THE IMPACT OF TIRZEPATIDE ON LIPID PROFILE BASED ON THE SURMOUNT CLINICAL TRIALS

Analiza wpływu tirzepatydu na profil lipidowy na podstawie badań klinicznych SURMOUNT

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Abstract

Hyperlipidaemia, or high blood lipid levels, is a significant risk factor for cardiovascular diseases. Tirzepatide is a dual agonist of glucose-dependent insulinotropic polypeptide receptor (GIPR) and the glucagon-like peptide-1 receptor (GLP-1R). Tirzepatide is indicated for patients with type 2 diabetes and adults with obesity and overweight to reduce body weight. In recent years, there have been reports that this drug also has beneficial effects on the lipid profile. This paper summarizes data from the SURMOUNT clinical trials to evaluate how tirzepatide affects lipid profile parameters. The analysis demonstrated numerous benefits resulting from tirzepatide therapy. The observed favourable safety profile additionally enhances the attractiveness of this drug as a therapy for individuals with lipid disorders. Tirzepatide could be a breakthrough drug not only for obesity and type 2 diabetes but also for dyslipidaemia. However, despite promising results, further research is needed to understand the long-term safety and cost implications associated with this agent. These studies will be crucial for developing individualized therapeutic plans and optimizing the use of tirzepatide in various patient subgroups.

Streszczenie

Hiperlipidemia, czyli wysokie stężenie lipidów we krwi, stanowi istotny czynnik ryzyka chorób sercowo-naczyniowych. Tirzepatyd to podwójny agonista receptorów polipeptydu insulinotropowego zależnego od glukozy oraz glukagonopodobnego peptydu-1. Według wskazań lek ten stosuje się w cukrzycy typu 2 oraz otyłości i nadwadze u dorosłych pacjentów w celu redukcji masy ciała. W ostatnich latach pojawiły się także doniesienia, że tirzepatyd korzystnie wpływa na profil lipidowy. W pracy podsumowano dane z badań klinicznych SURMOUNT, aby ocenić, jak tirzepatyd wpływa na profil lipidowy. Analiza wykazała wiele korzyści wynikających z przyjmowania tego leku. Dodatkowo korzystny profil bezpieczeństwa podnosi jego atrakcyjność jako leku stosowanego u osób z zaburzeniami lipidowymi. Tirzepatyd może być przełomowym lekiem w leczeniu nie tylko otyłości i cukrzycy typu 2, ale także dyslipidemii. Jednak pomimo obiecujących wyników, potrzebne są dalsze badania, aby zrozumieć długoterminowe bezpieczeństwo i koszty związanych ze stosowaniem tego leku. Będą one kluczowe dla opracowania indywidualnych planów terapeutycznych i optymalizacji wykorzystania tirzepatyd w różnych podgrupach pacjentów.

Keywords: lipid profile; tirzepatide; SURMOUNT

Słowa kluczowe: profil lipidowy; tirzepatyd; SURMOUNT

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Introduction

Lipid disorders are a major risk factor for cardiovascular disease (CVD) both in Poland and worldwide. They affect up to 21 million people, accounting for more than 60% of the adult population and up to 70% of >65 year-old population, in Poland. It is estimated that only 20% of the population are aware of their total or LDL cholesterol levels. Unawareness of lipid disorders prevents treatment initiation, leading to an increased risk of serious cardiovascular incidents, such as myocardial infarction and stroke [1].

High LDL cholesterol plays an important role in the pathogenesis of atherosclerosis. However, in the last two decades, many studies have demonstrated that excess cholesterol accumulation in various tissues and organs also contributes to the development of many other disorders. A positive correlation was found between hyperlipidaemia and chronic kidney disease, osteoporosis, Alzheimer's disease, non-alcoholic fatty liver disease, hypothyroidism and pituitary disorders [2].

Since hyperlipidaemia is a well-known modifiable risk factor for cardiovascular disease (CVD), its treatment is of particular importance. The primary treatment for hyperlipidaemia involves lifestyle management, including increased physical activity and an appropriate diet. Those with poor response to lifestyle changes are offered pharmacotherapy. Various lipid-lowering therapies are currently available, including statins, ezetimibe, PCSK9 inhibitors and ion-exchange resins [3]. There is also ample ongoing research on new blood lipid lowering treatments [4, 5]. Tirzepatide (TZP) is one of the possible future therapeutic options. To date, a number of randomised controlled trials have been conducted in different countries to assess the efficacy and safety of this drug. However, most of these mainly focused on assessing its impact on blood glucose and body weight in patients with or without type 2 diabetes mellitus (T2DM). Only a small number of studies have analysed the effect of this agent on lipid metabolism.

Aim

The aim of this paper was to summarise and analyse the current knowledge on the impact of TZP on the lipid profile based on the SURMOUNT trials.

Mechanism of action

Tirzepatide is a dual agonist of gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors. Its mechanism of action is to mimic incretin hormones by interacting with GLP-1 and GIP receptors. GLP-1 is released by intestinal cells in response to ingested food to regulate blood glucose. Tirzepatide acts in a glucose-dependent manner, increasing insulin secretion by pancreatic β-cells in response to elevated blood glucose. It also inhibits the release of glucagon and delays gastric emptying. GLP-1 receptors are not only found in the pancreas, but also in various other organs and systems, such as the central nervous system, heart, kidneys, lungs and gastrointestinal tract. There is evidence to suggest that GLP-1 may not only regulate glucose levels and supress appetite, but also has neurotrophic, neuroprotective and cardioprotective effects [6].

The action of TZP on the GIP receptor generates an effect similar to its agonist action on the GLP-1 receptor, stimulating insulin release from pancreatic β-cells. However, unlike its action on GLP-1 receptors, activation of the GIP receptor does not affect glucagon levels and has minimal impact on gastric digestive processes. The synergistic effect on both receptors is beneficial and effectively stabilises blood glucose levels [7].

Tirzepatide increases satiety and reduces hunger, suppressing appetite. As a result, the patient shows a reduced desire to eat, which in turn reduces body weight and body fat. This phenomenon has a beneficial effect on the patient's lipid profile. The exact mechanism of action of incretin hormone agonists on adipocytes is not fully understood. They are likely to act mainly indirectly by increasing sympathetic nervous system stimulation, leading to reduced lipogenesis and lower blood triglycerides [8].

The history of tirzepatide

Tirzepatide was invented by Eli Lilly and Company. In 2016, a phase I trial was launched with the main objectives of:

- assessing TZP safety and its possible adverse events;
- measuring TZP pharmacokinetics, i.e. distribution and elimination time;
- assessing the effects of TZP on blood glucose levels [9].

A year later, phase II trial was initiated to evaluate the efficacy of the investigational medicinal product in T2DM patients [10]. The results of the SURPASS clinical trial were published between 2020 and 2022. The phase III SURPASS programme was designed to assess the efficacy and safety of TZP as a therapy to improve blood glucose control in T2DM patients. The SURPASS programme comprises six global (SURPASS 1–6) [11–16], two Japanese (SURPASS-J mono, SURPASS-J combo) and one Asian-Pacific study (SURPASS-AP combo) [17–19]. The SURPASS study resulted in a decision by the US Food and Drug Administration (FDA) in May 2022 to approve TZP under the trade name Mounjaro. Treatment of T2DM in adults alongside appropriate diet and physical activity was the main indication. On 6 October 2022, the FDA granted Fast Track designation for TZP in the context of trials on the treatment of adults with obesity, or overweight with weight-related comorbidities [20]. As a result, the SURMOUNT programme was conducted between 2022 and 2023. On its basis, the FDA approved TZP under the trade name Zepbound for chronic weight management in adults with obesity (BMI ≥30 kg/m^2) or overweight (BMI ≥27 kg/m^2) with at least one weight-related condition (e.g. hypertension, dyslipidaemia, T2DM, obstructive sleep apnoea or CVD) in November 2023. Tirzepatide is intended to be used alongside a reduced-calorie diet and increased physical activity [21].

SURMOUNT trials – background

The SURMOUNT project is an innovative research endeavour to evaluate the efficacy and safety of TZP as a therapy for overweight and obese individuals. Under this programme, multicentre, randomised and double-blind clinical trials ensuring a high level of reliability of the results were conducted. The SURMOUNT programme encompasses five phase III clinical trials. SURMOUNT-1 (NCT04184622) and SURMOUNT-2 (NCT04657003) assed the efficacy and safety of TZP used at different doses. SURMOUNT-1 evaluated only patients without T2DM, while SURMOUNT-2 included only T2DM patients [22, 23]. SURMOUNT-3 (NCT04657016) and SURMOUNT-4 (NCT04660643) were designed to assess the efficacy and safety of TZP at maximum tolerated doses [24, 25]. SURMOUNT-5 was designed to compare TZP with semaglutide for efficacy and safety in non-diabetic overweight or obese adults with weight-related health problems. This study is currently underway and is expected to be completed in November 2024 [26]. The inclusion criteria for SURMOUNT-1, SURMOUNT-3, SURMOUNT-4, and SURMOUNT-5 were almost identical, with some differences for the SURMOUNT-2 trial, especially in terms of BMI values. All participants followed a reduced-calorie diet and increased their physical activity when entering the study. All patients were of legal age and gave informed consent to participate in the study. The trials were conducted in accordance with the recommendations for good clinical practice and the principles of the Declaration of Helsinki. Methodological details for each SURMOUNT study are summarised in table 1.

At baseline, demographic and clinical data were collected, including patients' sex and age, BMI, fasting body weight, waist circumference, as well as systolic and diastolic blood pressure. Metabolic parameters such as fasting glucose, HbA_{1c} and fasting lipids were also assessed. Body weight, HbA_{1c}, blood pressure and lipid profile were the primary endpoints of the study.

Table 2 summarises patents' demographic, anthropometric and clinical parameters, allowing analysis of their baseline health status.

A total of 5,066 patients participated in SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4. Women predominated in all studies, accounting for a total of 64.55% of patients. Total cholesterol ranged between 176.8 mg/dL and 194.6 mg/dL. The lowest (44.3 mg/dL) and the highest (51.1 mg/dL) HDL levels were observed in SURMOUNT-2 and SURMONUT-4, respectively. LDL levels ranged from 96.5 mg/dL to 116.8 mg/dL, depending on the study, while VLDL ranged from 60.4 mg/dL to 77.7 mg/dL. The lowest (135.7 mg/dL) and the high-

Table 1. Study objectives, inclusion criteria and methodology of the SURMOUNT clinical trial programme

Title	SURMOUNT-1 [22]	SURMOUNT-2 [23]	SURMOUNT-3 [24]	SURMOUNT-4 [25]	SURMOUNT-5 [26]
Number	NCT04184622	NCT04657003	NCT04657016	NCT04660643	NCT05822830
Objectives	To assess the efficacy and safety of TZP in obese or overweight adults	To assess the efficacy and safety of TZP in adults with obesity and T2DM	To investigate how TZP maintains BW or contributes to further BW loss in obese individuals following lifestyle modification	To assess the efficacy and safety of TZP used alongside diet and physical activity in adults with obesity or overweight	To assess the efficacy and safety of TZP vs. sema in obese or overweight adults with weight-related comorbidities
Inclusion criteria	BMI ≥30 kg/m², ≥1 comorbidity*, ≥1 weight loss failure, age ≥18 years	BMI ≥27 kg/m², T2DM**, ≥1 weight loss failure, age ≥18 years	BMI ≥30 kg/m², ≥1 comorbidity *, ≥1 weight loss failure, age ≥18 years	BMI ≥30 kg/m², ≥1 comorbidity *, ≥1 weight loss failure, age ≥18 years	BMI ≥30 kg/m², ≥1 comorbidity *, ≥1 weight loss failure, age ≥18 years
Randomisation	+	+	+	+	+
Double-blinded	+	+	+	+	-
PBO	+	+	+	+	-
Intervention	Once-weekly TZP (5 mg, 10 mg, 15 mg) and PBO at 1:1:1:1	Once-weekly TZP (10 mg, 15 mg) and PBO at 1:1:1	Once-weekly TZP MTD (10 mg or 15 mg) and PBO at 1:1	Once-weekly MTD TZP (10 mg or 15 mg) and PBO at 1:1	Once-weekly TZP 15 mg and sema 2.4 mg
Duration	72 weeks	72 weeks	72 weeks	88 weeks	74 weeks

TZP – tirzepatide; T2DM – type 2 diabetes mellitus 2; BMI – body mass index; PBO – placebo; sema – semaglutide; BW – body weight; MTD – maximum tolerated dose
* Hypertension, dyslipidaemia, obstructive sleep apnoea, cardiovascular disease
** The study included patients with T2DM with HbA_{1c} ≥7% to ≤10% at screening, with stable therapy for the last 3 months prior to the study

est (184.4 mg/dL) triglyceride levels were recorded in SURMOUNT-4 and SURMOUNT-2. Free acids were similar across all studies and ranged between 0.51 mEq/L and 0.6 mEq/L.

Analysis of results

The SURMOUNT trial programme demonstrated significantly improved lipid profile in TZP-treated patients compared to placebo as evidenced by percentage changes in laboratory parameters such as triglycerides, total cholesterol, LDL, VLDL, non-HDL, HDL, and free fatty acids compared to baseline. SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4 assessed statistical significance between the outcomes achieved by TZP-treated patients vs. placebo, while SURMOUNT-3 did not report *p*-values for changes in lipid profile parameters.

The greatest (33.3%) reduction in triglycerides was observed in SURMOUNT-4 patients, who were receiving the maximum tolerated dose (fig. 1). This was statistically significantly higher compared to placebo, which showed a 15.3% decrease (p <0.001). SURMOUNT-1 and SURMOUNT-2 also demonstrated a statistically significant difference (p <0.001) between the TZP-treated groups (decrease between 24.3–31.3%) and placebo. The reduction in total cholesterol in TZP-treated patients was 7.4–3% and was greater compared to placebo, where the changes ranged from −1.1% to +5.2%. SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4 showed statistically significant differences (p <0.05) between patients treated with TZP and those receiving placebo. The largest decrease in total cholesterol was observed in SURMOUNT-1, in the group receiving TZP 15 mg. Changes in LDL ranged from −8.6% to +2.3% in TZP-treated patients and from −0.9% to +6.3% in the placebo group (fig. 2). These differences were statistically significant (p <0.05) across SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4. The change in non-HDL cholesterol levels ranged from −13.4% to −6.6% in the TZP-treated group and from −1.8% to +5.6% in the placebo group. These differences were statistically significant (p <0.05) across SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4. HDL increased in TZP-treated patients from 15.4% to 7%, with an increase of 9.4% to 0.2% compared to placebo. These differences were statistically significant in SURMOUNT-1 and SURMOUNT-2. In contrast, no statistical significance (p >0.05) was found in SURMOUNT-4 despite using the maximum tolerated dose of TZP, with 12.3% increase in HDL in the TZP-treated group vs. 9.4% in the placebo group (fig. 3). The change in VLDL ranged from −32.6% to −24.2% in TZP-treated patients and from −6% to +3% in the placebo group. The change in free fatty acids ranged from −33.1% to −0.7% in TZP-treated patients, and from −15% to +6.1% in the placebo group. There were significant differences in VLDL and free fatty acids with respect to baseline between the TZP-treated group and the placebo group in SURMOUNT-1, SURMOUNT-2 and SURMOUNT-4.

Safety analysis

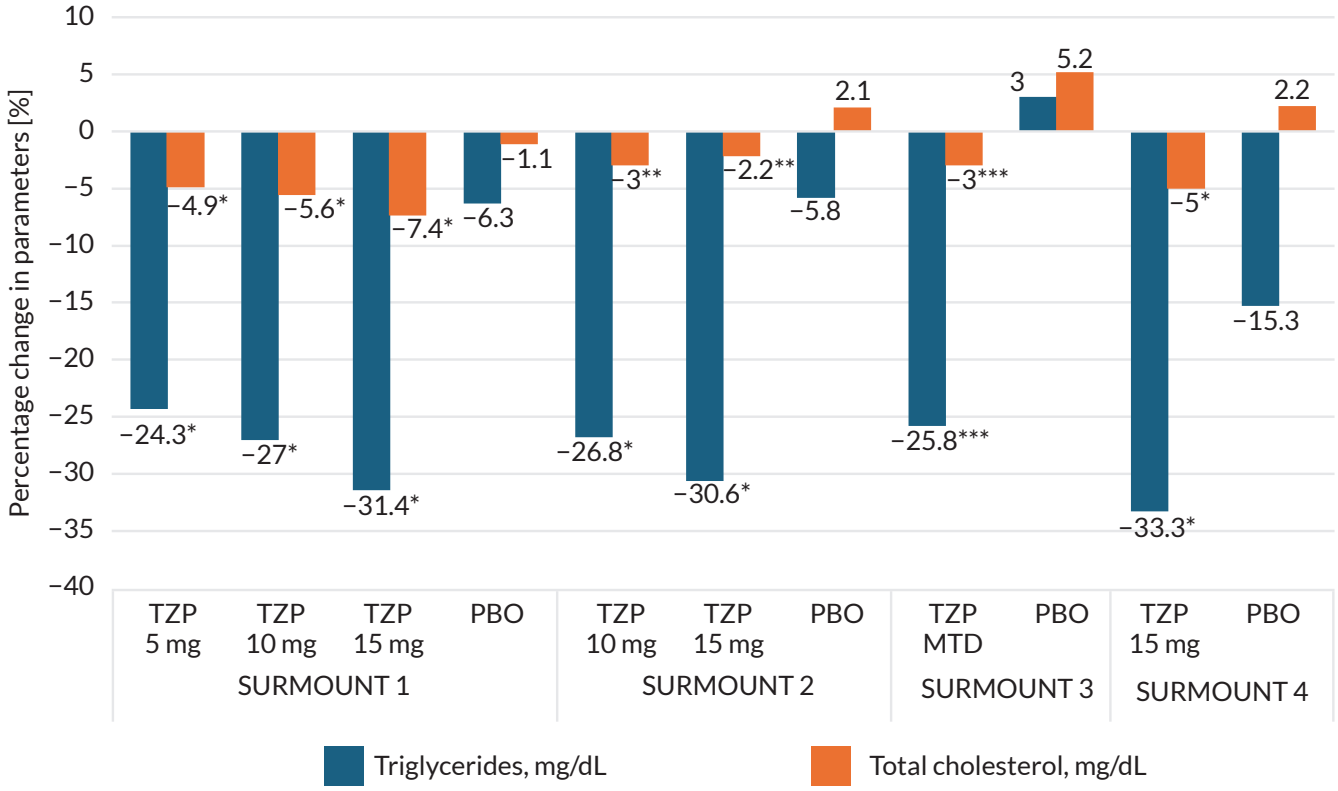
It was observed in SURMOUNT-1 that the proportion of patients reporting at least one treatment-emergent adverse event (TEAE) during TZP therapy ranged from 78.9% to 81.8% compared to 72% in the placebo group. Gastrointestinal symptoms such as nausea, diarrhoea and constipation were the most common TEAEs. A total of 160 cases of serious adverse events (SAE) were reported (6.3%). However, it should be emphasised that their incidence was similar between patients receiving TZP and placebo.

In SURMOUNT-2, 74.48% of TZP-treated patients reported at least one TEAE and a similar rate was reported for placebo (75.87%). Adverse events led to study withdrawal in 35 TZP-treated patients and 12 patients in the placebo group.

Table 2. Baseline characteristics of patients included in SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, SURMOUNT-4

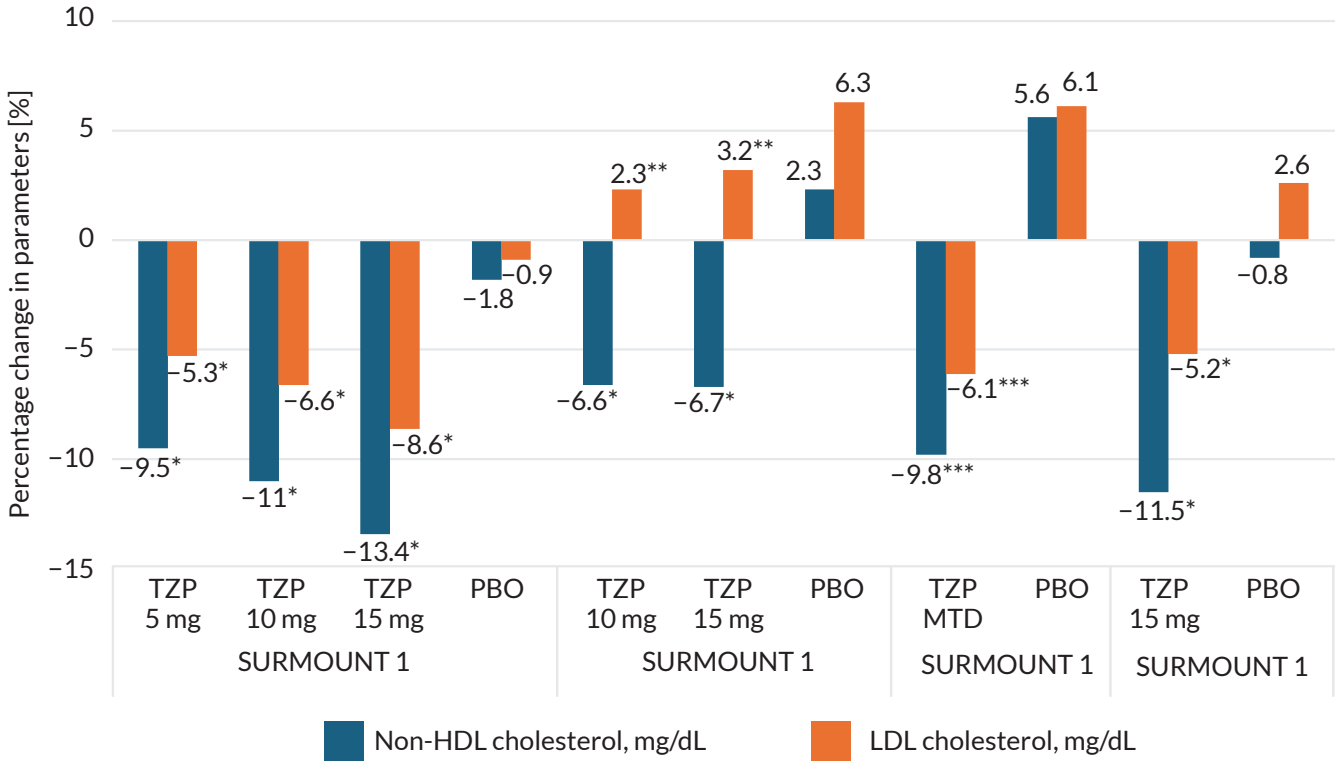
Title	SURMOUNT-1 [22]	SURMOUNT-2 [23]	SURMOUNT-3 [24]	SURMOUNT-4 [25]
Number	NCT04184622	NCT04657003	NCT04657016	NCT04660643
Number of patients (*n*)	2,539	938	806	783
Women, *n* (%)	1,714 (67.5)	476 (50.7)	534 (66.3)	546 (69.7)
Age (years), ± SD	44.9 ±12.5	54.2 ±10.6	44.9 ± 12.5	47.6 ±12.9
Body weight (kg), ± SD	104.8 ± 22.1	100.7 ± 21.1	109.7 ± 24.2	107.0 ± 22.5
BMI (kg/m^2) ± SD	38.0 ± 6.8	36.1 ± 6.6	38.9 ±7.1	38.3 ± 6.6
Total cholesterol (mg/dL) ± SD	191.7 ± 38.8	176.8 ± 42.0	194.6 ± 37.4	191.9 ± 39.2
HDL (mg/dL) ± SD	48.9 ± 13.0	44.3 ± 11.5	50.3 ± 13.9	51.1 ± 13.1
LDL (mg/dL) ± SD	114.2 ± 32.7	96.5 ± 34.7	116.8 ± 31.1	113.8 ± 32.9
VLDL (mg/dL) ± SD	63.9 ± 29.6	77.7 ± 33.6	60.8 ± 28.4	60.4 ± 27.9
Triglycerides (mg/dL) ± SD	145.7 ± 105.1	184.4 ± 127.9	138.2 ± 87.9	135.7 ± 78.6
Free fatty acids (mEq/L) ± SD	0.51 ± 0.21	0.60 ± 0.23	0.55 ± 0.22	0.53 ± 0.22

HDL – high-density lipoprotein; LDL – low-density lipoprotein; VLDL – very low-density lipoprotein; BMI – body mass index; SD – standard deviation



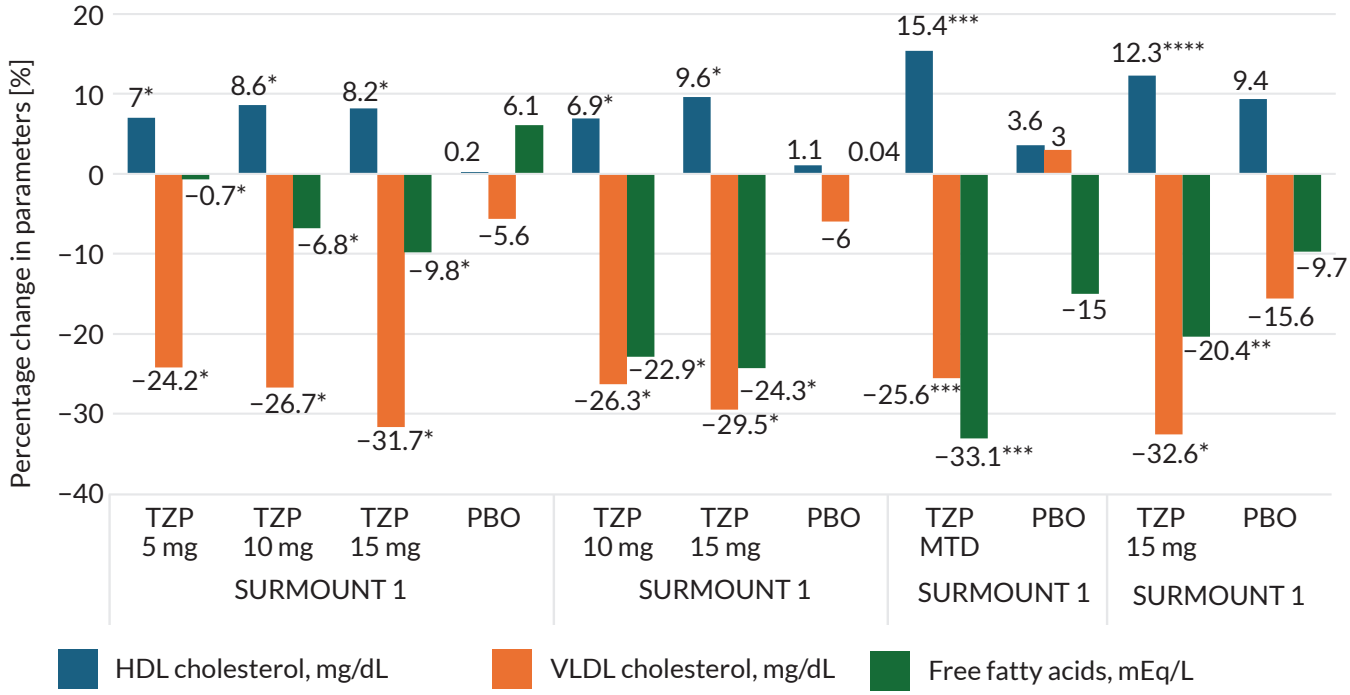
TZP – tirzepatide; PBO – placebo; MTD – maximum tolerated dose
The *p*-value refers to the comparison between the drug at a given dose and placebo.
* p <0.001, ** p = 0.001–0.05, *** Not reported

Figure 1. Comparison of percentage changes in triglycerides and total cholesterol in across SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4



TZP – tirzepatide; PBO – placebo; MTD – maximum tolerated dose
The *p*-value refers to the comparison between the drug at a given dose and placebo.
* p <0.001, ** p = 0.001–0.05, *** Not reported

Figure 2. Comparison of percentage changes in non-HDL and LDL across SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4



TZP – tirzepatide; PBO – placebo; MTD – maximum tolerated dose
The p-value refers to the comparison between the drug at a given dose and placebo.
* p <0.001, ** p = 0.001–0.05, *** Not reported, **** p >0.05

Figure 3. Comparison of percentage changes in HDL, VLDL and free fatty acids across SURMOUNT-1, SURMOUNT-2, SURMOUNT-3, and SURMOUNT-4

In SURMOUNT-3, the overall proportion of patients who reported at least one TEAE was 87.1% in the TZP group (287 patients), and 76.7%. in the placebo group (292 patients). Gastrointestinal symptoms such as nausea, diarrhoea and constipation were the most common TEAEs. These were more common in patients receiving the maximum tolerated dose of TZP than in the other groups.

In SURMOUNT-4, 81.0% of participants reported at least one TEAE during TZP therapy. Gastrointestinal TEAEs such as nausea (35.5%), diarrhoea (21.1%), constipation (20.7%) and vomiting (16.3%) were most common. These symptoms were more frequent in the TZP group vs. placebo.

A detailed analysis of TZP safety profile in the SURMOUNT study is shown in table 3.

Conclusions

Despite the well-known pathological consequences of hyperlipidaemia, there is little public awareness of the

Table 3. SURMOUNT – safety analysis

Study	Investigated subgroup	Patients with ≥1 AE, *n* (%)	Serious TEAEs, *n* (%)	TEAEs leading to treatment discontinuation, *n* (%)
SURMOUNT-1 [22]	TZP 5 mg (*n* = 630)	510 (80.95)	40 (6.35)	27 (4.29)
	TZP 10 mg (*n* = 636)	520 (81.76)	44 (6.92)	45 (7.08)
	TZP 15 mg (*n* = 630)	497 (78.89)	32 (5.01)	39 (6.19)
	PBO (*n* = 643)	463 (72.01)	44 (6.84)	17 (2.64)
SURMOUNT-2 [23]	TZP 10 mg (*n* = 312)	242 (77.56)	18 (5.77)	12 (3.85)
	TZP 15 mg (*n* = 311)	222 (71.38)	27 (8.68)	23 (7.40)
	PBO (*n* = 315)	239 (75.87)	23 (7.30)	12 (3.81)
SURMOUNT-3 [24]	TZP MTD (*n* = 287)	250 (87.12)	17 (5.92)	30 (10.45)
	PBO (*n* = 292)	224 (76.71)	14 (4.79)	6 (2.05)
SURMOUNT-4 [25]	TZP MTD (*n* = 335)	202 (60.30)	10 (2.99)	6 (1.79)
	PBO (*n* = 335)	187 (55.82)	10 (2.30)	3 (0.89)
TZP – tirzepatide; PBO – placebo; MTD – maximum tolerated dose; TEAE – treatment-emergent adverse event				

benefits of treating this disorder. The new treatment, tirzepatide, seems a promising alternative for the management of hyperlipidaemia. This review summarised the efficacy and safety of TZP based on the results of the phase III SURMOUNT clinical trials. These trials have shown that TZP not only effectively regulates blood glucose and leads to weight loss in T2DM patients, but it also significantly reduces blood lipids, with a relatively favourable safety profile. These studies are a key step in assessing the efficacy of this drug and its potential introduction into clinical practice. Continued research assessing the effects of TZP on the lipid profile and metabolic syndrome is needed. Despite such promising results, attention should be paid to gastrointestinal adverse events. Although these were mostly mild to moderate, further research is needed to better understand the long-term consequences of TZP therapy and to reduce the risk of treatment-emergent adverse events.

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