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Tirzepatide in weight management and metabolic fitness: clinical efficacy, safety, and future applications in type 2 diabetes, obesity, and sports nutrition

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ABSTRACT

Type 2 diabetes mellitus (T2DM) is a disease which states as most serious global health problems of current times, described as global pandemic. The history of diabetes treatment has been evolving over the past decades, starting with the invention of an animal-derived insulin in the early 20th century, with still developing therapies, ending. One of the most promising drug groups in diabetes treatment is twincretins (dual GIP and GLP-1R agonists), which entered the market in the 20s of the XXI century. Tirzepatide, which show combines antihyperglycemic effect, reduces cardiovascular risk and helps patient with weight management is a a representative of twincretins.

Keywords: Tirzepatide, Dual GIP/GLP-1 agonist, SURPASS clinical trials, Incretin-based therapy, Cardiovascular risk reduction, Type 2 diabetes mellitus (T2DM), Metabolic fitness, Weight loss

1. INTRODUCTION

The development of Type 2 diabetes mellitus (T2DM) treatment represents a significant advancement in the field of diabetology. The introduction of the insulin derived from animals in 1922 set the diabetes treatment in train. The first human insulin (Humulin®) was possible in 1982, due to DNA recombination technology (Qiu et al., 2024).

The first rapid-acting insulin analog insulin lispro (Humalog) received FDA approval in 1996 followed by the long-acting insulin analog glargine (Lantus) in 2000 (Sims et al.,2021). The medical field adopted sulfonylurea derivatives through the introduction of third-generation agents which included glimepiride. The development of new drug classes included α-glucosidase inhibitors (acarbose and

miglitol) and thiazolidinediones (rosiglitazone and pioglitazone) and meglitinides (repaglinide and nateglinide) (Sims et al.,2021).

The discovery of incretin system importance in 2005 brought about fundamental changes to T2DM pharmacotherapy. The first incretin medication that received approval was exenatide (Byetta) as a GLP-1 receptor (GLP-1R) agonist. The GLP-1R agonist class expanded with the introduction of long-acting liraglutide (Victoza) and oral semaglutide (Rybelsus) during subsequent years. The medical field introduced DPP-4 inhibitors (sitagliptin and vildagliptin) as incretin activity extenders starting from 2006.

SGLT2 inhibitors known as flozins entered the market after 2010 when dapagliflozin and empagliflozin became available. This drug group offered not only glycemic control but also cardioprotective and nephroprotective benefits (Vasilakou et al., 2013).

The 2020s brought Twincretins to the market as dual GIP and GLP-1R agonists which represented a new class of medications. The FDA approved tirzepatide (Mounjaro) as a dual GIP and GLP-1R agonist for T2DM treatment in 2022 before adding obesity treatment to its indications (Nicholls et al., 2024; Davies et al., 2022).

The dynamic revolution of T2DM pharmacotherapy, described above, allowed for improvement of personalization and effectiveness of T2DM treatment. Thanks to the dual GIP and GLP-1R agonist nowadays, we can target not only glycemic control in patients, but also the reduction of metabolic and cardiovascular complications. Tirzepatide is the representation of these multifaceted benefits (Nicholls et al., 2024, Davies et al., 2022).

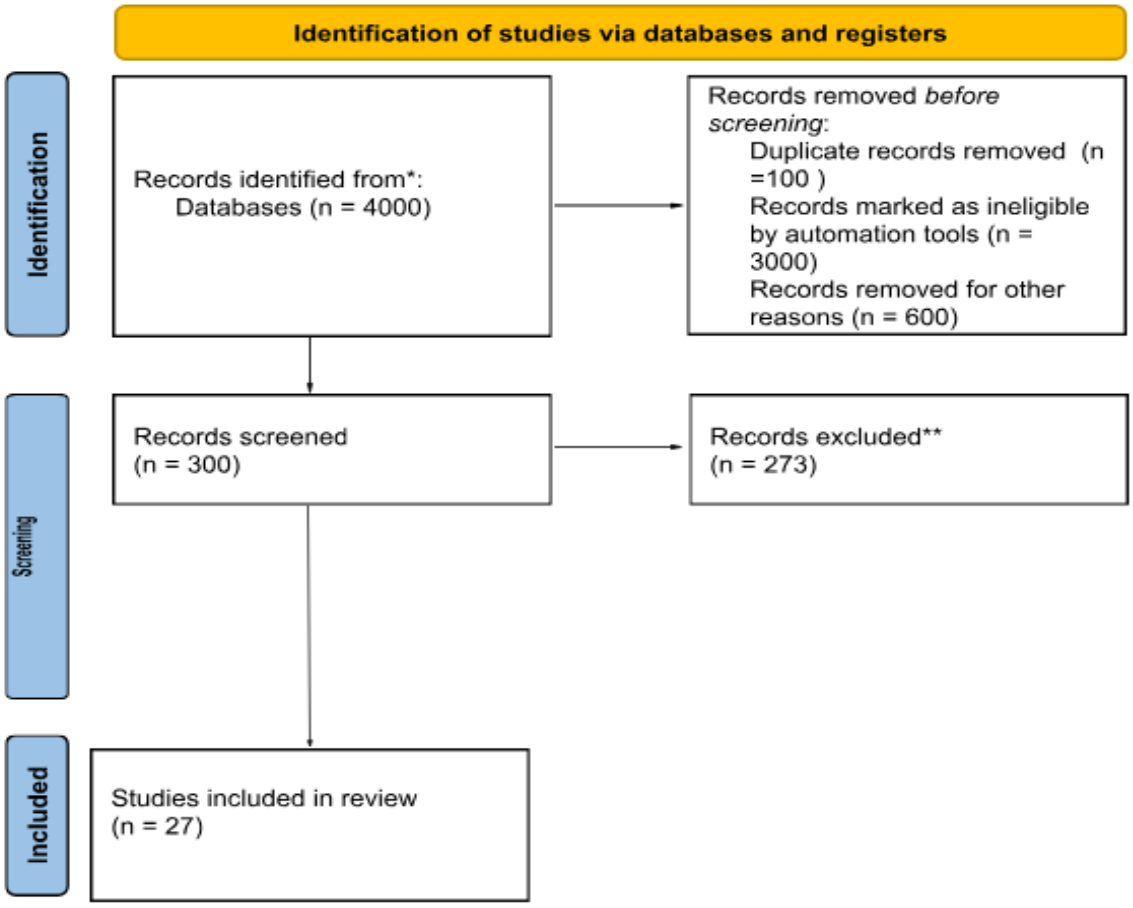

Figure 1. The PRISMA flow diagram shows the process of study identification and screening

2. REVIEW METHODS

The authors searched the PubMed, Scopus, and Google Scholar databases using phrases such as T2DM, twincretins, tirzepatide, SURPASS clinical trials and cardiovascular risk reduction to refine and optimize the search results. We analysed 53 articles published in English between 2005 and November 2024.

The articles were selected for their direct relevance to understanding the pathogenesis of T2DM, disease epidemiology, and modern treatment methods, with particular emphasis on the incretin-based therapies and their comparison with other available medications.

The selection was determined by abstract and title analysis. The evidence base also included actual American Diabetes Association guidelines, which provided comprehensive recommendations for the management of T2DM.

Furthermore, additional articles were identified by screening the bibliographies of studies retrieved through the database searches. The article screening process adhered to the PRISMA guidelines (Figure 1).

3. RESULTS & DISCUSSION

3.1. Physiology of Incretins

Understanding the physiology of incretin hormones: glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) is crucial to understand the role of tirzepatyde in T2DM (selective, dual agonist of incretin hormone receptors - GIP and GLP-1) pharmacotherapy (Forzano et al., 2022).

The locations of incretin hormone secretion are: for GIP – K cells, the duodenum and the upper part of the small intestine, whereas for GLP-1 – L cells, in the ileum, colon, and rectum. Secretion of incretins is activated in response to food intake. Afterwards, the incretins bind (depending on glucose level) to their specific receptors (GLP-1R and GIPR), which are located in pancreatic β-cells. As a result, insulin secretion by these cells is intensified. Through their combined action, incretins are responsible for 50–70% of total postprandial insulin secretion. Dipeptidyl peptidase 4 (DPP-4) degrades incretin hormones.

However, the role of incretin hormones is not limited only to responding to food intake and the pancreatic secretion of insulin - both of these promote the proliferation of pancreatic β-cells. At the same time, they inhibit β-cells apoptosis, as a result increasing pancreatic mass. Additionally, they influence gastric emptying time: GIP suppresses gastric acid secretion, whereas GLP-1 delays the transit of food to the distal segments of the gastrointestinal tract.

Their antagonistic effects are evident in their interaction with glucagon - GIP promotes its postprandial secretion, while GLP-1 inhibits it. However, this is not the only difference between these incretin hormones: GIP facilitates lipogenesis and promotes bone formation, whereas GLP-1 suppresses bone mass accumulation and exerts cardioprotective effects.

Pancreatic β-cells secrete amylin. It cooperates with incretins at the central nervous system level. They regulate together satiety, metabolism, and glucose homeostasis. Amylin reduces hunger sensation in brain regions, specifically the nucleus tractus solitarius (NTS) and area postrema (AP), which are involved in appetite control. It also slows gastric emptying and suppresses the secretion of glucagon. GLP-1 binds in the central nervous system to specific GLP-1R, which are located in the hypothalamic paraventricular nucleus (PVH). By acting on PVH, amylin decreases appetite and increases feelings of fullness (Forzano et al., 2022).

3.2. Epidemiology of T2DM

T2DM is one of the most important global health problems of the modern era. Together with the obesity pandemic, they have become a leading challenge for contemporary medicine. According to the actual statistics, in 2022, 828 million people were suffering from diabetes (420 million women and 408 million men). A lower number of diabetic patients was observed in Western Europe and Eastern Africa for both women and men. In contrast, the highest rates were recorded in India, China, and the United States.

The NCD Risk Factor Collaboration's research, which was conducted in 2022, exposed a concerning upward trend in particular society groups: there are more diabetic patients in low- and middle-income countries in comparison to highly developed nations (NCD Risk Factor Collaboration, 2024).

3.3. Pathomechanism of T2DM

Multifactorial molecular processes are involved in T2DM pathogenesis, among the most important ones we can list: (1) impaired secretory function of pancreatic β-cells, (2) insulin resistance (IR) in peripheral tissues with its consequences (Roden and Shulman, 2019). These abnormalities lead to dysfunctional glycemic homeostasis, which results in progressive decompensation of β-cells and their inadequate insulin production.

3.3.1. Genetic factors of T2DM

A significant role in modulating susceptibility to T2DM in patients is played not only by genetic factors and positive family history of the disease, but also by a specific phenotype (Sinha et al., 2024). Researches that have been conducted over the past decades indicate a polygenic basis for T2DM. Genetic abnormalities identified within research include: impaired insulin secretion under conditions of

hyperglycemia and fasting normoglycemia, defective processing of proinsulin into its biologically active form, and mutations that alter peripheral tissue sensitivity to insulin action.

3.3.2. Nutritional factors and physical activity

The profile of the patient suffering from T2DM can be easily portrayed by discussing the disease's risk factors. A typical lifestyle leading to the illness can be classified as sedentary with a lack of physical activity, accompanied by an overconsumption of food high in calories, often highly processed. All the above, in the long run, equal abdominal obesity (observed in 85% of diabetic patients) and body mass index (BMI) values ≥30 kg/m², often coexisting with arterial hypertension and lipid metabolism disorders (Roden and Shulman, 2019).

Elevated levels of very-low-density lipoproteins (VLDL), chylomicrons (CM), and triglyceride-rich chylomicron remnants (CMR) are one of the most common lipid metabolism disorders linked to diabetes, causing an increased generation of reactive oxygen species (ROS). Oxidative stress, in turn, exerts a harmful effect on pancreatic β-cells, impairing their function and also negatively impacting angiogenesis, epigenetic mechanisms, and mitochondrial function (Hummasti and Hotamisligil, 2010).

Described mechanisms lead to oxidative stress and permanent inflammation. In this process participate pro-inflammatory molecules: interleukin-6 (IL-6), interleukin-1 (IL-1), C-reactive protein (CRP), and tumor necrosis factor-α (TNF-α), which induce β-cell apoptosis (Strasser, 2013).

3.3.3. Mechanisms of pancreatic β-Cell dysfunction

According to current knowledge, pancreatic β-cell dysfunction is associated with prolonged metabolic and oxidative stress resulting from sustained hyperglycemia and elevated levels of saturated free fatty acids (FFA). Compensatory overproduction of insulin is a response to an increased metabolic demand. During that process, some molecules of the insulin are misfolded and stored in β-cells. Additionally, the deposition of islet amyloid polypeptides (IAPP) disrupts intracellular signaling pathways, initiates inflammatory processes, and promotes the induction of β-cell apoptosis (Christensen and Gannon, 2019)

3.3.4. Intestinal dysbiosis

A disruption in the homeostasis of the normal gut microbiome is caused by genetic, environmental, and lifestyle factors described above. The main reason behind intestinal dysbiosis is the imbalance between the increased production of lipopolysaccharides (LPS) by Gram-negative bacteria and decreased production of short-chain fatty acids (SCFAs), resulting in promoted inflammation (LPS) leading to β-cell apoptosis and impaired intestinal barrier integrity, less intensive pancreatic β-cell proliferation, and pathological insulin biosynthesis (SCFAs) (Christensen and Gannon, 2019)

3.3.5. Metabolic memory

The biological factors that affect insulin function properly work through multiple interactions between insulin receptor sensitivity in target tissues and insulin molecules and blood glucose levels and IGF-1 and glucocorticoids and catecholamines and glucagon.

The body uses GLUT2 and GLUT4 as its two primary transporters to let glucose enter tissues. The GLUT2 transporter exists in four main locations of the body which include liver cells for glycogen production and metabolic pathway integration and pancreatic β-cells for insulin release and small intestinal enterocytes for glucose absorption and renal tubules for glucose reabsorption from urine.

GLUT4 is expressed in adipose tissue and striated muscle. In muscles, glucose can also be transported independently in part. In such cases, GLUT4 translocation to the cell membrane is stimulated by contraction-dependent mechanisms, including AMPK (AMP-activated protein kinase) pathway activation or calcium-dependent signaling. That mechanism occurs particularly in physically active individuals (Pearson et al., 2016).

3.3.6. Incretin effect

Disturbances in the incretin effect play an important role in the pathogenesis of T2DM. Physiologically, thanks to the incretin effect, insulin is secreted more efficiently in response to oral glucose administration than to intravenous administration. In individuals with T2DM, this response is impaired - the increase in insulin secretion occurs more slowly, with a lower peak value, achieved later in time. The dose-response relationship between the amount of glucose consumed and insulin released in patients with T2DM is preserved, but this effect is significantly attenuated (Nauck and Müller, 2023).

Abnormalities in incretin function in T2DM patients result from impaired action of endogenous GIP (which generates the majority of the incretin effect compared to GLP-1, even when GLP-1 activity is partially preserved in T2DM) (Nauck and Müller, 2023). A reduced response to the released hormone causes the diminished GIP effect. Patients suffering from impaired glucose tolerance and elevated BMI (even when maintaining normal glucose tolerance) deal with similar incretin effect disturbances (Nauck and Müller, 2023).

T2DM results from multiple factors including genetic elements and environmental triggers such as obesity and physical inactivity and gut dysbiosis and metabolic memory and insulin resistance and impaired incretin effect. The different components of the disease system create a feedback loop, which results in insulin deficiency and abnormal glucose and lipid processing (Table 1).

Table 1. Summary of T2DM pathomechanism

Pathogenic mechanism and its factors		**Clinical implications**
Genetic factors	Polygenic basis: ✓ impaired insulin secretion, ✓ defective processing or proinsulin into the active form, ✓ mutations altering peripheral tissue sensitivity to insulin action.	Higher risk of T2DM in patients who exhibit specific phenotypic traits or have a positive family history of the disease.
Nutritional and lifestyle factors	✓ Abdominal obesity (BMI > ≥30 kg/m²). ✓ Hypertension. ✓ Lipid metabolism disorders. ✓ High-calorie processed food. ✓ Aging of the population. ✓ Reduced level of physical activity. ✓ Sedentary lifestyle.	Chronic elevations of inflammatory markers (IL-6, IL-1, CRP, TNF-α) which impair β-cell function and induce their apoptosis.
Pancreatic β-Cell dysfunction	✓ Chronic overnutrition. ✓ Oxidative stress (hyperglycemia).	✓ Overproduction of insulin. ✓ Misfolding of insulin molecules. ✓ Accumulation of misfolded insulin and IAPP in β-cells. ✓ Leading to β-cells-cell apoptosis.
Intestinal dysbiosis	✓ Genetic factors. ✓ Overproduction of (LPS) by Gram-negative bacteria.	✓ Promoting inflammation ✓ Reducing the synthesis of SCFAs ✓ Disabled: barrier integrity, pancreatic β-cell proliferation, and insulin biosynthesis
Metabolic memory	✓ Persistent epigenetic modifications. ✓ Non-enzymatic protein glycation. ✓ Oxidative stress.	Epigenetic gene modulation and protein glycation, resulting in tissue and organ dysfunction, persist even after achieving glycemic control.
Insulin resistance	Disabled GLUT4 translocation to the cell membrane (AMPK pathway activation / calcium-dependent signaling).	Ineffective glucose transport to insulin-dependent tissues.

Impaired incretin effect	✓ Impaired dose-glucose effect. ✓ Disturbances in incretin effect: mainly endogenous GIP.	Too little insulin is secreted due to oral glucose intake.

3.4. Complications of T2DM

3.4.1. Diabetic macroangiopathy

Coronary artery disease

T2DM patients face a 2-4 times higher risk of death from ischemic heart disease than the average population. The increased risk of death from ischemic heart disease in T2DM patients stems from diabetes complications known as macroangiopathy rather than the disease itself. Both of these, combined with coexisting cardiovascular risk factors, including arterial hypertension, lipid disorders, and elevated BMI, remain a great risk factor for ischemic heart disease (Soedamah-Muthu et al., 2006).

Stroke

Macroangiopathy in diabetic patients affects not only the coronary arteries, but yield in higher risk of ischemic stroke across all age groups compared to the general population (significantly higher risk was revealed within the Greater Cincinnati/Northern Kentucky Stroke Study). Particularly distinct differences were observed in age groups below 65 years in the Caucasian population and below 55 years among African Americans. The study also demonstrated that prediabetes may constitute a significant risk factor for increased incidence of cerebral strokes. (Soedamah-Muthu et al., 2006).

Peripheral Artery Disease (PAD)

Peripheral Artery Disease is a T2DM complication. Risk of its development rises by 30% with each 1% of glycated hemoglobin (HbA1c). The clinical signs of PAD appear earlier in diabetic patients than in people with normal blood sugar levels (Achim et al., 2022). The long-term atherosclerotic condition PAD restricts blood flow through lower body arteries. The disease begins without symptoms until it progresses into noticeable ischemia that produces intermittent claudication and rest pain. These characteristic ischemic symptoms impair functional capacity and remarkably reduce patients' quality of life (Soedamah-Muthu et al., 2006).

3.4.2. Diabetic microangiopathy

Diabetic retinopathy

Diabetic retinopathy remains the most common retinal vascular disease. Its development depends on several factors. We can list: a) the duration of diabetes (the longer the duration of the illness, the greater risk), b) degree of metabolic control (higher HbA1c levels are more dangerous), c) coexistence of hypertension, dyslipidemia, and diabetic nephropathy, d) on pregnancy status, e) on genetic diversity (Fung et al., 2022).

Diabetic nephropathy

40% of patients with T2DM suffer from diabetic kidney disease (DKD). In their's case, it is recognised as a key mortality risk factor (Alicic et al., 2017).

Diabetic neuropathy

The primary complication of diabetes occurs as diabetic neuropathy which affects half of patients during their first twenty years with the disease. The two main factors that increase the risk of developing this condition are elevated HbA1c levels and extended diabetes duration. The two main types of diabetic neuropathy exist as peripheral neuropathy and autonomic neuropathy which impacts both sympathetic and parasympathetic nervous systems. The development of nerve damage results from multiple factors including metabolic processes, microvascular issues, inflammation, and oxidative stress mechanisms (Feldman et al., 2019).

3.5. Tirzepatide and its mechanism of action

The mechanism of impaired incretin homeostasis described above is a target of currently approved and applied medications. Modern diabetes pharmacotherapy concentrates on two key aspects. Some agents imitate GLP-1, they are called GLP-1R agonists, providing the

supra-physiological stimulation of the receptor. Other groups (DPP-4 inhibitors) inhibit degradation of incretins, prolonging their half-life (Gilbert and Pratley, 2020).

Tirzepatide is a novel twincretin medication that synergistically activates both GIP and GLP-1R. Despite showing delayed receptor internalization kinetics, studies demonstrate its full agonistic activity at GIP receptors (GIPR) – equivalent to native hormone effects (Forzano et al., 2022). Tirzepatide demonstrated weaker effects on GLP-1R internalization compared to its natural counterpart (5-fold less potent).

3.6. Tirzepatide in the SURPASS Clinical Trials

The SURPASS Clinical Trials goal was to explore the efficacy of the tirzepatide, defined as a decrease in HbA1c levels and body weight loss. Additionally crucial was the assessment of tirzepatide safety in the treatment of patients with T2DM.

3.6.1. The SURPASS-1 trial (2020)

The participants in the SURPASS-1 clinical trial were patients with T2DM, with the diabetes not controlled by only diet and exercise. Patients were divided into two groups: a) the placebo group and b) tirzepatide treatment group. The patients in the treatment group were receiving subcutaneous injections of tirzepatide once a week in doses of 5mg, 10mg, and 15mg.

The change in HbA1c levels was the primary parameter evaluated during the trial.

A statistically significant reduction in HbA1c was demonstrated across all tirzepatide-treated groups, with the effect consistently greater than in the placebo group. The effects were greater regardless of the administered tirzepatide dose. Furthermore, 31–52% of patients achieved normoglycemia (HbA1c <5.7%). The therapy's significant efficacy in restoring metabolic control in T2DM patients was definitely demonstrated (Table 2).

Regarding weight reduction effects, the study demonstrated statistically major body weight loss among treated patients, with a mean reduction of 7.0-9.5 kg compared to placebo. (Table 2). During the trial, a favorable safety profile was maintained (the weight loss was not associated with increased hypoglycemia risk, confirming the drug's beneficial metabolic characteristics).

Table 2. SURPASS-1 results

Measure	Group	Change from Baseline at 40 Weeks
HbA1c (%)	Placebo	+0.04
	Tirzepatide 5 mg	-1.87
	Tirzepatide 10 mg	-1.89
	Tirzepatide 15 mg	-2.07
Body weight (kg)	Placebo	-0.7
	Tirzepatide 5 mg	-7.0
	Tirzepatide 10 mg	-7.8
	Tirzepatide 15 mg	-9.5

3.6.2. SURPASS-2

The SURPASS-2 clinical trial compared two drugs: tirzepatide and semaglutide. The participants were adult patients with T2DM, who all continued metformin as background therapy. The add-on treatment in groups was tirzepatide in doses of 5 mg, 10 mg, and 15 mg or semaglitide in a dose of 1 mg (Frías et al., 2021).

Greater HbA1c reductions were achieved in patients who were taking tirzepatide: −2.01 percentage points with a 5 mg dose, −2.24 percentage points with a 10 mg dose, and −2.30 percentage points with a 15 mg dose (Table 3). 27–45% of tirzepatide-treated patients achieved normal glucose levels, while in the semaglutide-treated group, only 19% (Forzano et al., 2022).

Regarding weight reduction, tirzepatide once again turned out to be more effective - it induced mean body weight losses of -7.6 kg at a 5 mg dose, -9.3 kg at a 10 mg dose, and -11.2 kg at a 15 mg dose (Frías et al., 2021) (table 3).

Table 3. SURPASS-2 results

Measure	Group	Change from Baseline at 40 Weeks
HbA1c (%)	Semaglutide 1mg	-1.86
	Tirzepatide 5 mg	−2.01
	Tirzepatide 10 mg	−2.24
	Tirzepatide 15 mg	−2.30
Body weight (kg)	Semaglutide 1mg	-5.7
	Tirzepatide 5 mg	-7.6
	Tirzepatide 10 mg	-9.3
	Tirzepatide 15 mg	-11.2

3.6.3. The SURPASS-3

The SURPASS-3 clinical trial evaluated the effectiveness and safety profile of once-weekly subcutaneous tirzepatide administered at 5 mg, 10 mg and 15 mg doses against basal insulin degludec in patients with uncontrolled type 2 diabetes who received metformin or no previous medication treatment.

The hypoglycemic effect of tirzepatide exceeded that of insulin degludec in this study. The HbA1c reduction reached -1.93 percentage points with 5mg tirzepatide and -2.2 percentage points with 10mg and -2.37 percentage points with 15mg (Table 4). The treatment of tirzepatide resulted in normoglycemia for 26–45% of patients. The target HbA1c levels were achieved by 93% of patients. The glycemic control achieved by tirzepatide treatment exceeded that of insulin degludec according to continuous glucose monitoring (CGM) results. In terms of body weight reduction, tirzepatide once again turned out to work better, inducing weight loss: a reduction of 7,5 kg was observed at the 5 mg dose, 10,7 kg at the 10 mg dose, while the maximum dose of 15 mg resulted in a reduction of 12,9 kg (Table 4) (Bailey, 2021).

Table 4. SURPASS-3 results

Measure	Group	Change from Baseline at 52 Weeks
HbA1c (%)	Insulin Degludec	-1,24
	Tirzepatide 5 mg	−1,93
	Tirzepatide 10 mg	−2,2
	Tirzepatide 15 mg	−2.37
Body weight (kg)	Insulin Degludec	+2,3
	Tirzepatide 5 mg	-7.5
	Tirzepatide 10 mg	-10,7
	Tirzepatide 15 mg	-12,9

3.6.4. SURPASS-4 trial

In the SURPASS-4 trial, tirzepatide and insulin glargine were compared in patients with T2DM and high cardiovascular risk. All tested doses of tirzepatide achieved better results in glycemic body weight reduction in comparison to insulin glargine. In conclusion, tirzepatyde had a more favorable impact on the cardiovascular risk profile in treated patients (Table 5) (Del Prato et al., 2021).

Table 5. SURPASS-4 results

Measure	Group	Change from Baseline at 52 Weeks
HbA1c (%)	Insulin Glargine	-1,44
	Tirzepatide 5 mg	−2,24
	Tirzepatide 10 mg	−2,43
	Tirzepatide 15 mg	−2,58
Body weight (kg)	Insulin Glargine	+1.9
	Tirzepatide 5 mg	-7,1
	Tirzepatide 10 mg	-9,5
	Tirzepatide 15 mg	-11,7

3.6.5. The SURPASS-5 trial

This trial assessed the effect of combined (tirzepatyde and insulin glargine) in patients with T2DM who did not achieve metabolic control despite while being treated only with insulin glargine. After 40 weeks of trial, in the group treated with combined therapy, there was a significant improvement in glycemic control, as presented in Table 6 (Dahl et al., 2022).

Table 6. SURPASS-5 results

Measure	Group	Change from Baseline at 40 Weeks
HbA1c (%)	Insulin Glargine + placebo	-0.04
	Insulin Glargine + tirzepatide 5 mg	-2,11
	Insulin Glargine + tirzepatide 10 mg	-2,24
	Insulin Glargine + tirzepatide 15 mg	-2,30
Body weight (kg)	Insulin Glargine + placebo	+1.6
	Insulin Glargine + tirzepatide 5 mg	-5,4
	Insulin Glargine + tirzepatide 10 mg	-7,5
	Insulin Glargine + tirzepatide 15 mg	-8,8

3.7. Tirzepatide in Obesity and Cardiovascular Risk (SURMOUNT-1 Trial)

The SURMOUNT-1 trial was a study designed to assess the effects of tirzepatide in obese and overweight patients. The doses of the drug administered during the SURMOUNT-1 trial were the same as in the SURPASS trials. Once again, tirzepatide turned out to be more effective, causing dose-dependent weight reduction in participants (Jastreboff et al., 2022). In the group receiving a dose of 5 mg, there was observed a mean weight reduction of 15%. Higher doses - 10 mg and 15 mg, yielded even greater effects, with reductions of 19.5% and 20.9%. In comparison, the patients in the placebo group achieved only a mean weight loss of 3.1% (Davidson et al., 2022).

Tirzepatide reduces cardiovascular risk via inducing weight loss (BMI), lowering the waist circumference, as presented in Table 7 (reduction of visceral obesity being a part of metabolic syndrome). Those results suggest that tirzepatide may become a therapeutic intervention brought into play in obese patients (with or without T2DM) in the prevention of cardiometabolic complications (Nicholls et al., 2024).

Table 7 SURMOUNT-1 Trial results

Measure	Group	Percentage Weight Change
Body weight (kg)	Placebo	-3,1%
	Tirzepatide 5 mg	- 15,0%
	Tirzepatide 10 mg	-19,5%
	Tirzepatide 15 mg	-20,9%

3.8. Tirzepatide and hypertension

Above metioned studies show the positive effect of tirzepatide on arterial hypertension. In the SURPASS-1 trial, the reduction in systolic blood pressure (SBP), which was observed, ranged from -4.7 to -5.2 mmHg in tirzepatide-treated groups.

The SURPASS-2 trial revealed the tirzepatyde's revealed its dose-dependent effect. The highest tirzepatide dose (15 mg) reduced SBP by -6.5 mmHg and DBP by -2.9 mmHg. In the group treated only with semaglutide, the SBP was lowered only by -3.6 mmHg. Successively in SURPASS-3, the mean SBP reduction ranged from -4.9 to -6.6 mmHg, while in SURPASS-4, it varied between -2.8 and -4.8 mmHg, alongside an observed increase in blood pressure in the insulin glargine treatment group. SURPASS-5 trial showed the most pronounced effects of tirzepatide, where it reduced SBP by up to -12.6 mmHg and DBP by -4.5 mmHg. Similar results were obtained in SURMOUNT-1, with SBP reduction of -7.2 mmHg and DBP reduction of -4.8 mmHg in tirzepatide-treated groups, whereas placebo showed minimal effect (-1.0/-0.8 mmHg).

The consistent reduction of SBP was shown in the SURPASS trials in groups of patients treated by tirzepatyde. The most pronounced effects were observed at higher doses (10-15 mg). The changes in DBP were less marked.

3.9. Therapeutic Applications of Tirzepatide

Tirzepatide (MOUNJARO™) is indicated for the treatment of adults with T2DM. Used as an adjunct, it helps improve glycemic control in patients treated by diet and physical exercise. It may be used either as monotherapy or in combination with other antihyperglycemic agents, such as metformin or SGLT2 inhibitors (Davies et al., 2022).

Patients with BMI ≥30 kg/m² (obesity) or BMI ≥27 kg/m² (excess weight) can also benefit from tirzepatide treatment. The two exceptions aside patients need to show evidence of one weight-related risk factor between hypertension dyslipidemia cardiovascular disease and prediabetes (Davies et al., 2022). Research studies are currently investigating how tirzepatide benefits patients who have obesity-related hypertension within the cardiometabolic field.

3.10. Adverse effects of tirzepatide

Given the relatively short time since tirzepatide's approval for the aforementioned indications, currently available safety data require further long-term monitoring. Initial characterization of the drug's adverse effects is based on results from the SURPASS clinical trial series.

Analysis of available data indicates that the most frequently reported adverse effects of tirzepatide concern mostly the gastrointestinal tract. There can be listed: nausea, diarrhea, and constipation. The incidence of serious adverse events in the tirzepatide group (6.3%) was comparable to the level observed in the control group (Jastreboff et al., 2022). Regarding the above data, tirzepatide demonstrates an acceptable safety profile even though continued monitoring under real-world clinical conditions remains necessary.

4. CONCLUSION

SURPASS clinical trials proved that tirzepatide marks an advancement in the pharmacotherapy of T2DM and obesity. The novel drug shows its superior efficacy not only in lowering HbA1c levels, but also in weight reduction, in comparison to existing therapies. Thanks to its ability to decrease SBP, it potentially can become a part of therapies reducing cardiovascular risk. Although it's a relatively new drug on the market, current data indicate its favorable safety profile. The characterized adverse effects were primarily mild to moderate. Due to its significant efficacy, additional metabolic benefits, and generally well-tolerated safety profile, tirzepatide is positioned as a leading option among contemporary antidiabetic agents.

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The authors confirm that the data supporting the findings of this study are available within the article's bibliography.

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