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Tirzepatide — a dual GIP/GLP-1 receptor agonist — a new antidiabetic drug with potential metabolic activity in the treatment of type 2 diabetes

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Abstract

The incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are responsible for up to 65% of postprandial insulin secretion. Tirzepatide, developed by Eli Lilly, is a dual GIP/GLP-1 receptor agonist in the form of a synthetic linear peptide; its acylation technology allows it to bind to albumin, thus making it possible to dose the drug once a week. This review summarizes the key characteristics and pharmacokinetics of tirzepatide.

The authors present the results of a phase 1, 2, and 3 clinical trial on the effects of tirzepatide on glycaemic and lipid control and the beneficial effects on body weight in a dose-dependent manner in patients with type 2 diabetes mellitus (T2DM). Tirzepatide has the ability to reduce glycaemic levels, improve insulin sensitivity, reduce body weight, and improve lipid metabolism, which is critically important in T2DM. Tirzepatide administered by weekly subcutaneous injections appears to be a promising drug for the treatment of T2DM as well as cardiometabolic disorders. The mechanism of action and safety profile of tirzepatide potentially fills important gaps in the current treatment of T2DM. **(Endokrynol Pol 2022; 73 (4): 745–755)**

Key words: *type 2 diabetes; glucagon-like peptide-1 (GLP-1); glucose-dependent insulinotropic polypeptide (GIP); tirzepatide*

Introduction

Known factors implicated in the complex pathogenesis of type 2 diabetes mellitus (T2DM) include the following: insulin resistance (IR), progressive failure and finally dysfunction of pancreatic β-cells resulting in absolute insulin deficiency in the late phase of the disease, excessive glucagon secretion from α-cells of pancreatic islets with increased hepatic glucose production (especially in postprandial period), hypothalamic insulin resistance and increased tension of sympathetic nervous system, increased ability of renal tubules to resorb glucose — increased expression of sodium glucose cotransporter type 2 (SGLT-2), and the so-called incretin defect. A key modifiable risk factor for T2DM is obesity, which is strongly associated with IR — one of the barriers to achieving good glycaemic control.

In the last 15 years, new classes of antidiabetic drugs have been developed, and others are being intensively studied in clinical trials, showing not only hypoglycaemic effects but also influencing the comorbid metabolic components of the disease. These include the following: 1 — activin type II receptor modulators (bimagrumab), 2 — amylin or dual amylin-calcitonin receptor agonists (Pramlintide-amylin agonist), 3 — activator of adenosine monophosphate-activated protein kinase (AMPK) (A-769,662, thienopyridone), 4 — analogues of fibroblast growth factor 21 (pegbelfermin), 5 — fructose-1,6-bisphosphatase inhibitors (VK0612; MB07803), 6 — new GLP-1 receptor agonists (albiglutide, dulaglutide, exenatide, liraglutide, lyxisenatide, semaglutide, efpeglenatide, glutazumab, ITCA-650), 7 — drugs affecting the activity of the sodium-glucose cotransporter (SGLT 1 and 2) (SGLT 1 — licogliflozin, sotagliflozin and LX2761; SGLT 2 — kanagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, luseogliflozin, remogliflozin and tofogliflozin), or 8 — imeglimin belonging to a new group of drugs, so-called glimin [1, 2].

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Elrick et al. were the first to demonstrate significantly higher plasma insulin concentrations after oral glucose loading compared with parenteral administration [3]. This phenomenon was called the "incretin effect" and was shown to be responsible for up to 65% of postprandial insulin secretion [4]. Incretin hormones include glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP, formerly known as gastric inhibitory polypeptide) [5].

GLP-1 is a peptide hormone composed of 30 amino acids, which is synthesized in L cells of the intestine. Once released into the circulation, GLP-1 binds to the specific GLP-1R receptor, which is expressed in the pancreas, gastrointestinal tract, kidney, heart, and brain [5]. GLP-1 has a short half-life of 1-2 min and is metabolized by dipeptidylpeptidase-4 (DPP-4). It stimulates pancreatic beta-cell proliferation and increases insulin synthesis and secretion. In α-cells, it inhibits glucagon secretion (in hyperglycaemic and normoglycaemic states). GLP-1 slows down gastric emptying, intestinal peristalsis, and glucose absorption and induces a feeling of satiety [6].

GIP is a 4 amino acid peptide secreted by K cells of the duodenum and the proximal part of the small intestine. GIP is released in response to nutrients, especially carbohydrates and lipids. Receptors for GIP (GIPR) are present in various tissues such as pancreas, adipose tissue, gastric mucosa, heart, adrenal cortex, bone, and brain [5]. Similarly to GLP-1, it stimulates insulin secretion in response to a glycaemic stimulus [7]. GIP has a dual function: glucagonotropic in the normoglycaemic and hypoglycaemic state, and glucagonostatic in the hyperglycaemic state [8].

Plasma concentrations of GLP-1 and GIP are very low on fasting and increase 15–30 min after eating. The incretin effect is very short-term; the hormones remain active 1–2 min after their secretion and are then inactivated by the enzyme dipeptidylpeptidase-4 (DPP-4) [9].

Incretin hormones in the pathogenesis of T2DM

The incretin effect is significantly reduced in patients with T2DM compared to non-diabetic individuals [5]. Two mechanisms have been proposed for the attenuation of the incretin effect in T2DM: reduced incretin hormone production in response to food (hyposecretion) [10] and reduced insulinotropic effect on pancreatic beta cells [11]. Supraphysiological doses of GLP-1 receptor agonists partially restore the incretin effect. No reduction in GIP secretion has been demonstrated in patients with T2DM [12]. However, GIP resistance, a complete loss of the insulinotropic effect of GIP at both physiological and supraphysiological concentrations, has been observed in T2DM subjects [13], and the glucagonotropic effect of GIP persists even in the hyperglycaemic state [14].

An ideal antidiabetic drug should have proven efficacy in lowering elevated glucose levels and promoting weight loss, have a low risk of hypoglycaemia, and have cardiovascular benefits. The attempt to develop a drug with simultaneous activation of receptors for GIP and GLP-1 seems to be an attractive idea for the treatment of T2DM because it can significantly increase insulin secretion and improve insulin sensitivity [15].

Simultaneous administration of GIP and a GLP-1 receptor agonist in healthy subjects has a synergistic effect, increasing insulin secretion compared with separate administration of each hormone [16]. Such a synergistic effect of GIP and GLP-1 was first described by Finan et al., who developed a single-molecule dual agonist of GIP and GLP-1 receptors, termed "twincretin" [17]. Twincretin has been shown to have high affinity for GLP-1 and GIP receptors with negligible activity toward receptors for glucagon [17].

Tirzepatide structure and preclinical studies

Tirzepatide (LY3298176, TZP), developed by Eli Lilly, is a dual GIP/GLP-1 receptor agonist in the form of a synthetic linear peptide containing 39 amino acids conjugated with the C20 fatty acid molecule via a linker connected to a lysine residue at position 20. The TZP peptide sequence also contains two non-coding amino acid residues at positions 2 and 13 (Aib, α-aminoisobutyric acid), and the C-terminal end is amidated. The acylation technology allows its binding to albumin, thus making it possible to dose the drug once a week.

TZP has been shown to bind both receptors with high affinity (GIPR Ki = 0.135, SEM = 0.020 nM; GLP-1R Ki = 4.23, SEM = 0.23 nM); the affinity is comparable to native GIP for GIPR and approximately 5-fold weaker than native GLP-1 for GLP-1R [15, 18–20].

The effects of TZP on β-cell function and glycaemic control were examined in an animal model using mice (wild-type — WT) expressing both incretin receptors and transgenic mice lacking GIPR (GIPR–/–) or GLP-1R (GLP-1R–/–). TZP stimulated glycaemia-dependent insulin secretion from pancreatic islet β-cells isolated from all three mouse genotypes. In islets lacking receptors, receptor-specific antagonists blocked insulin secretion as predicted (exendin-4 in islets from GIPR–/– mice and a modified GIPR antagonist, GIP(3-30)NH2, in islets from GLP-1PR–/– mice). This indicates that TZP is specific for GIPR and GLP-1R and active against both incretin receptors [19].

Glycaemic control was studied by the authors using intraperitoneal glucose tolerance tests (ipGTT) in normal mice and in mice lacking individual incretin receptors. TZP improved the glycaemic profile in all three mouse genotypes, and the response was comparable to that observed for semaglutide and the DPP 4-resistant GIP analogue [d-Ala2] GIP in GIPR–/– and GLP-1R–/– mice, respectively [19].

Coscun et al. [19] studied the effects of TZP on body weight and food intake in an animal model using DIO strain C57/Bl6 mice. Chronic use of a long-acting GLP-1R agonist (semaglutide) resulted in a dose-dependent reduction in body weight, mainly due to a reduction in fat mass, which seemed to reach a maximum effect at a dose of 30 nmoL/kg, with only a slight reduction in plasma glucose [19]. Application of semaglutide had no significant effect on animal weight but was effective in lowering fasting blood glucose at all doses tested. The use of TZP influenced a significant dose-dependent reduction in the body weight of mice, significantly greater than that observed with semaglutide. Weight loss during TZP treatment was primarily due to loss of fat mass.

Clinical evidence for the tirzepatide effects

The clinical efficacy, safety, and tolerability of tirzepatide have been demonstrated in phase 1, 2, and 3 clinical trials.

Phase 1 study

Coskun et al. published a phase 1 clinical trial (CRT) (POC trial) performed on 53 T2DM patients aged 56.8 ± 6.9 years with a body mass index (BMI) of 31.2 ± 4.0 kg/m^2 and a glycosylated haemoglobin (HbA_{1c}) level of 8.4 ± 0.8%. Subjects were divided into two groups that received a fixed dose of TZP once a week subcutaneously (0.5 mg and 5.0 mg) and two groups that received weekly increasing doses of TZP up to 10 mg (5/5/10/10 mg) and 15 mg (5/5/10/15 mg) [19]. After 4 weeks of treatment, dose-dependent reductions in HbA_{1c} were observed in all TZP treatment groups relative to baseline and compared to placebo. Statistically significant differences were observed in the groups with increasing doses of TZP up to 10 and 15 mg/week — least square mean (LSM) differences [95% confidence interval (CI)]: –0.84% (–1.17– –0.52) and –0.58% (–0.92– –0.24), respectively, in the groups. The authors demonstrated a significant reduction in fasting glucose and insulin levels in subjects treated with increasing doses of TZP up to 10 and 15 mg/week compared with placebo on day 23 of the study. OGTT glucose levels, expressed as area under the curve (AUC; 0–2 h), were significantly reduced with all tested doses of TZP except the 0.5 mg/week dose, compared to placebo, and OGTT insulin levels, expressed as AUC (0–2 h), were significantly increased after administration of TZP at the 5/5/10/15 mg/week doses compared to placebo [19]. Similarly, glycaemia assessed as a 7-point self-monitoring of blood glucose levels showed postprandial reductions in a dose-dependent manner with TZP. As with HbA_{1c} levels, a dose- and time-dependent reduction in body weight was observed in the TZP-treated groups compared with the placebo group. The 0.5/5/10/10 mg and 0.5/5/10/15 mg groups achieved weight reductions of 2.39 kg and 2.95 kg, respectively, on day 29 of the study, but less compared to healthy subjects [19].

Another phase 1 CRT was designed to evaluate the efficacy and safety of TZP [21, 22]. Subjects were divided into groups receiving TZP at doses of 5 mg (5 mg, weeks 1–8), 10 mg (2.5 mg/week in weeks 1 and 2; 5 mg/week in weeks 3 and 4; 10 mg/week in weeks 5 to 8), and 15 mg (5 mg/week in weeks 1 and 2, 10 mg/week in weeks 3 and 4, 15 mg/week in weeks 5 to 8). Forty-eight T2DM patients with a mean age of 57.4 ± 8.8 years with a BMI of 25.4 ± 3.2 kg/m^2 and an HbA_{1c} level of 8.0 ± 0.8% were included in the study. Compared to placebo, there was a significant reduction in HbA_{1c} levels from baseline in all groups receiving TZP (–1.62%, –1.78%, –2.05% in the 5 mg, 10 mg, and 15 mg TZP groups, respectively). There was also a significant reduction in body weight in all three TZP-treated groups (weight reductions of 1.9 kg, 3.6 kg, and 5.1 kg in the 5 mg, 10 mg, and 15 mg TZP groups, respectively). After 8 weeks of treatment, fasting plasma glucose levels decreased compared with placebo by 52.7 (35.9–69.6), 69.1 (52.3–85.9), and 68.9 (53.2–84.6) mg/dL in the 5, 10, and 15 mg treatment groups, respectively ($p < 0.0001$ for all treatment groups) [21, 22].

Phase 2 clinical trials

Frias et al. [23] published the results of a phase 2 study, which was a 26-week, placebo-controlled, double-blind, randomized CRT involving 318 patients with T2DM, treated behaviourally with or without metformin monotherapy. The mean age was 57 ± 9 years, BMI 32.6 ± 5.9 kg/m^2, duration of T2DM 9 ± 6 years, and HbA_{1c} level 8.1% ± 1%. The study was conducted in groups treated with TZP at a fixed dose (1 mg and 5 mg weekly), two groups with increasing doses of the drug (5 mg for 2 weeks and 10 mg for the remainder of the study, and in a second group of 5 mg for 2 weeks, 10 mg for 4 weeks, and 15 mg for the remainder of the study), and a placebo group or a group additionally treated with the GLP-1R selective agonist, dulaglutide. Treatment with TZP resulted in dose-dependent reductions in HbA_{1c} levels from

baseline of 0.7%, 1.6%, 2.0%, and 2.4% for weekly doses of 1 mg, 5 mg, 10 mg, and 15 mg, respectively. The 5 mg, 10 mg, and 15 mg doses of TZP also produced greater reductions in HbA_{1c} levels at week 26, compared with dulaglutide used at dose 1.5 mg weekly. The mean weight loss from baseline was –0.9 kg, –4.8 kg, –8.7 kg, and –11.3 kg in the 1 mg, 5 mg, 10 mg, and 15 mg TZP treatment groups, respectively, compared with –0.4 kg in the placebo group and –2.7 kg in the dulaglutide group. The authors of the study concluded that treatment with TZP at doses of 5 and 10 mg significantly improves clinical efficacy without increasing gastrointestinal side effects compared with dulaglutide. Since the 15 mg dose was shown in this study to be more effective than lower doses in terms of both glycaemic control and weight loss, improving its tolerability profile in the treatment of T2DM may be clinically important.

Frias et al. reported the results of a second 12-week phase 2 CTR conducted at 13 centres in the United States [24]. The study was performed in 111 T2DM patients with glycaemia inadequately controlled by diet and exercise or metformin treatment, with a mean HbA_{1c} of 8.4% (67.8 mmol/mol) [7.0–10.5% (53.0–91.3 mmol/mol)] and a mean BMI of 31.9 kg/m^2 (23 to 45 kg/m^2). The study was designed to evaluate the efficacy and tolerability of higher doses of TZP (12 and 15 mg/week) using three different dose increasing regimens. The treatment regimen for the increasing dose up to 12 mg was 4 mg for 4 weeks, then 8 mg for 4 weeks, and 12 mg for the final 4 weeks. For administration for the increasing dose up to 15 mg, the first scheme (15 mg-1), was 2.5 mg for 2 weeks, followed by 5 mg for 2 weeks, 10 mg for 4 weeks, and 15 mg for the final 4 weeks. The second regimen in the 15 mg group (15 mg-2) was 2.5 mg for 4 weeks, then 7.5 mg for 4 weeks, and 15 mg for the final 4 weeks.

After 12 weeks of treatment, HbA_{1c} levels decreased from baseline by an average of –1.9% (–2.5, –1.4), $p < 0.001$ for the 12 mg group, –2.2% (–2.8, –1.7), $p < 0.001$ for the 15 mg-1 group, and –2.0% (–2.5, –1.4), $p < 0.001$ for the 15 mg-2 group. The reduction in fasting blood glucose ranged from –12.3 mg/dL (–0.7 mmol/L) in the placebo group to –74.2 mg/dL (–4.1 mmol/L) in the 15 mg TZP-treated group in the 15 mg-2 regimen. The mean change compared with placebo was –48.5 mg/dL (–70.6, –26.3), $p < 0.001$ for the 12 mg group, –58.0 mg/dL (–80.7, –35.2), $p < 0.001$ for the 15 mg-1 group, and –61.9 mg/dL (–84.6, –39.2), $p < 0.001$ for the 15 mg-2 group. The authors also demonstrated a reduction in body weight in each TZP treatment group at week 12. The mean weight reduction compared with placebo was –4.8 kg (–7.1, –2.6), $p < 0.001$ for the 12 mg group; –5.0 kg (–7.2, –2.7), $p < 0.001$ for the 15 mg-1 group; and –5.2 kg (–7.5, –2.9), $p < 0.001$ for the 15 mg-2 group [24].

Thomas et al. published the results of a phase 2 CTR evaluating the effects of TZP on β-cell function and insulin sensitivity in patients with T2DM [25]. The study enrolled 316 T2DM patients aged 18-75 years with poor glycaemic control treated with diet and exercise with or without metformin treatment, a baseline HbA_{1c} level of 7.0% to 10.5% (53–91.3 mmol/mol), and a BMI of 23 to 50 kg/m^2. Participants were randomly assigned to receive once-weekly TZP (1 mg, 5 mg, 10 mg, or 15 mg), dulaglutide (1.5 mg), or placebo for 26 weeks. Indicators for assessment of the homeostatic model of β-cell function (HOMA2-B) or insulin resistance (HOMA2-IR) were calculated from fasting glucose and insulin or C-peptide levels. The study demonstrated improved β-cell function by evaluating markers of its function in the groups treated with TZP. There was a change in HOMA2-B (calculated from fasting C-peptide levels) expressed as a percentage increase from baseline values depending on the dose of TZP from 93% to 163% for increasing doses of 5 to 15 mg ($p < 0.001$), 72% for dulaglutide ($p < 0.001$), 29% for TZP at 1 mg ($p = 0.049$), and 1% for placebo ($p = 0.932$), respectively [25].

Impaired conversion of proinsulin to insulin under conditions of increased insulin demand is considered an indicator of pancreatic β-cell stress in T2DM [26].

Thomas et al. [25] examined levels of untransformed proinsulin to assess potential changes in its conversion to the active form of insulin in response to treatment of TZP. The percentage change from baseline proinsulin decreased significantly with 5, 10, and 15 mg TZP from 28% to 48% ($p < 0.001$), whereas it did not change significantly with 1 mg TZP and dulaglutide ($p = 0.350$ and $p = 0.981$, respectively) but increased significantly (+18%, $p = 0.035$) in the placebo group after 26 weeks. The change in the proinsulin/insulin ratio from baseline was significantly different for all doses of TZP compared with placebo ($p \leq 0.016$), and when using TZP at 10 and 15 mg compared with dulaglutide ($p \leq 0.007$) at week 26 [25]. This study demonstrated that TZP improved insulin sensitivity as assessed by the HOMA2-IR index and circulating biomarkers associated with improved insulin sensitivity in response to diet, bariatric surgery, or weight loss (adiponectin, fasting IGF-binding proteins — IGFBP-1 and IGFBP-2) [27, 28]. Insulin resistance as assessed by the HOMA2-IR index was significantly reduced in the 10 mg TZP-treated group compared with the placebo ($p = 0.004$) and dulaglutide-treated group ($p = 0.004$) at week 26. The difference in HOMA2-IR in the 15 mg TZP-treated group compared with those in the placebo and dulaglutide groups showed no statistical significance ($p = 0.063$

and 0.067, respectively). Because hyperinsulinaemia is strongly correlated with IR [29], investigators also evaluated changes in fasting insulin concentrations after TZP treatment. There was a significant reduction in fasting insulin levels in the 10 mg and 15 mg TZP treatment groups compared with placebo ($p = 0.004$) and dulaglutide ($p = 0.014$) at 26 weeks. There was also a significant increase in adiponectin from baseline from 12% to 26% with TZP at increasing doses from 5 to 15 mg ($p \leq 0.015$) and by 11% for the dulaglutide treatment group, and a significant increase in IGFBP-1 and IGFBP-2 compared with the placebo group [25]. The authors concluded that treatment of T2DM patients with a novel dual GIP and GLP-1R agonist, TZP, improved both markers of β-cell function and insulin sensitivity compared with the selective GLP-1R agonist dulaglutide. By reducing IR, TZP reduced metabolic demand for insulin, reducing β-cell stress. Improvements in insulin resistance with TZP at doses of 10 and 15 mg were only partially associated with weight loss, suggesting additional mechanisms by which it affects IR reduction.

Phase 3 clinical trials

A comprehensive phase 3 CRT program (SURPASS study) is underway to confirm the efficacy, safety, and cardiovascular effects of TZP for the treatment of T2DM.

The SURPASS-1 trial [30], the first randomized, multicentre phase 3 trial of TZP, enrolled 478 patients with T2DM whose glycaemia was inadequately controlled with diet and exercise alone. The study group had a mean HbA_{1c} of 7.9% (63 mmol/mol), age 54.1 years (SD 11–9), disease duration 4.7 years, mean baseline weight 85.9 kg, and BMI 31.9 kg/m^2. Subjects were divided into groups treated once weekly with TZP 5 mg [n = 121 (25%)], 10 mg [n =121 (25%)], 15 mg [n = 121 (25%)], and placebo [n = 115 (24%)]. After 40 weeks of treatment, all doses of TZP were superior to placebo in reducing HbA_{1c} levels and fasting serum glucose levels, weight loss, and achieving a target HbA_{1c} of less than 7.0% (< 53 mmol/mol). HbA_{1c} levels decreased by 1.87% (20 mmol/mol) with 5 mg, 1.89% (21 mmol/mol) with 10 mg, and by 2.07% (23 mmol/mol) with 15 mg of TZP. More subjects receiving TZP (regardless of dose) compared to placebo achieved target HbA_{1c} values, i.e. below 7.0% (< 53 mmol/mol; 87–92% *vs.* 20%), below 6.5% (≤ 48 mmol/mol; 81–86% *vs.* 10%), and 31–52% of subjects compared to 1% of the placebo group achieved HbA_{1c} levels below 5.7% (< 39 mmol/mol). TZP had a dose-dependent effect on weight loss ranging from 7.0 to 9.5 kg [30]. The most common adverse effects during dose-dependent use of TZP were mild to moderate and transient gastrointestinal symptoms, including nausea (12–18% *vs.* 6%), diarrhoea (12–14% *vs.* 8%), and vomiting (2–6% *vs.* 2%). No clinically significant [< 54 mg/dL (< 3 mmol/L)] or severe hypoglycaemia was reported during TZP use.

The purpose of the recently published 40-week phase 3 SURPASS-2 trial [31] was to compare the efficacy and safety of different doses of TZP (5 mg, 10 mg, or 15 mg weekly) and a GLP-1 agonist (semaglutide) at 1 mg weekly. The study was conducted in a group of 1879 T2DM patients with inadequately controlled glycaemia with metformin monotherapy. At the beginning of the study, the mean HbA_{1c} level was 8.28%, subjects' mean age was 56.6 years, and mean body weight was 93.7 kg. When TZP was added, regardless of dose, greater reductions in HbA_{1c} levels and body weight were achieved compared with the semaglutide treatment group. The mean change in HbA_{1c} levels was –2.01%, –2.24%, and –2.30% for TZP doses of 5 mg, 10 mg, and 15 mg, respectively, and –1.86% in the semaglutide group. Weight reduction was greater with TZP than with semaglutide at –1.9 kg, –3.6 kg, and –5.5 kg, respectively; $p < 0.001$ for all comparisons [31]. The most common adverse reactions recorded in the study were gastrointestinal and were mild to moderate in severity (nausea: 17 to 22% and 18% in the semaglutide group, respectively; diarrhoea: 13 to 16% and 12% in the semaglutide group; and vomiting: 6 to 10% and 8% in the semaglutide group). In the groups that received TZP, hypoglycaemia (blood glucose, < 54 mg%) was reported in 0.6% (5 mg group), 0.2% (10 mg group), and 1.7% (15 mg group) compared with 0.4% in the semaglutide group. Serious adverse events were reported in 5 to 7% of subjects who received TZP and in 3% of patients who received semaglutide [31].

The aim of the multicentre (122 centres), multinational (13 countries), phase 3 SURPASS-3 trial [32] was to evaluate the efficacy and safety of TZP administered once weekly compared with insulin degludec administered once daily in addition to ongoing treatment with metformin alone or in combination with SGLT 2 inhibitors for at least 3 months prior to the study, in patients with inadequately controlled T2DM. The study included 1444 T2DM patients (aged ≥ 18 years) with baseline HbA_{1c} levels of 7.0–10.5%, a BMI of at least 25 kg/m^2, and stable body weight. The study was conducted for 52 weeks, and subjects were divided into groups receiving once-weekly TZP (5, 10, or 15 mg) or once-daily insulin degludec with maintenance of previous oral hypoglycaemic treatment. TZP was initially administered at 2–5 mg, and the dose was increased by 2–5 mg every 4 weeks until the assigned dose was reached. Insulin degludec was initially administered at a dose of 10 U per day and increased weekly until

fasting self-monitored blood glucose levels were below 5.0 mmol/L (< 90 mg/dL). There was a mean reduction in HbA_{1c} levels at week 52 of 1.93% for TZP at 5 mg/week, 2.20% for TZP at 10 mg/week, and 2.37% for TZP at 15 mg/week and 1.34% in the insulin degludec group, respectively. The number of subjects who achieved HbA_{1c} levels below 7.0% (< 53 mmol/mol) at week 52 was greater ($p < 0.0001$) in all three TZP groups (82%-93%) compared with the insulin degludec treatment group (61%). At week 52 of the study (mean baseline weight 94.3 kg, SD 20.1), all three TZP doses resulted in a decrease in body weight (7.5 kg to 12.9 kg, respectively, depending on the dose), while the insulin degludec treatment group showed a mean increase in body weight of 2–3 kg. A higher incidence of nausea (12–24%), diarrhoea (15–17%), decreased appetite (6–12%), and vomiting (6–10%) was reported in the TZP-treated groups than in the insulin degludec-treated group (2%, 4%, 1%, and 1%, respectively). Hypoglycaemia (< 54 mg/dL or severe) was noted in 5 (1%), 4 (1%), and 8 (2%) subjects receiving TZP at doses of 5, 10, and 15 mg, respectively, compared with 26 (7%) subjects receiving insulin degludec.

The objective of the phase 3 SURPASS-4 trial [33], conducted at 187 centres in 14 countries on five continents, was to evaluate the efficacy and safety (with particular emphasis on cardiovascular safety) of TZP compared with insulin glargine in patients poorly controlled with oral medication T2DM and at high risk of cardiovascular disease. A group of 4004 T2DM patients (aged 18 years) treated with a combination of metformin, a sulfonylurea, or an SGLT 2 inhibitor, a baseline HbA_{1c} of 7.5–10.5% (58–91 mmol/mol), a BMI greater than 25 kg/m^2, and a known history of cardiovascular disease or high risk of cardiovascular events were enrolled in the study. Subjects were randomized to groups receiving an additional once-weekly dose of either TZP (5 mg, 10 mg, or 15 mg) or insulin glargine (100 U/mL), at doses increased to achieve fasting blood glucose levels below 100 mg/dL. At week 52 of the study, the mean reduction in HbA_{1c} in the groups treated with TZP was 2.43% on the 10 mg/week and 2.58% on the 15 mg/week regimen, compared to 1.44% for the insulin glargine addition treatment group.

The most commonly observed adverse events were nausea (12–23%), diarrhoea (13–22%), decreased appetite (9–11%), and vomiting (5–9%), which occurred more frequently with TZP than with glargine (nausea 2%, diarrhoea 4%, decreased appetite < 1%, and vomiting 2%, respectively); most cases were mild to moderate and occurred during the dose escalation phase of TZP. The proportion of subjects who had hypoglycaemia was lower with TZP (6–9%) compared with glargine (19%), particularly in those not receiving a sulfonylurea (TZP 1–3% *vs.* glargine 16%). MACE-4 incidents (cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina) occurred in 109 participants and were not more frequent with TZP compared with glargine (hazard ratio: 0.74, 95% CI: 0.51–1.08). Thus, treatment with TZP was not associated with an increased cardiovascular risk. Sixty deaths occurred during the study [n = 25 (3%) TZP; n = 35 (4%) glargine] [33].

Dahl et al. reported the results of a phase 3 study, SURPASS-5, evaluating the efficacy and safety of TZP compared with placebo in patients with T2DM as an addition to insulin glargine with or without metformin [34].

A group of 475 T2DM patients with a mean age of 60.6 years, disease duration of 13.3 years, HbA_{1c} level of 8.31%, and BMI of 33.4 kg/m^2 were included in the study. Subjects were randomized to additional treatment with TZP (5 mg, 10 mg, 15 mg weekly) or placebo in combination with their current treatment. At week 40, the study showed a reduction in HbA_{1c} levels from baseline in the TZP treated groups by –2.23 ± 0.08%, –2.59 ± 0.08%, and –2.59 ± 0.08%, respectively, and in the placebo group by -0.93±0.08%. Accordingly, 93.0%, 97.4%, and 94.0% of those in the TZP treated groups achieved HbA_{1c} levels below 7% compared with 33.9% in the placebo group. HbA_{1c} levels below 6.5% were achieved in 80.0%, 94.7%, and 92.3%, respectively, according to increasing weekly doses of TZP. Mean body weight reduction across the study groups was –6.2, –8.2, and –10.9 kg (> 10% of baseline weight in 22.6%, 46.9%, and 51.3% of subjects, respectively) in groups with increasing weekly doses of TZP.

The aim of the phase 3 SURPASS-6 trial [35] is to evaluate the effect of adjunctive treatment, TZP (5, 10, or 15 mg) given once weekly versus the addition of insulin lispro (U100) given three times daily in patients with T2DM (n = 1182) insufficiently controlled with insulin glargine (U100) with or without metformin, on HbA_{1c} levels after 52 weeks of follow-up. Inclusion criteria for the study group are HbA_{1c} levels between 7.5% and 11%, treatment with once- or twice-daily basal insulin with or without metformin (≥ 1500 mg/day), sulfonylurea, or DPP-4 inhibitors for at least 90 days prior to study inclusion, stable body weight (± 5%) for at least 90 days prior to the study, and BMI 23–45 kg/m^2. The study is ongoing, and the results are expected in the autumn of 2022.

SURPASS-CVOT is a multicentre CRT conducted in 30 countries comparing the efficacy of TZP *vs.* dulaglutide (1.5 mg weekly) [36]. The SURPASS-CVOT study is designed to screen 12,500 T2DM patients over 40 years of age with HbA_{1c} levels between 7.5% and 10.5%, BMI ≥ 25 kg/m^2, and coexisting atherosclerotic cardiovascular disease. The primary objective is

to assess time to first occurrence of cardiovascular (CV) death, myocardial infarction (MI), or stroke (MACE-3). The planned follow-up time is 54 months, and the study is expected to end in the autumn of 2024.

Effect of tirzepatide on lipid metabolism

Despite the current high standards of treatment, patients with T2DM have a high risk of developing atherosclerosis and associated cardiovascular incidents [37, 38].

GLP-1R agonists have been shown to effectively reduce major adverse cardiac events in T2DM patients [39, 40] by reducing body weight, lowering blood pressure, improving renal function, reducing chronic inflammation, lowering lipoprotein and chylomicron levels, and increasing postprandial triglycerides, very low-density lipoprotein (VLDL) cholesterol, and free fatty acids [41–44].

Preclinical in vivo and in vitro studies have shown that GIP increases lipoprotein lipase (LPL) expression in adipocytes [45]. GLP-1R activation also increases blood flow and stimulates lipid uptake in adipose tissue [46].

Tirzepatide has been shown to increase adiponectin [25], decrease serum alanine aminotransferase [47], and decrease lipoprotein biomarkers such as apolipoprotein C-III, apolipoprotein B, and large triglyceride-rich lipoprotein particles as well as small low-density lipoprotein particles [38]. It has been shown that only 13% and 21% of the reduction in IR can be attributed to TZP-induced body-weight reduction [14], suggesting a possible, independent of body-weight reduction, effect of TZP on biochemical pathways related to insulin action.

Wilson et al. [38] published the results of a phase 2 CRT in which they evaluated the effects of TZP on selected lipoprotein biomarkers associated with IR and cardiovascular disease. A total of 318 behaviourally treated T2DM patients with or without metformin monotherapy were included in the study. Mean age was 57 ± 9 years, BMI 32.6 ± 5.9 kg/m^2, diabetes duration 9 ± 6 years, and HbA_{1c} level 8.1 ± 1%. The study was conducted in groups treated with fixed-dose TZP (1 mg and 5 mg) and two groups with increasing doses of the drug (5 mg for 2 weeks and 10 mg for the remainder of the study and 5 mg for 2 weeks, 10 mg for 4 weeks, and 15 mg for the remainder of the study) and dulaglutide (1.5 mg) or placebo for 26 weeks.

At week 26, the investigators showed that TZP at 5 mg, 10 mg, and 15 mg and dulaglutide reduced triglyceride (TAG) levels by 28.8% ($p < 0.001$), 37.7% ($p < 0.001$), 41. 4% ($p < 0.001$), and 18.8%, respectively, ($p = 0.010$) compared with placebo, and doses of TZP 10 mg and 15 mg also significantly reduced their levels compared with the dulaglutide-treated group [by 23.3% ($p < 0.001$) and 27.9% ($p < 0.001$), respectively]. Dose-dependently, TZP also significantly reduced apolipoprotein C-III (25.6% to 46.2%, $p < 0.001$) and apolipoprotein B (11.0% to 17.4%, $p < 0.001$) concentrations compared with the placebo group. Tirzepatide 15 mg and dulaglutide significantly reduced LDL-C concentrations by 19.0% (–36.0%, –1.9%; $p = 0.029$) and 17.8% (–33.7%, –2.0%; $p = 0.028$), respectively, compared with placebo. Tirzepatide dose-dependently reduced non-HDL-C levels by 16.4%, 21.3%, and 24.8% ($p < 0.001$) compared with the placebo group [38].

Several metabolites or groups of metabolites have been identified that are associated with the risk of developing obesity, insulin resistance, and the risk of future T2DM. These include branched-chain amino acids (BCAA) and products of BCAA catabolism [branched-chain ketoacids (BCKA), glutamic acid, 3-hydroxyisobutyric acid (3-HIB), and C3 acylcarnitines], aromatic amino acids, or TAG with short, highly saturated acyl chains [48, 49].

Elevated serum levels of these metabolites are predictors of future risk of T2DM [50], whereas decreasing their levels is associated with improved IR and body weight reduction [51].

Pirro et al. [52] in a phase 2 clinical trial conducted in a group of 259 T2DM patients treated with different doses of TZP (1, 5, 10, 15 mg weekly), after 26 weeks, showed a significant reduction in the concentration of branched-chain amino acids and direct products of their catabolism such as glutamate, 3-hydroxyisobutyrate, branched-chain ketoacids, and 2-hydroxybutyrate compared to the placebo group and the group receiving dulaglutide (1.5 mg). The authors also found a significant reduction, expressed as a percentage from baseline, in total TAG, diglycerides (DAG), and phosphatidylethanolamines (PE) and phosphatidylcholine (PC) during dose-dependent treatment with TZP compared with the placebo and dulaglutide groups at week 26.

The authors concluded that, in addition to its effects related to weight reduction and improved glycaemic control, TZP has a unique effect on modifying metabolic factors that have been shown to be associated with T2DM risk, by changing their profile in a direction that improves metabolic status.

Safety and tolerability and other potential beneficial effects of tirzepatide

Worldwide, non-alcoholic fatty liver disease (NAFLD) has a prevalence of 25.24% (95% CI: 22.10–28.65), with the highest prevalence in the Middle East and South America and the lowest in Africa. Meta-

bolic diseases comorbid with NAFLD include obesity (51.34%; 95% CI: 41.38–61.20), T2DM (22.51%; 95% CI: 17.92–27.89), hyperlipidaemia (69.16%; 95% CI: 49.91–83.46%), hypertension (39.34%; 95% CI: 33.15–45.88), and metabolic syndrome (42.54%; 95% CI: 30.06–56.05) [53].

Non-alcoholic steatohepatitis (NASH) (NAFLD with inflammation and hepatocyte damage, with or without fibrosis) can progress to cirrhosis, liver failure, hepatocellular carcinoma, and increased cardiovascular risk [54]. T2DM increases the risk of NASH twofold [55].

Hartman et al. [47] reported the results of a study designed to evaluate the effects of TZP on biomarkers of NASH and liver fibrosis in patients with T2DM. The authors conducted the study as a post hoc study in material secured from patients from a phase 2 study (n = 316). Full details of the study group are presented in the phase 2 CRT section of the paper [23]. The study showed a significant reduction in serum alanine aminotransferase (ALT) levels from baseline in all groups at week 26 ($p \leq 0.010$). The reduction in the 10- and 15-mg/week TZP groups was significant compared with dulaglutide [–6.8 units/L (95% CI: 11.8– –1.8) and –6.4 units/L (–11.7– –1.1); $p = 0.008$ and $p = 0.018$, respectively]. Serum aspartate aminotransferase (AST) levels also decreased significantly from baseline in all groups (except TZP 10 mg) at week 26 ($p \leq 0.033$), but not significantly compared with placebo and the dulaglutide-treated group [47]. Fragments of keratin-18 [cytokeratin-18 (K18)] can be detected in serum and serve as a circulating biomarker indicating apoptosis of epithelial and parenchymal cells including hepatocytes. The authors demonstrated a significant reduction in K18 levels relative to baseline in the groups receiving TZP at 5, 10, and 15 mg ($p \leq 0.015$). The reduction in the 10 mg TZP group differed significantly compared with the placebo group [–135.2 units/L (95% CI: –239.0– –31.3); $p = 0.011$] [47]. Procollagen III (Pro-C3, a biomarker of fibrosis) concentration decreased significantly from baseline in the TZP 15 mg group at week 26 ($p = 0.041$), and the decrease was significant compared with placebo [–2.1 ng/mL (–3.6, –0.6); $p = 0.007$] but not with the dulaglutide group. In contrast, adiponectin (an adipokine with antifibrogenic and antiestrogenic effects in the liver) concentration significantly increased compared with baseline in the groups receiving TZP 10 and 15 mg at week 26, and this increase was significant compared with the placebo group [by 0.9 mg/L (0.3–0.5) and 1.0 mg/L (0.3–1.6), $p = 0.003$ and $p = 0.004$, respectively] [47].

A dose-dependent reduction in ALT and AST levels from baseline was observed in the TZP-treated study groups, but without significance compared to the placebo group. This may be due to the study sample size and the fact that only a minority of patients with T2DM have NASH. Although patients with NASH may have normal levels of both ALT and AST, their higher levels correlate with a more severe degree of both hepatic inflammation and steatosis [56]. In a large pooled analysis of four clinical trials (n = 1499), dulaglutide treatment of patients with T2DM and probable NAFLD was associated with a significant reduction in ALT and AST levels compared with placebo [57].

Approximately 1/3 of diabetic patients (type 1 or type 2) are diagnosed with diabetic nephropathy [58,59]. Diabetic nephropathy is characterized by persistent albuminuria and/or progressive impairment of renal function. Pharmacokinetics (PK) of standard antidiabetic drugs may be impaired in patients with impaired renal function [60]. Reduced drug clearance due to impaired renal function may lead to an increased risk of adverse effects, such as hypoglycaemia, in T2DM patients [61].

Urva et al. [62] reported the PK and tolerability of TZP in patients with or without T2DM and various degrees of renal impairment compared to healthy subjects. Forty-five subjects (30 men and 15 women) aged 40 to 84 years, with BMI ≥ 19.0 and ≤ 40.0 kg/m^2, were included in the study. Subjects were divided into groups according to baseline renal function as mild [n = 8, glomerular filtration rate (eGFR): 60–89 mL/min/1.73 m^2], moderate (n = 8, eGFR: 30–59 mL/min/1.73 m^2), severe renal impairment (n = 7, eGFR < 30 mL/min/1.73 m^2), end-stage renal disease requiring dialysis (ESRD) (n = 8), and normal renal function (n = 14, eGFR ≥ 90 mL/min/1.73 m^2). Each renal impairment group contained at least one subject with T2DM, whereas the mild and severe renal impairment groups each contained two patients with T2DM.

After administration of a single 5 mg dose of TZP, plasma samples were collected for PK evaluation (immediately after TZP administration — 0 h and at 8, 12, 24, 48, 72, 96, 168, 336, and 648 h). The area under the curve of the zero-to-infinity time dependence of the plasma drug concentration (AUC∞), the AUC from zero time to the time of the last measurable drug concentration (AUC last), and the maximum observed plasma drug concentration (C max) were examined. AUC last and AUC∞ values showed no differences between the mild renal failure, severe renal failure, and ESRD groups compared with the control group. Mean AUC last and AUC∞ values were 25% (90% CI: 1.04–1.52) and 29% (90% CI: 1.07–1.56) higher, respectively, for the moderate renal impairment group compared with the control group. There was no clinically significant effect of renal impairment on the PK of tirzepatide, so it appears that dose adjustment of TZP may not be required in patients with renal impairment.

A large comparative study showed that when comparing several GLP-1R agonists with DPP-4 inhibitors in patients with initial cardiovascular risk, the incidence of adverse events was significantly lower with the former [63, 64].

The incidence of adverse effects of TZP has been evaluated in several clinical trials [21–24].

Ohwaki et al. and Furihata et al. [21, 22] in a phase 1 CRT conducted in a group of 48 T2DM patients with a mean age of 57.4 ± 8.8 years with a BMI of 25.4 ± 3.2 kg/m^2 and an HbA_{1c} level of 8.0 ± 0.8% showed that the most commonly reported treatment-related adverse effects of various doses of TZP were decreased appetite and gastrointestinal side effects, which were generally dose-dependent and mild in severity. The authors evaluated the effects of different doses of TZP (5 mg, 10 mg, and 15 mg weekly) on meal intake and appetite. Standardized meals (700 kCal; 20% protein, 25% fat, 55% carbohydrate) were administered on days 1, 2, and 51 of the study. The amount (%) of food consumed was recorded. The subjects' appetite decreased on day 2 (tirzepatide 5 mg) in a dose-dependent manner. The number of meals with ≥ 50% post-meal residual was 0% in the placebo group and 16.7% (TZP 5 mg) on day 2 and 0% in the placebo group and 13.6% (TZP 5 mg), 18.2% (TZP 10 mg), and 30.0% (TZP 15 mg) in the study groups on day 51, respectively.

In a phase 2 CRT, Frias et al. [23] showed that the incidence of gastrointestinal side effects was 23.1% for the 1 mg dose, 32.7% for the 5 mg dose, 51.0% for the 10 mg dose, and 66.0% for the 15 mg weekly dose, demonstrating dose-dependent behaviour (compared to 42.6% for dulaglutide and 9.8% for placebo). The second most common adverse effect was decreased appetite, with an incidence ranging from 3.8% to 18.9% in the TZP treatment groups. The incidence of discontinuation due to adverse effects was higher with higher doses of TZP (25% in the 15 mg group, 9.1% in the 10 mg group, and 5.1% in the 5 mg group); the incidence of discontinuation with dulaglutide was 11.1% [23].

In another study, Frias et al. [24] evaluated the safety and tolerability of TZP. The study group and clinical trial conditions are described in the phase 2 CRT section of the paper [24]. The most commonly reported adverse events were diarrhoea (27.0%), nausea (27.0%), decreased appetite (16.2%), vomiting (14.4%), and headache (13.5%). The incidence of events was similar in each of the TZP treatment groups, except for a lower incidence of nausea in the 12 mg TZP group. The percentages of patients who reported nausea were as follows: in the placebo group 7.7%, in the 12 mg TZP maximum dose group 24.1%, in the 15 mg TZP maximum dose group under regimen 1 (15 mg-1) 39.3%, and in the 15 mg under 2 regimen (15 mg-2) 35.7%. Two subjects in the TZP treatment groups (12 mg and 15 mg-1) discontinued the study because of gastrointestinal side effects in the form of diarrhoea. The combined incidence of adverse reactions in the form of nausea, vomiting, and/or diarrhoea was higher in the 15 mg-1 TZP treatment group (57.1%) compared with the 12 mg dose group (48.3%) and the 15 mg-2 dose group (46.4%). The incidence of hypoglycaemic episodes was low in all TZP treatment groups. Twelve patients had at least one hypoglycaemic episode [plasma glucose ≤ 70 mg/dL (3.9 mmol/L)]. The authors reported no cardiovascular events during the study.

Conclusion

The development of a pharmacological agent such as tirzepatide, which has the ability to significantly reduce glycaemic levels as well as improve insulin sensitivity, reduce body weight, and improve lipid metabolism in the early clinical stage of T2DM, is critically important. Therefore, this compound appears to be not only a new antidiabetic drug. Tirzepatide, administered by weekly subcutaneous injections, and additional dual GLP-1/GIP receptor agonists that may be developed in the future, appear to be promising drugs for the treatment of many cardiometabolic disorders as well [65]. Tirzepatide's mechanism of action and safety profile could potentially fill important gaps in the current treatment of T2DM.

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