, and in achieving HbA1c targets below 7.0% (<53 mmol/mol) and 5.7% (<39 mmol/mol). Mean reductions in HbA1c from baseline were 1.87% (20 mmol/mol) with 5 mg, 1.89% (21 mmol/mol) with 10 mg, and 2.07% (23 mmol/mol) with 15 mg of tirzepatide, compared to a slight increase of 0.04% (0.4 mmol/mol) in the placebo group. The corresponding estimated treatment differences versus placebo were -1.91% (-21 mmol/mol), -1.93% (-21 mmol/mol), and -2.11% (-23 mmol/mol) for the 5 mg, 10 mg, and 15 mg doses respectively- all statistically significant ($p < 0.0001$). Tirzepatide demonstrated strong glycemic efficacy without increasing the risk of hypoglycemia and was associated with meaningful weight loss. Its safety profile was consistent with that of existing GLP-1 receptor agonists. [2,40]

7. Tirzepatide versus Semaglutide

In 2021, a clinical trial was conducted to evaluate the effectiveness of once-weekly tirzepatide versus semaglutide in individuals with type 2 diabetes. A total of 1,879 participants were randomly allocated in equal proportions (1:1:1:1) to receive once-weekly subcutaneous injections of tirzepatide at doses of 5 mg, 10 mg, or 15 mg (administered in a double-blind manner), or semaglutide at a dose of 1 mg. The treatment phase lasted 40 weeks, followed by a 4-week safety monitoring period. After 40 weeks of treatment, the average reduction in HbA1c was- 2.01 percentage points with tirzepatide 5 mg, -2.24 percentage points with 10 mg, and- 2.30 percentage points with 15 mg, compared to a reduction of -1.86 percentage points observed with semaglutide. Weight reduction with tirzepatide followed a dose-dependent pattern. After 40 weeks, the average

weight loss was -7.6 kg with the 5 mg dose, -9.3 kg with the 10 mg dose, and -11.2 kg with the 15 mg dose, compared to -5.7 kg observed in the semaglutide group. Tirzepatide outperformed semaglutide at all dose levels, with estimated differences of -1.9 kg (95% CI, -2.8 to -1.0) for 5 mg, -3.6 kg (95% CI, -4.5 to -2.7) for 10 mg, and -5.5 kg (95% CI, -6.4 to -4.6) for 15 mg (all comparisons statistically significant, $P < 0.001$). The results showed that all tirzepatide groups achieved greater reductions in HbA1c and body weight compared to the semaglutide group. Tirzepatide was also associated with improvements in blood pressure and lipid parameters. Both treatment arms had similar safety profiles, with the most common adverse events being mild to moderate gastrointestinal symptoms. [2,38]

Conclusions

The therapeutic landscape for type 2 diabetes has evolved significantly with the introduction of advanced injectable medications. GLP-1 receptor agonists and dual GIP/GLP-1 receptor agonists, such as semaglutide and tirzepatide, offer highly effective options not only for glycemic control but also for weight management and reduction of cardiovascular risk. Clinical trials consistently show that these agents outperform earlier treatments like DPP-4 inhibitors and sulfonylureas in key metabolic outcomes, while maintaining favorable safety profiles.

Tirzepatide, in particular, represents a new generation of incretin-based therapies, demonstrating superior efficacy in both HbA1c reduction and weight loss compared to established GLP-1 RAs like semaglutide. Moreover, the availability of semaglutide in an oral formulation has addressed some of the limitations associated with injectable therapies, enhancing treatment flexibility and patient adherence.

Despite these advancements, long-term safety data, especially concerning cardiovascular and renal endpoints, continue to be monitored. The integration of these injectable agents into clinical practice should be individualized, considering patient comorbidities, tolerability, and treatment goals. Ongoing research and head-to-head comparisons will further clarify the optimal use of these therapies in real-world settings.

Overall, the development of newer injectable medications has significantly broadened the scope of effective, personalized treatment options for patients with type 2 diabetes, with the potential to improve both glycemic control and long-term health outcomes.

Disclosure

Authors do not report any disclosures.

Author's contributions

Conceptualization: Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Methodology: Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Software - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Check - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Formal analysis - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Investigation - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Resources - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Data curation - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Writing - rough preparation - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Writing - review and editing - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Visualization - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Supervision - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

Project administration - Katarzyna Jurkiewicz, Marek Ciechański, Aleksandra Kasprzyk, Klaudia Wilk, Edyta Witkowska, Szymon Cholewiński, Bernadetta Wilk, Piotr Stachura, Piotr Rejman, Katarzyna Pszczoła

All authors have read and agreed with the published version of the manuscript.

Funding Statement: This research received no external funding.
Institutional Review Board Statement: not applicable
Informed Consent Statement: not applicable
Data Availability Statement: not applicable
Acknowledgments: not applicable
Conflict of Interest Statement: The authors declare no conflict of interest.

REFERENCES

1. Malik A, Ahmed M, Mansoor S, Ambreen S, Usman B, Shehryar M. Cognitive Impairment in Type 2 Diabetes Mellitus. Cureus. 2022 Feb 14;14(2):e22193. doi: 10.7759/cureus.22193. Erratum in: Cureus. 2022 Mar 18;14(3):c59. doi: 10.7759/cureus.c59. PMID: 35308758; PMCID: PMC8925983.
2. Młynarska E, Czarnik W, Dzieża N, Jędraszak W, Majchrowicz G, Prusinowski F, Stabrawa M, Rysz J, Franczyk B. Type 2 Diabetes Mellitus: New Pathogenetic Mechanisms, Treatment and the Most Important Complications. Int J Mol Sci. 2025 Jan 27;26(3):1094. doi: 10.3390/ijms26031094. PMID: 39940862; PMCID: PMC11817707.
3. Landgraf R, Aberle J, Birkenfeld AL, Gallwitz B, Kellerer M, Klein H, Müller-Wieland D, Nauck MA, Reuter HM, Siegel E. Therapy of Type 2 Diabetes. Exp Clin Endocrinol Diabetes. 2019 Dec;127(S 01):S73-S92. doi: 10.1055/a-1018-9106. Epub 2019 Dec 20. PMID: 31860927.
4. Zhao M, Sun S, Huang Z, Wang T, Tang H. Network Meta-Analysis of Novel Glucose-Lowering Drugs on Risk of Acute Kidney Injury. Clin J Am Soc Nephrol. 2020 Dec 31;16(1):70-78. doi: 10.2215/CJN.11220720. Epub 2020 Dec 29. PMID: 33376101; PMCID: PMC7792639.
5. Iwasaki H, Yagyu H, Shimano H. A Comprehensive Analysis of Diabetic Complications and Advances in Management Strategies. J Atheroscler Thromb. 2025 May 1;32(5):550-559. doi: 10.5551/jat.65551. Epub 2025 Jan 10. PMID: 39805627; PMCID: PMC12055507.
6. Javeed N, Matveyenko AV. Circadian Etiology of Type 2 Diabetes Mellitus. Physiology (Bethesda). 2018 Mar 1;33(2):138-150. doi: 10.1152/physiol.00003.2018. PMID: 29412061; PMCID: PMC5899235.
7. Lu X, Xie Q, Pan X, Zhang R, Zhang X, Peng G, Zhang Y, Shen S, Tong N. Type 2 diabetes mellitus in adults: pathogenesis, prevention and therapy. Signal Transduct Target Ther. 2024 Oct 2;9(1):262. doi: 10.1038/s41392-024-01951-9. PMID: 39353925; PMCID: PMC11445387.
8. Ismail L, Materwala H, Al Kaabi J. Association of risk factors with type 2 diabetes: A systematic review. Comput Struct Biotechnol J. 2021 Mar 10;19:1759-1785. doi: 10.1016/j.csbj.2021.03.003. PMID: 33897980; PMCID: PMC8050730.
9. Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, Ostolaza H, Martín C. Pathophysiology of Type 2 Diabetes Mellitus. Int J Mol Sci. 2020 Aug 30;21(17):6275. doi: 10.3390/ijms21176275. PMID: 32872570; PMCID: PMC7503727.
10. Zhang Y, Pan XF, Chen J, Xia L, Cao A, Zhang Y, Wang J, Li H, Yang K, Guo K, He M, Pan A. Combined lifestyle factors and risk of incident type 2 diabetes and prognosis among individuals with type 2 diabetes: a systematic review and meta-analysis of prospective cohort studies. Diabetologia. 2020 Jan;63(1):21-33. doi: 10.1007/s00125-019-04985-9. Epub 2019 Sep 4. PMID: 31482198.
11. Khan RMM, Chua ZJY, Tan JC, Yang Y, Liao Z, Zhao Y. From Pre-Diabetes to Diabetes: Diagnosis, Treatments and Translational Research. Medicina (Kaunas). 2019 Aug 29;55(9):546. doi: 10.3390/medicina55090546. PMID: 31470636; PMCID: PMC6780236.
12. Chandrasekaran P, Weiskirchen R. The Role of Obesity in Type 2 Diabetes Mellitus-An Overview. Int J Mol Sci. 2024 Feb 4;25(3):1882. doi: 10.3390/ijms25031882. PMID: 38339160; PMCID: PMC10855901.
13. Cloostermans L, Wendel-Vos W, Doornbos G, Howard B, Craig CL, Kivimäki M, Tabak AG, Jefferis BJ, Ronkainen K, Brown WJ, Picavet SH, Ben-Shlomo Y, Laukkanen JA, Kauhanen J, Bemelmans WJ. Independent and combined effects of physical activity and body mass index on the development of Type 2 Diabetes - a meta-analysis of 9 prospective cohort studies. Int J Behav Nutr Phys Act. 2015 Dec 1;12:147. doi: 10.1186/s12966-015-0304-3. PMID: 26619831; PMCID: PMC4666059.

14. Debnath DJ, Ray J, Jah SM, Marimuthu Y. Smoking and the Risk of Type 2 Diabetes: A Cross-sectional Analytical Study. Indian J Community Med. 2024 Jul-Aug;49(4):588-592. doi: 10.4103/ijcm.ijcm_1009_22. Epub 2024 Jul 9. PMID: 39291121; PMCID: PMC11404421.
15. Maddatu J, Anderson-Baucum E, Evans-Molina C. Smoking and the risk of type 2 diabetes. Transl Res. 2017 Jun;184:101-107. doi: 10.1016/j.trsl.2017.02.004. Epub 2017 Mar 6. PMID: 28336465; PMCID: PMC5429867.
16. Rouland A, Thuillier P, Al-Salameh A, Benzerouk F, Bahougne T, Tramunt B, Berlin I, Clair C, Thomas D, Le Faou AL, Vergès B, Durlach V. Smoking and diabetes. Ann Endocrinol (Paris). 2024 Dec;85(6):614-622. doi: 10.1016/j.ando.2024.08.001. Epub 2024 Aug 30. PMID: 39218351.
17. Knott C, Bell S, Britton A. Alcohol Consumption and the Risk of Type 2 Diabetes: A Systematic Review and Dose-Response Meta-analysis of More Than 1.9 Million Individuals From 38 Observational Studies. Diabetes Care. 2015 Sep;38(9):1804-12. doi: 10.2337/dc15-0710. PMID: 26294775.
18. Chong K, Chang JK, Chuang LM. Recent advances in the treatment of type 2 diabetes mellitus using new drug therapies. Kaohsiung J Med Sci. 2024 Mar;40(3):212-220. doi: 10.1002/kjm2.12800. Epub 2024 Jan 6. PMID: 38183334; PMCID: PMC11895656.
19. Thrasher J. Pharmacologic Management of Type 2 Diabetes Mellitus: Available Therapies. Am J Med. 2017 Jun;130(6S):S4-S17. doi: 10.1016/j.amjmed.2017.04.004. PMID: 28526182.
20. Majety P, Lozada Orquera FA, Edem D, Hamdy O. Pharmacological approaches to the prevention of type 2 diabetes mellitus. Front Endocrinol (Lausanne). 2023 Mar 9;14:1118848. doi: 10.3389/fendo.2023.1118848. PMID: 36967777; PMCID: PMC10033948.
21. Taylor SI, Yazdi ZS, Beitelshees AL. Pharmacological treatment of hyperglycemia in type 2 diabetes. J Clin Invest. 2021 Jan 19;131(2):e142243. doi: 10.1172/JCI142243. PMID: 33463546; PMCID: PMC7810496.
22. Blahova J, Martiniakova M, Babikova M, Kovacova V, Mondockova V, Omelka R. Pharmaceutical Drugs and Natural Therapeutic Products for the Treatment of Type 2 Diabetes Mellitus. Pharmaceuticals (Basel). 2021 Aug 17;14(8):806. doi: 10.3390/ph14080806. PMID: 34451903; PMCID: PMC8398612.
23. Rao S. Use of Sodium-Glucose Cotransporter-2 Inhibitors in Clinical Practice for Heart Failure Prevention and Treatment: Beyond Type 2 Diabetes. A Narrative Review. Adv Ther. 2022 Feb;39(2):845-861. doi: 10.1007/s12325-021-01989-z. Epub 2021 Dec 9. PMID: 34881413; PMCID: PMC8866261.
24. Moradi-Marjaneh R, Paseban M, Sahebkar A. Natural products with SGLT2 inhibitory activity: Possibilities of application for the treatment of diabetes. Phytother Res. 2019 Oct;33(10):2518-2530. doi: 10.1002/ptr.6421. Epub 2019 Jul 29. PMID: 31359514.
25. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021 Apr;46:101102. doi: 10.1016/j.molmet.2020.101102. Epub 2020 Oct 14. PMID: 33068776; PMCID: PMC8085572.
26. Marx N, Husain M, Lehrke M, Verma S, Sattar N. GLP-1 Receptor Agonists for the Reduction of Atherosclerotic Cardiovascular Risk in Patients With Type 2 Diabetes. Circulation. 2022 Dec 13;146(24):1882-1894. doi: 10.1161/CIRCULATIONAHA.122.059595. Epub 2022 Dec 12. PMID: 36508493.
27. Nauck MA, Meier JJ, Cavender MA, Abd El Aziz M, Drucker DJ. Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors. Circulation. 2017 Aug 29;136(9):849-870. doi: 10.1161/CIRCULATIONAHA.117.028136. PMID: 28847797.
28. Aroda VR, Blonde L, Pratley RE. A new era for oral peptides: SNAC and the development of oral semaglutide for the treatment of type 2 diabetes. Rev Endocr Metab Disord. 2022 Oct;23(5):979-994. doi: 10.1007/s11154-022-09735-8. Epub 2022 Jul 15. PMID: 35838946; PMCID: PMC9515042.
29. Gilbert MP, Pratley RE. GLP-1 Analogs and DPP-4 Inhibitors in Type 2 Diabetes Therapy: Review of Head-to-Head Clinical Trials. Front Endocrinol (Lausanne). 2020 Apr 3;11:178. doi: 10.3389/fendo.2020.00178. PMID: 32308645; PMCID: PMC7145895.
30. Makrilakis K. The Role of DPP-4 Inhibitors in the Treatment Algorithm of Type 2 Diabetes Mellitus: When to Select, What to Expect. Int J Environ Res Public Health. 2019 Jul 30;16(15):2720. doi: 10.3390/ijerph16152720. PMID: 31366085; PMCID: PMC6696077.
31. Razavi M, Wei YY, Rao XQ, Zhong JX. DPP-4 inhibitors and GLP-1RAs: cardiovascular safety and benefits. Mil Med Res. 2022 Aug 20;9(1):45. doi: 10.1186/s40779-022-00410-2. PMID: 35986429; PMCID: PMC9392232.
32. Carr RD, Solomon A. Inhibitors of dipeptidyl peptidase-4 as therapeutic agents for individuals with type 2 diabetes: a 25-year journey. Diabet Med. 2020 Aug;37(8):1230-1233. doi: 10.1111/dme.14325. Epub 2020 Jun 8. PMID: 32426859; PMCID: PMC7496331.
33. Sardar MB, Nadeem ZA, Babar M. Tirzepatide: A novel cardiovascular protective agent in type 2 diabetes mellitus and obesity. Curr Probl Cardiol. 2024 May;49(5):102489. doi: 10.1016/j.cpcardiol.2024.102489. Epub 2024 Feb 28. PMID: 38417475.
34. Willard FS, Douros JD, Gabe MB, Showalter AD, Wainscott DB, Suter TM, Capozzi ME, van der Velden WJ, Stutsman C, Cardona GR, Urva S, Emmerson PJ, Holst JJ, D'Alessio DA, Coghlan MP, Rosenkilde MM, Campbell JE, Sloop KW. Tirzepatide is an imbalanced and biased dual GIP and GLP-1 receptor agonist. JCI Insight. 2020 Sep 3;5(17):e140532. doi: 10.1172/jci.insight.140532. PMID: 32730231; PMCID: PMC7526454.

35. De Block C, Bailey C, Wysham C, Hemmingway A, Allen SE, Peleshok J. Tirzepatide for the treatment of adults with type 2 diabetes: An endocrine perspective. Diabetes Obes Metab. 2023 Jan;25(1):3-17. doi: 10.1111/dom.14831. Epub 2022 Aug 31. PMID: 35929488; PMCID: PMC10087310.
36. Heise T, DeVries JH, Urva S, Li J, Pratt EJ, Thomas MK, Mather KJ, Karanikas CA, Dunn J, Haupt A, Milicevic Z, Coskun T. Tirzepatide Reduces Appetite, Energy Intake, and Fat Mass in People With Type 2 Diabetes. Diabetes Care. 2023 May 1;46(5):998-1004. doi: 10.2337/dc22-1710. PMID: 36857477; PMCID: PMC10154650.
37. Hamza M, Papamargaritis D, Davies MJ. Tirzepatide for overweight and obesity management. Expert Opin Pharmacother. 2025 Jan;26(1):31-49. doi: 10.1080/14656566.2024.2436595. Epub 2024 Dec 4. PMID: 39632534.
38. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, Liu B, Cui X, Brown K; SURPASS-2 Investigators. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021 Aug 5;385(6):503-515. doi: 10.1056/NEJMoa2107519. Epub 2021 Jun 25. PMID: 34170647.
39. Rodriguez PJ, Goodwin Cartwright BM, Gratzl S, Brar R, Baker C, Gluckman TJ, Stucky NL. Semaglutide vs Tirzepatide for Weight Loss in Adults With Overweight or Obesity. JAMA Intern Med. 2024 Sep 1;184(9):1056-1064. doi: 10.1001/jamainternmed.2024.2525. PMID: 38976257; PMCID: PMC11231910.
40. Rosenstock J, Wysham C, Frías JP, Kaneko S, Lee CJ, Fernández Landó L, Mao H, Cui X, Karanikas CA, Thieu VT. Efficacy and safety of a novel dual GIP and GLP-1 receptor agonist tirzepatide in patients with type 2 diabetes (SURPASS-1): a double-blind, randomised, phase 3 trial. Lancet. 2021 Jul 10;398(10295):143-155. doi: 10.1016/S0140-6736(21)01324-6. Epub 2021 Jun 27. Erratum in: Lancet. 2021 Jul 17;398(10296):212. doi: 10.1016/S0140-6736(21)01556-7. PMID: 34186022.