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Comparative study of the efficacy and safety of tirzepatide drugs in metabolic syndrome

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In the last decade, developed countries have seen a steady increase in the prevalence of metabolic disorders. The most significant among them are obesity and type 2 diabetes mellitus. Tirzepatide is an innovative drug, representing the first-in-class dual agonist of glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) receptors. Tirzepatide combines the action of two key incretin hormones, providing more comprehensive and effective regulation of glycemia and metabolism compared to traditional GLP-1 monoagonists. Tirzepatide was unavailable in Russia for a long time. However, in 2025, the first domestically produced tirzepatide drug, Tirzetta® (LLC "PROMMOMED RUS"), appeared.

The aim. To conduct a comparative evaluation of the efficacy and safety of the reproduced drug Tirzetta® (INN: Tirzepatide, manufacturer LLC "PROMMOMED RUS") and the reference drug Mounjaro® (INN: Tirzepatide, manufacturer "Eli Lilly") in a mouse model with induced metabolic syndrome (MS).

Materials and methods. The study was conducted on male mice of the C57BL/6 line. To metabolic syndrome (MS) was induced in animals with a diet high in fat and carbohydrates. Three batches of Tirzetta® and one series of Munjaro® were investigated. The drugs were administered at a dosage of 150 μg/kg subcutaneously once every three days for 15 days. During the experiment, glucose tolerance and insulin sensitivity tests were performed. The type of metabolism was determined by indirect calorimetry data. Mice were euthanized on 25th day for humane reasons upon reaching any of the following criteria: body weight loss of more than 15% in a week; serious injuries (fractures, amputations, etc.), appearance of non-healing wounds; seizures; unconscious state. A complete blood count was performed, and the following parameters were determined: glucose, triglycerides, cholesterol, AST, ALT. Necropsy was performed after euthanasia. During necropsy, the thoracic and abdominal organs of the animals were examined, and organs were dissected and weighed.

Results. In the MS group animals, body weight increased to 39.5 ± 0.6 g compared to the control group (31.9 ± 0.6 g), representing a 24% increase. Significant hyperglycemia was recorded with a glucose concentration of 14.9 ± 2.7 mmol/L versus 6.1 ± 0.4 mmol/L in the control, as well as a pronounced decrease in glucose tolerance in the loading test. The investigated tirzepatide drugs demonstrated a pronounced hypophagic effect with a 26–28% reduction in body weight, normalization of glycemia with a 48–53% decrease in glucose concentration, and improvement in glucose tolerance and

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insulin sensitivity. Indirect calorimetry data indicated a decrease in the respiratory exchange ratio, suggesting lipolysis activation. A significant reduction in triglyceride content in blood serum and liver was revealed. The bioequivalence of the investigated drugs Tirzetta® and Mounjaro® was established in the experimental MS model in mice based on a set of therapeutic efficacy and safety indicators.

Conclusion. Studies on an experimental model of induced MS in mice showed equivalent efficacy of Tirzetta® (INN: Tirzepatide, manufacturer LLC "PROMMOMED RUS", Russia) and Mounjaro® (INN: Tirzepatide, manufacturer "Eli Lilly", USA).

Keywords: tirzepatide; bioequivalence; metabolic syndrome; mice; indirect calorimetry; glucose tolerance test; hypophagic effect; lipolysis; glycemia; insulin sensitivity; preclinical study

Abbreviations: GLP-1 — glucagon-like peptide-1; GIP — glucose-dependent insulinotropic polypeptide; GTT — glucose tolerance test; T2DM — type 2 diabetes mellitus; MS — metabolic syndrome; BMI — body mass index; EMA — European Medicines Agency; INN — international nonproprietary name; EAEU — Eurasian Economic Union; IS — insulin sensitivity; MS — metabolic syndrome; BW — body weight; SOP — standard operating procedure; TG — triglycerides; FS — physiological saline; VCO_2 — carbon dioxide production rate; VO_2 — oxygen consumption rate; CS — comparator product; SPF — specific pathogen free.

Сравнительное исследование эффективности и безопасности лекарственных препаратов тирзепатида при метаболическом синдроме

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В последнее десятилетие в развитых странах отмечается устойчивое увеличение распространённости метаболических нарушений. Среди них наиболее значимыми являются ожирение и сахарный диабет 2 типа. Тирзепатид — это инновационный лекарственный препарат (ЛП), представляющий собой первый в своем классе двойной агонист рецепторов глюкагоноподобного пептида-1 (ГПП-1) и глюкозозависимого инсулинотропного полипептида (ГИП). Тирзепатид объединяет действие двух ключевых инкретиновых гормонов, что обеспечивает более комплексное и эффективное регулирование гликемии и метаболизма по сравнению с традиционными моноагонистами ГПП-1. Долгое время тирзепатид был недоступен в России, однако в 2025 году появился первый препарат тирзепатида отечественного производства — Тирзетта® (ООО «ПРОМОМЕД РУС»).

Цель. Провести сравнительную оценку эффективности и безопасности воспроизведённого препарат Тирзетта® (МНН: Тирзепатид, производитель ООО «ПРОМОМЕД РУС») и референтного препарата Мунджаро® (МНН: Тирзепатид, производитель «Эли Лилли») на модели мышей с индуцированным метаболическим синдромом (МС).

Материалы и методы. В исследовании использовали самцов мышей линии C57BL/6. Для проведения исследования у животных был индуцирован метаболический синдром (МС) при помощи диеты с высоким содержанием жира и углеводов. Далее исследовали эффективность ЛП тирзепатида, используя три серии препарата Тирзетта® и одну серию Мунджаро®. Исследовали три серии препарата Тирзетта® и одну серию Мунджаро®. Препараты вводили в дозировке 150 мкг/кг подкожно один раз в три дня в течение 15 дней. В ходе эксперимента проводили тесты на переносимость глюкозы и чувствительность к инсулину. Тип метаболизма определяли по данным непрямой калориметрии. Мышей подвергали эвтаназии на 25 день по соображениям гуманности при достижении любого из перечисленных ниже критериев: снижение массы тела более, чем на 15% за неделю; серьёзные травмы (переломы, ампутации и т.п.); появление незаживающих ран; судороги; бессознательное состояние. Проводили общий анализ крови и определяли следующие показатели: глюкоза, триглицериды, холестерин, АСТ, АЛТ. Некропсию проводили после эвтаназии. В ходе некропсии осматривали органы грудной и брюшной полости животных, иссекали и взвешивали их.

Результаты. У животных группы МС масса тела увеличилась до 39,5±0,6 г по сравнению с контрольной группой (31,9±0,6 г), что составляет прирост в 24%. В группе МС до лечения была зарегистрирована значительная гипергликемия с концентрацией глюкозы 14,9±2,7 ммоль/л против 6,1±0,4 ммоль/л в контроле, а также выраженное снижение переносимости глюкозы в нагрузочном тесте. Исследуемые препараты тирзепатида продемонстрировали выраженное гипофагическое действие со снижением массы тела на 26–28%, нормализацию гликемии с уменьшением концентрации глюкозы на 48–53 %, улучшение толерантности к глюкозе и инсулиновой чувствительности. По данным непрямой калориметрии на фоне приёма ЛП тирзепатида отмечено снижение дыхательного коэффициента, свидетельствующих об активации липолиза. Выявлено значительное снижение содержания триглицеридов в сыворотке крови и печени. Установлена биоэквивалентность исследуемых препаратов Тирзетта® и Мунджаро® в экспериментальной модели МС у мышей по комплексу показателей терапевтической эффективности и безопасности.

Заключение. Исследования на экспериментальной модели мышей с индуцированным МС показали эквивалентную эффективность ЛП Тирзетта® (МНН: Тирзепатид, производитель ООО «ПРОМОМЕД РУС», Россия) и Мунджаро® (МНН: Тирзепатид, производитель «Эли Лилли», США).

Ключевые слова: тирзепатид; биоэквивалентность; метаболический синдром; мыши; непрямая калориметрия; глюкозотолерантный тест; гипофагическое действие; липолиз; гликемия; инсулиновая чувствительность; доклиническое исследование

Список сокращений: ГПП-1 — глюкагоноподобный пептид-1; ГИП — глюкозозависимый инсулинотропный полипептид; ГТТ — глюкозотолерантный тест; СД2 — сахарный диабет 2 типа; МС — метаболический синдром; ИМТ — индекс массы тела; ЕМА — Европейское агентство по лекарственным средствам; ЛП — лекарственный препарат; МНН — международное непатентованное наименование; ЕАЭС — Евразийский экономический союз; ИЧ — чувствительность к инсулину; МС — метаболический синдром; МТ — масса тела; СОП — стандартная операционная процедура; ТГ — триглицериды; ФР — физиологический раствор; VCO_2 — скорость продукции углекислого газа; VO_2 — скорость потребления кислорода; ПС — препарат сравнения; СПФ — свободные от патогенной флоры.

INTRODUCTION

According to World Health Organization (WHO)[1] data, in 2022, there were over 2.5 billion individuals over 18 years of age with overweight (BMI = 25–29 kg/m^2) and over 890 million people suffering from obesity (BMI > 30 kg/m^2) worldwide. As of 2021, the prevalence of obesity in the USA is 56%, in the UK — 52 %, in Israel — about 50 % of women and 60% of men have overweight or obesity. Russia does not significantly differ from the aforementioned countries in this indicator: over 60% of the adult population of Russia is overweight, and about 26 % is obese[2].

It is important to note that individuals with overweight and obesity are diagnosed significantly more often with diabetes mellitus (5–20 %), hypertension (34–64 %), gallbladder diseases (35–45 %), and osteoarthritis (5–17 %). It has been established that the epidemiological links between BMI and type 2 diabetes mellitus (T2DM) are very strong: over 75 % of cases of the disease are associated with overweight and obesity. More than 2/3 of patients with T2DM have a BMI > 27 kg/m^2, and more than 50 % have a BMI > 30 kg/m^2 [1, 2].

Tirzepatide is a polypeptide with affinity for two receptors of the incretin axis — glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor. Native GIP and GLP-1 are

[1] WHO. Obesity and overweight. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

[2] Fatness. A modern view on pathogenesis and therapy. Vol. I; A.S. Ametov [et al.]. Moscow: GEOTAR-Media; 2021. 384 p. Russian

key incretin hormones secreted by intestinal cells in response to food intake. They enhance glucose-dependent insulin secretion from pancreatic β-cells, suppress postprandial glucose and glucagon surges from α-cells. In addition, GIP and GLP-1 regulate gastric and intestinal motility, appetite, and, primarily, lipolysis. However, GIP and GLP-1 have a short half-life, which makes the development of exogenous incretin receptor agonists highly promising for the treatment of obesity, overweight, and associated diseases [3–5].

Tirzepatide is a linear peptide of 39 amino acids conjugated with a C20 fatty acid at the N-terminus. This conjugation increases the stability of the compound by effectively binding to plasma albumin, which significantly prolongs the drug's half-life and allows for a once-weekly dosing regimen. The amino acid sequence of tirzepatide is based on the sequence of endogenous GIP but with key substitutions that increase affinity for GLP-1 receptors and mediate pharmacological action comparable to endogenous GLP-1 [6].

As a drug, tirzepatide was approved by the FDA on May 13, 2022, under the brand name Mounjaro® (Eli Lilly, USA)[3] for the treatment of adults with T2DM, making it the first and only GIP and GLP-1 receptor agonist for this indication. Later, on November 8, 2023, tirzepatide was approved as a drug for weight management in adults with obesity or overweight with comorbidities under the brand name Zepbound® (Eli Lilly, USA)[4]. Previously, on September 15, 2022, tirzepatide was also approved by the European Commission[5].

In the Russian Federation, tirzepatide was first registered on January 23, 2025, under the brand name Tirzetta® (PROMED RUS LLC, Russia)[6]. This drug is effective for several indications: obesity, overweight, prediabetes, and T2DM.

MATERIALS AND METHODS

Test system

The study used 80 male C57BL/6 mice aged 8–10 weeks. The animals were obtained from the FRC IC&G SB RAS (Novosibirsk, Russia) nursery. According to the health certificate provided by the manufacturer, the mice were specific pathogen-free (SPF) according to the FELASA–2014 list. The adaptation period after receiving the animals was 10 days.

The animals were housed in groups (n = 10) in individually ventilated cages GM500 (Tecniplast, Italy) with a floor area of 500 cm2. Wood shavings (fraction 3, IP Filonich, Russia) were used as bedding. Throughout the study, except for periods before glucose tolerance testing and necropsy, the animals had unlimited access to food and purified water. A complete feed P22 (BioPro, Russia) was used for feeding the control group mice.

For environmental enrichment, mice were provided with nesting material (paper tissues) and shelters (red plastic houses). Materials supplied to the animals were sterilized by autoclaving. Routine animal care was carried out in accordance with current GLP regulations.

The temperature in the animal housing rooms ranged from 20 to 26 °C, relative humidity from 30 % to 70 %, the light cycle was 12 hours, and illumination was approximately 400 Lux at 1 m above the floor. The animals were under regular observation by a veterinarian.

Design of Experiment

A population of 54 mice (males) with MS was developed in the first stage. The animals were divided into 6 experimental groups of 10–12 individuals each. The control group of mice (K) consisted of individuals without MS, and the remaining groups consisted of mice with induced MS. Mice in the control group K and one of the MS groups received placebo. The other four groups of mice with MS received tirzepatide: as part of the reference drug Mounjaro® (RD), or as part of the drug Tirzetta® from one of three batches (T1, T2, T3) (Fig. 1, Table 1).

Animals were assigned to experimental groups by randomization using GraphPad software. All mice were individually marked with ear tags (model 1005, National Band and Tag Company, USA; weight 0.25 g).

Induction of metabolic syndrome

MS was induced in all mice, except for animals in group K, using a modified diet consisting of high-fat and high-carbohydrate feed and fructose syrup for drinking [1, 2].

The high-fat feed was prepared in the laboratory with the following composition (by mass): complete feed — 35 %; rendered beef fat — 30 %; whole condensed milk with sugar 8.5–35 %.

To prepare the feed, melted beef fat was added to the non-pelleted (powdered) complete feed in a mixer bowl at a rate of 300 g per 350 g of complete feed and

[3] FDA. Drug Trials Snapshots: MOUNJARO. Available from: https://www.fda.gov/drugs/drug-approvals-and-databases/drug-trials-snapshots-mounjaro

[4] FDA. FDA Approves New Medication for Chronic Weight Management. Available from: https://www.fda.gov/ news-events/press-announcements/fda-approves-new-medication-chronic-weight-management

[5] EMA. Mounjaro. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/mounjaro

[6] Tirzetta®. The State Register of Medicines of the Russian Federation. Available from: https://grls.minzdrav.gov.ru/Grls_View_v2.aspx?routingGuid=f72153a0-29eb-4756-9a93-0b5455cf8423. Russian

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mixed for 2–3 minutes until the fat was absorbed into the feed. Then, 350 g of condensed milk was added to the mixture and mixed for another 3–5 minutes until homogeneous. The prepared mixture was distributed into silicone molds, frozen, and stored at a temperature not exceeding –18 C until use, but no longer than 1 month.

The actual nutritional value of the feed was (by mass): crude protein — 10.9 ± 0.5 %; fats — 33.7 ± 0.8 %; carbohydrates — 45.5 %; moisture — 7.4 ± 0.4 %; total ash — 2.5 ± 0.3 %; energy value — 5315 kcal/kg.

A 30 % fructose syrup was prepared in the laboratory by placing a known weight of fructose in a graduated cylinder, bringing the volume to 2 L with purified water, and mixing until dissolved. The prepared syrup was poured into sterile bottles and stored at a temperature not exceeding 8 C until use, but no longer than 2 weeks.

The “high-fat” feed was provided in the feeder grid without restriction, similar to the standard complete feed, and was replaced with fresh feed at least once a week. Animals were provided with fructose syrup as drinking water. Water bottles were replaced at least once every 3 days. During the testing period in PhenoMaster, feed and syrup were provided in the PhenoMaster feeders /waterers.

The metabolic status of all mice was assessed monthly, starting from the 2nd month from the beginning of MS induction, but not exceeding 6 months. Animals were used in experiments upon reaching the following criteria: average body weight (for all mice receiving the modified diet) of at least 40 g, reduced glucose tolerance compared to control group mice, or after 6 months of feeding the modified diet.

Mouse body weight was measured weekly. Weighing was performed with an accuracy of ±0. g using Vibra CJ-2200CE scales (Vibra, Japan).

Samples

To form a representative quality profile and obtain reliable comparability data, three batches of the reproduced drug Tirzetta® were used in the studies. Information on the investigated batches is presented in Table 2.

A “placebo” was used as a vehicle for the investigated drugs, which was a solution containing (per 0.5 mL): sodium chloride (4.1 mg), disodium hydrogen phosphate heptahydrate (0.7 mg); 1 M sodium hydroxide solution or 1 M hydrochloric acid solution (to pH 6.5–7.5), water for injection (up to 0.5 mL). All samples were stored at a temperature of 2 to 8 C for the duration of the shelf life indicated by the manufacturer.

Working solutions of tirzepatide for administration to animals were prepared by mixing the investigated drugs at a concentration of 5 mg/mL and placebo to obtain a solution with a concentration of 0.15 mg/mL. Working solutions were prepared immediately before use and used within 2 hours of preparation.

Dosing regimen

To accustom mice to subcutaneous administration procedures and minimize the impact of associated stress on study results, mice were injected with physiological saline from day 1 to day 7 (d1…d7, =7 injections). Investigated substances were administered from day 8 to day 23 of the experiment.

T1, T2, T3, RD, and placebo were administered subcutaneously once every three days (see Table 1). Administration was carried out in the scruff area using 0.5 mL syringes with G 29 needles (5 mL/kg). Administration was performed in the afternoon (from 18:00 to 21:00), before the evening peak of food consumption. Investigated drugs were administered at a dose of 150 µg/kg subcutaneously, every third day — from day 8 to day 23 of the experiment. The tirzepatide dose was selected based on the literature data [7].

Observation

During the study, food and water intake, feeding behavior, and physiological parameters were determined using the PhenoMaster system, and blood glucose concentration was measured. Food and water intake were assessed individually. In the specified system, feeder weight registration is carried out with high temporal resolution, allowing for the analysis of animal feeding behavior: amount eaten / drunk per feeding / drinking episode, number of feeding and drinking bouts, and duration of intervals between them.

Non-fasting blood glucose concentration was measured on days 6, 9, 12, 15, and 18 of the experiment using a portable glucose meter OneTouch Verio Reflect (LifeScan, Switzerland) and test strips according to the manufacturer’s instructions. Blood for measurement (3–5 µL) was obtained by tail tip puncture. Measurements were taken in the evening, before the peak food consumption, prior to drug administration.

Monitoring of physiological parameters in the PhenoMaster system was conducted from day 6 to day 15 of the experiment inclusive (2 days before and 8 days after the start of substance administration).

During monitoring, the following parameters from Table 1 were recorded. System setup, calibration, startup, and control were performed according to the manufacturer’s instructions.

Challenge tests

During the experiment, glucose tolerance and insulin sensitivity tests were performed. The tests were conducted after a 9-hour fast and 15–18 hours after the last drug administration. The glucose tolerance test was performed once on day 21 of the experiment. Insulin sensitivity was tested once on day 24 of the experiment.

In the evening before the testing (21:30 ± 30 min), food was removed from the animals; mice consuming fructose syrup were given water instead of syrup. Testing was conducted the next day in the morning (11:30 ± 40 min).

The glucose tolerance test consisted of measuring mouse blood glucose concentration 15 minutes and immediately before (0 minutes) intragastric administration of 2 g/kg glucose (administration volume 5 mL/kg), and at 15, 30, 45, 60, 90, and 120 minutes after glucose administration. Data analysis involved comparing blood glucose concentration curves and areas under the curves.

The insulin sensitivity test consisted of measuring mouse blood glucose concentration immediately before (0 min) intravenous administration of 4 U/kg insulin (administration volume 5 mL/kg), and at 15, 30, 60 minutes, 2, 3, 4, and 6 hours after insulin administration. Data analysis involved comparing the blood glucose concentration curves themselves and the time to recovery of concentration.

Metabolic assessment

Metabolic type was determined by indirect calorimetry data. For this purpose, oxygen consumption and carbon dioxide production by animals were measured in the PhenoMaster system for 2 days before the start of substance administration and 8 days after the start of dosing. Based on these data, the respiratory exchange ratio (RER) was calculated, which determined the spectrum of utilized substrates. RER was calculated as the ratio of carbon dioxide volume produced to oxygen volume consumed.

Heat production (energy expenditure) was determined using the oxygen equivalent EE, the value of which depends on the RER value:

$$M = V_{O2} \times EE(RER),$$

where M is heat production (energy expenditure, kcal/kg/h); V_{O2} is oxygen consumption (mL/kg/h); EE(RER) is the energy equivalent of oxygen, kcal/L O_2.

Euthanasia and blood sample collection

Mice were euthanized on day 25 for humane reasons upon reaching any of the following criteria:

- body weight loss of more than 15 % in a week;
- serious injuries (fractures, amputations, etc.), appearance of non-healing wounds;
- seizures;
- unconsciousness.

Euthanasia, combined with blood sample collection, was performed by inhalation of 2 % isoflurane in an induction chamber. In the evening before euthanasia, food was removed from the animals, and mice consuming fructose syrup were given water instead.

Blood tests

Collected blood was divided into 2 samples: for complete blood count (CBC) and for serum preparation. Blood for CBC was stabilized with EDTA and stored at room temperature until analysis, but no longer than 2 hours.

To obtain serum, blood was placed in tubes with a clotting activator and separation gel. After clotting, but no later than 1 hour after collection, serum was separated by centrifugation (Centrifuge Neuation iFuge UC02R, Neuation, China) at 2500 g and room temperature for 15 minutes. Serum was transferred to labeled microcentrifuge tubes, frozen, and stored at a temperature not exceeding –18 °C until biochemical analysis, but no longer than 3 months.

CBC was performed on the Balio-560 instrument (Balio Diagnostics, France) using reagents Diluent, Lyc 1, Lyc 2 (Dymind, China) and control materials “Veterinary Gemkontrol 5D” (MBS Technology, Russia).

Biochemical analysis of serum was performed on the A25 analyzer (Biosystems, Spain) using reagent kits and control materials from Hospitex Diagnostics (Italy) according to the instructions of the reagent and equipment manufacturers. The following parameters were determined: glucose, triglycerides, cholesterol, AST, ALT.

Necropsy

Necropsy was performed after euthanasia. During necropsy, organs of the thoracic and abdominal cavities of the animals were examined, and the following organs were dissected and weighed: brain, heart, lungs, kidneys, salivary glands, pancreas, liver, thymus, spleen, testes, epididymides, accessory glands, gastrocnemius muscle, soleus muscle, visceral fat, adrenal glands.

During the study, a visual assessment of the following fat depots was performed:

1. Subcutaneous:
   - interscapular;
   - anterior subcutaneous (right and left);
   - shoulder (right and left);

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– inguinal (right and left);
– popliteal (right and left).

2. Visceral:
– pericardial;
– perirenal (right and left);
– mesenteric;
– gonadal (right and left).

Assessment was performed using the following scoring scale: not expressed (adipose tissue practically absent); weakly expressed (little adipose tissue); moderately expressed (adipose tissue present); strongly expressed (a lot of adipose tissue).

The total score for an animal was calculated as the sum of scores for all fat depots.

Measurement of triglyceride and cholesterol content in the liver

To determine triglyceride content, a fragment of the right lateral lobe of the liver weighing approximately 100 mg was dissected and weighed (± 1 mg, Vibra ALE323R). The sample was homogenized in 20 volumes of a chloroform-methanol mixture (in a volume ratio of 2:1), after which the sample was mixed for 20 minutes on an automatic shaker. Then, the precipitate was separated by centrifugation at 20,000 g for 10 minutes. The supernatant was collected and mixed with 400 µL of physiological saline and thoroughly mixed on a vortex mixer. To separate the phases, the sample was centrifuged at 20,000 g for 10 minutes. The lower phase, containing lipids, was collected and stored at a temperature not exceeding –18 °C until lipid and cholesterol concentration analysis, but no longer than 3 months.

Quantitative determination of triglycerides and cholesterol in liver extracts was performed using reagent kits and control materials from Hospitex Diagnostics (Italy) according to the manufacturer's instructions. The optical density of the samples was measured on a Plate Screen microplate spectrophotometer (Hospitex Diagnostics, Italy).

Ethical review

The study was approved by the Ethics Committee of the Federal State Budgetary Institution of Science "State Research Center of the Russian Federation — Institute of Biomedical Problems of the Russian Academy of Sciences" for Biomedical Ethics (No. 681 dated March 17, 2025).

Data analysis

The difference in efficacy between the comparator product (Mounjaro®) and the three batches of the investigated product (Tirzetta®) was analyzed.

For primary analysis, data were tabulated and descriptive statistics were calculated: mean (M), standard deviation (SD), standard error (SEM).

For group comparisons, analysis of variance (ANOVA) methods were used, followed by pairwise group comparisons using Sidak or Tukey, as well as multiple linear regression. The statistical significance threshold was $p \leq 0.05$.

The overall comparison of drug effects was carried out by determining Cohen's d for all 53 investigated parameters. Based on Cohen's d, metrics RE (relative efficacy), SS (safety assessment), Sel (selectivity), and CS (composite score) were determined:

$$RE = \frac{|\, d \text{ Drug } vs\ MC \,|}{|\, d \text{ CS } vs\ MC \,|} + 0.01,$$

RE=1.0 means equivalence to CS; RE > 1.0 indicates superiority over CS (stronger recovery); RE < 1.0 means a weaker effect.

$$SS = \frac{1}{1 + e^{(-6 \times ln\,(SS))}},$$

The coefficient 6 was chosen empirically for optimal differentiation. The result is in the range from 0 to 1, where 0.5 ≈ equivalence to CS, > 0.5 indicates better safety, <0.5 indicates worse safety.

$$Sel = \frac{|\, d \text{ Drug } vs\ MS \,|}{|\, d \text{ Drug } vs\ Con \,|} + 0.01,$$

With subsequent normalization:

$$Sel = \min\left(1.0 \times \frac{\ln(1 + Selectivity)}{2.5}\right),$$

High selectivity (close to 1) means that the drug's action against MS is more pronounced than against Con.

The composite score combines all three metrics into a single indicator for drug ranking:

$$CS = 0.70 \times RE + 0.20 \times SS + 0.1 \times Sel,$$

Bootstrap analysis (10,000 iterations) was used to determine the statistical significance of differences in composite scores between drugs. Normality of residuals was checked using the Shapiro-Wilk test. Homogeneity of variances was confirmed by Levene's test. Intergroup analysis was performed using analysis of variance (ANOVA).

If ANOVA showed significance ($p < 0.05$), Tukey HSD post-hoc tests were performed for all pairwise comparisons. Particular attention was paid to contrasts of each drug with CS. If the contrast with CS was not significant, the drug was considered statistically equivalent to CS for that parameter.

Multivariate analysis of variance (MANOVA) was used to check if drugs differed simultaneously on two

dependent variables: efficacy (d_vs_MS) and safety (d_vs_Con). Pillai's Trace test statistic, based on the eigenvalues of the matrix, was used. If the MANOVA result was significant, ANOVA was performed for each variable separately to determine which indicator caused the difference. Holm's correction for multiplicity was applied for all pairwise comparisons.

To quantitatively compare the structure of biological effects between drugs, three complementary metrics were used:

- Adjusted Rand Index (ARI) — measures the proportion of pairs of parameters that are in the same cluster for both the comparator drug and the investigated drug (or in different clusters in both cases).
- Normalized Mutual Information (NMI) — based on mutual information between two clusterings.
- Jaccard Index — the proportion of agreement in the classification of parameter pairs.

Statistical significance of similarity was assessed by a permutation test: clusters of the drug were randomly permuted, metrics were recalculated, and a distribution under the null hypothesis was collected. P-value was calculated as the proportion of permutations where ARI/NMI/Jaccard ≥ observed value. If $p < 0.05$, the similarity was statistically significant.

In addition to clustering, a direct comparison of the profiles of all 53 parameters was performed: an integrated similarity index was calculated as a weighted sum of three indices: Euclidean distance, Cosine similarity, Pearson correlation. Based on these indices, an integrated similarity index was calculated as a weighted sum of these three indices. Weights: 40% Euclidean (absolute differences in values), 40 % Cosine (pattern and direction of effects), 20% Pearson (synchronicity). The result was converted to a percentage of similarity (multiplied by 100).

Comparative analysis of effect magnitudes was implemented in R. Main packages:

- tidyverse — data manipulation (filter, mutate, summarize)
- stats — ANOVA, MANOVA, k-means
- car — Levene, Type III ANOVA tests
- mclust — Adjusted Rand Index
- custom functions for NMI, Jaccard Index, and permutation test.

RESULTS

Induction of metabolic syndrome

In mice receiving the "high-fat" diet, body weight gradually increased and significantly exceeded the weight of control mice from week 8 of feeding (Fig. 2). After three months of feeding, the BW of mice on the "high-fat" diet was 39.5 ± 0.6 g, which is 24 % higher than in mice on standard feed (31.9 ± 0.6 g).

Intragastric administration of 2 g/kg glucose led to a more pronounced increase in blood glucose concentration in mice on the "high-fat" diet and fructose syrup than in individuals consuming standard feed (Fig. 3A). Thus, in mice on the modified diet, the maximum blood glucose concentration was 20.3 ± 3.7 mmol/L, and on the control feed — 14.9 ± 2.7 mmol/L (Fig. 3B); the increase in the area under the blood glucose concentration curve was 19.8±3.2 and 28.0 ± 6.2 mmol/L×h in mice on standard and modified diets, respectively (Fig. 3C). The half-time for blood glucose recovery in mice on standard feed and water was 30 minutes, and in mice on "high-fat" feed and fructose syrup — 56 minutes ($F(1, 470) = 6.01$, $p = 0.0146$).

Thus, at the time of use in experiments, mice receiving the modified diet had 25 % greater BW than individuals on the standard diet, and glucose tolerance was significantly lower.

Therefore, it can be concluded that the experimental model of MS was successfully reproduced.

Effect of tirzepatide drugs on body weight

The BW of mice receiving tirzepatide (RD, T1, T2, and T3) was significantly lower than in mice with untreated MS and control individuals. Significant differences in BW persisted throughout the experiment (Fig. 4A). To assess the integral changes in mouse BW over the experimental period, areas under the BW change curve relative to baseline (before substance administration) values were calculated for the interval from day 1 to day 18 of the experiment (Fig. 4B).

By day 18 of the experiment, the BW of the control group mice receiving standard feed had practically not changed (-0.5 ± 1.0 %). Mice with untreated MS lost 8.5 ± 1.5 %, presumably due to numerous experimental stress manipulations (PhenoMaster monitoring, blood glucose measurement, etc.). In mice receiving tirzepatide, BW reduction was 25.9 ± 1.1 % for RD, and 28.2 ± 1.1 %, 27.4 ± 1.2 %, and 26.8 ± 1.6 % for the investigated tirzepatide drugs T1, T2, and T3, respectively.

Thus, it can be concluded that the administration of 150 µg/kg tirzepatide led to a pronounced reduction in BW of mice with MS, with mouse BW being lower than control group values, without signs of MS. The reduction in BW upon administration of the investigated tirzepatide drugs and the comparator product was equally pronounced and occurred with indistinguishable dynamics. The T1, T2, and T3 drugs did not differ from the comparator product or from each other in any of the analyzed BW characteristics.

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Table 1 — Experimental scheme for assessing the effect of tirzepatide on mice with induced metabolic syndrome

Group	Number of animals, *n*	Administered substance, administration regimen	Recorded parameters (registration graph)
Con	12	Placebo, 5 ml/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	1. BW (daily — d_1…d_{25}); 2. Food and water/syrup intake in housing cages (daily — d_1…d_{25}); 3. Physiological parameter monitoring in PhenoMaster (d_6…d_{15}): • food intake, min^{-1}; • water intake, min^{-1}; • motor activity, min^{-1}; • O_2 consumption, h^{-1}; • CO_2 production, h^{-1}. 4. Non-fasting blood glucose, glucometer (weekly — d_5, d_9, d_{12}, d_{15}, d_{18}); 5. Glucose challenge test (once — d_{20}); 6. Insulin challenge test (once — d_{24}); 7. Organ weight (terminal — d_{25})*; 8. Visual assessment of fat depots (terminal — d_{25}); 9. CBC (terminal — d_{25}); 10. Blood biochemistry (terminal — d_{25})**; 11. Liver triglycerides (terminal — d_{25}).
MS	12	Placebo, 5 ml/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
RD	10	Mounjaro, 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
T1	10	Tirzepatide (batch 1), 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
T2	10	Tirzepatide (batch 2), 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	
T3	10	Tirzepatide (batch 3), 150 µg/kg SC, every third day, d_8, d_{11}, d_{14}, d_{17}, d_{20}, d_{23}	

Notes: * — brain, heart, lungs, kidney, salivary glands, pancreas, liver, thymus, spleen, adrenal glands, testes, epididymides, accessory glands, gastrocnemius muscle, visceral fat; ** — glucose, triglycerides, cholesterol, AST, ALT. Con — control group; MS — metabolic syndrome; CS — reference drug; T1, T2, T3 — Tirzetta® drug batch; BW — body weight; CBC — complete blood count.

Table 2 — Characteristics of investigated batches of the reproduced drug and comparator product

Drug Name	Manufacturer	Batch
Tirzetta®, solution for subcutaneous injection, 5 mg/mL (T1)	JSC “Biokhimik”, Russia	OP030524
Tirzetta®, solution for subcutaneous injection, 5 mg/mL (T2)	JSC “Biokhimik”, Russia	OP050524
Tirzetta®, solution for subcutaneous injection, 5 mg/mL (T3)	JSC “Biokhimik”, Russia	OP060524
Mounjaro®, solution for injection, 5 mg/mL (RD)	Eli Lilly, USA	D665365A

Table 3 — Comparative analysis of effect differences in composite scores

Comparison	Difference	95% Confidence Interval		*p*
T1 vs. T2	0,113	-0,527	0,835	0,378
T1 vs. T3	-0,257	-0,883	0,174	0,811
T2 vs. T3	-0,147	-0,646	0,227	0,733

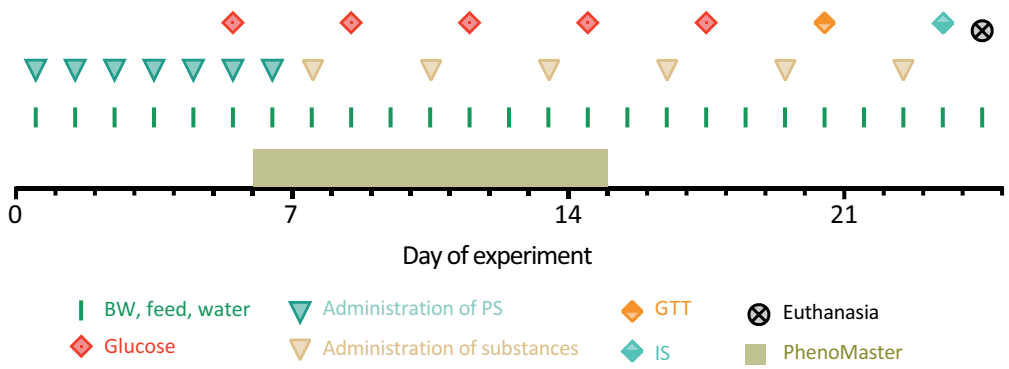

Figure 1 — Experimental schedule for assessing the effect of tirzepatide on mice with diet-induced metabolic syndrome.
Note: BW — body weight; PS — physiological solution; GTT — glucose tolerance test; IS — insulin sensitivity.

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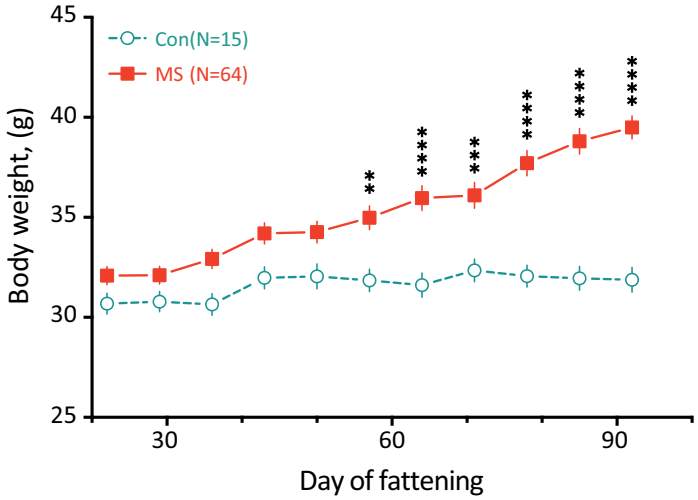

Figure 2 — Body weight of mice on a standard diet (K) and fed a "fatty" diet with 30% fructose syrup during the fattening period (MS).

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test.

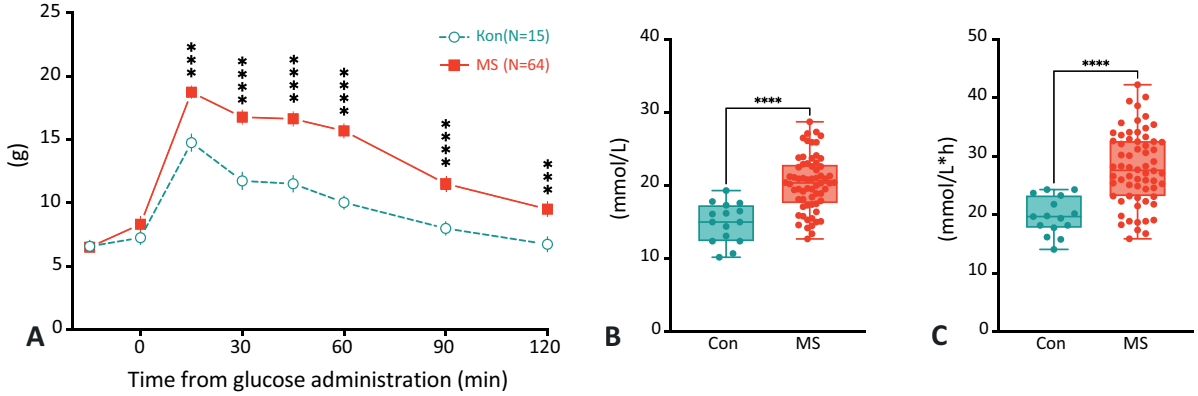

Figure 3 — Blood glucose concentration in experimental animals.

Note: A — blood glucose concentration in mice after intragastric administration of 2 g/kg glucose; B — maximum blood glucose concentration; C — increment of the area under the blood glucose concentration curve. * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test.

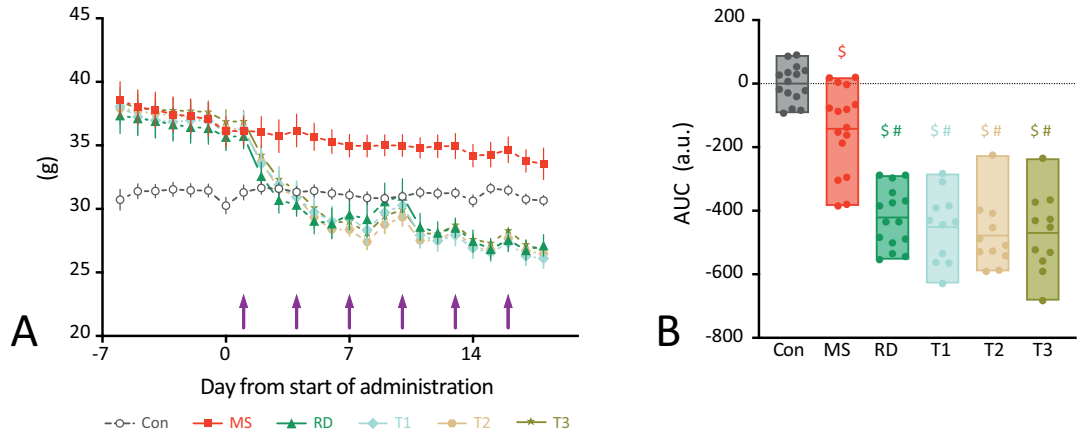

Figure 4 — Dynamics of body weight changes in mice during the experiment (A) and by day 18 (B).

Note: $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test.

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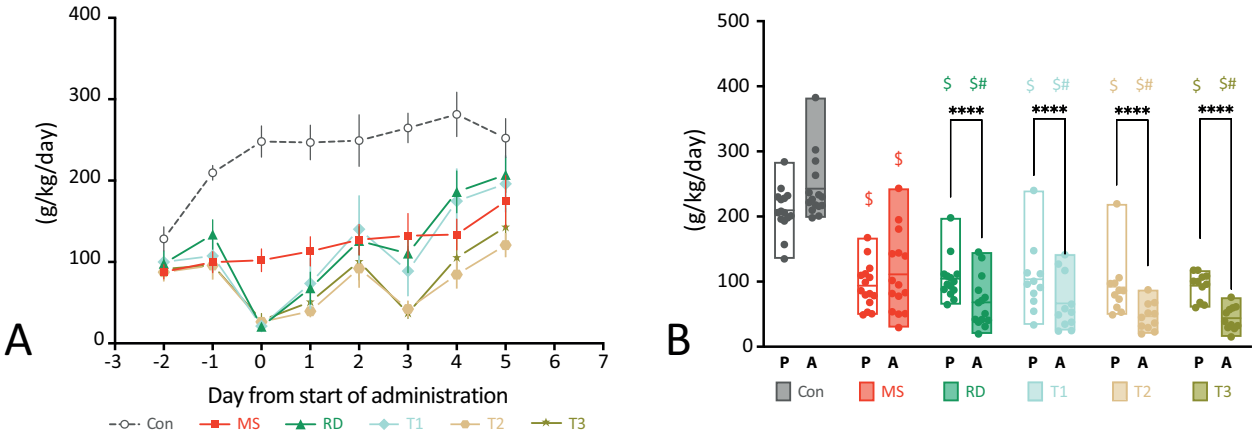

Figure 5 — Daily feed intake by mice during their stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

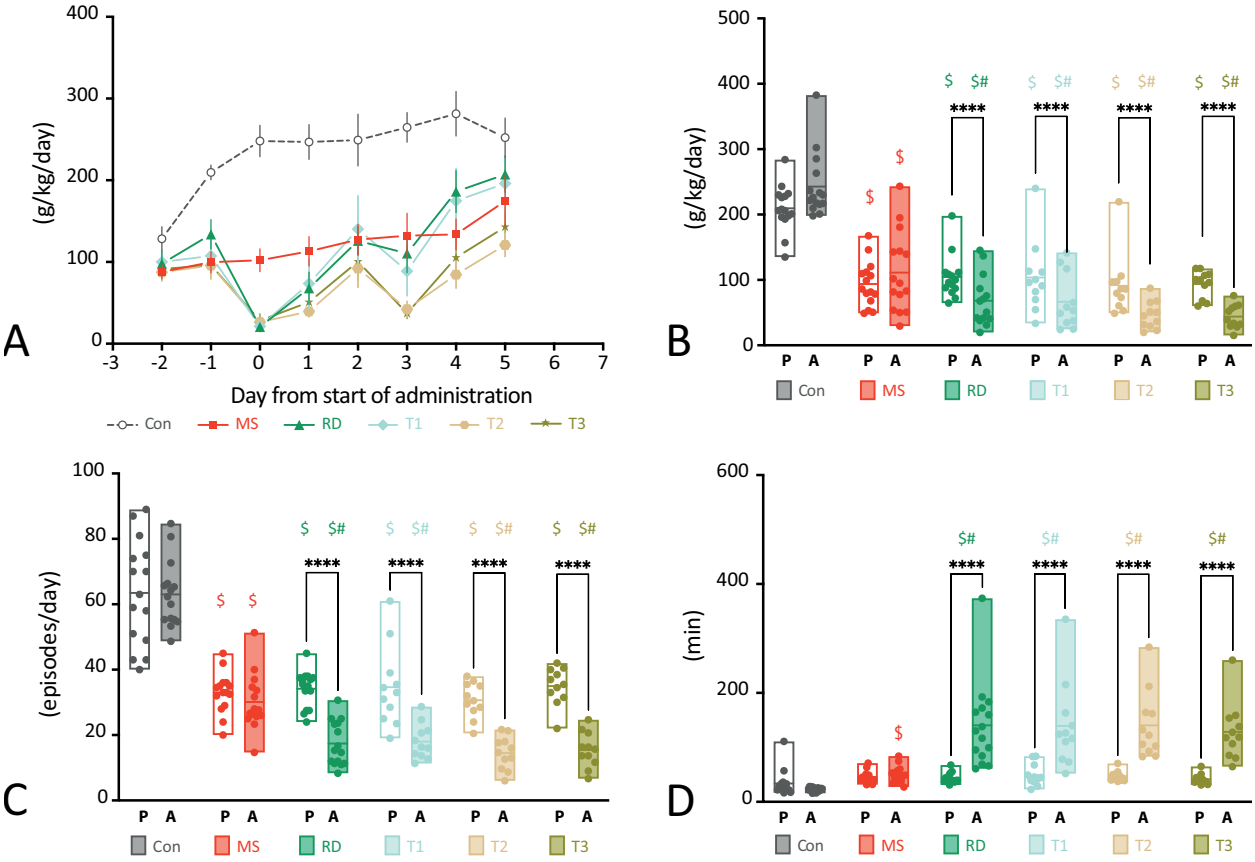

Figure 6 — Daily feed intake (A, B), average feed intake per feeding episode (C), and number of feeding episodes (D) in mice during their stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

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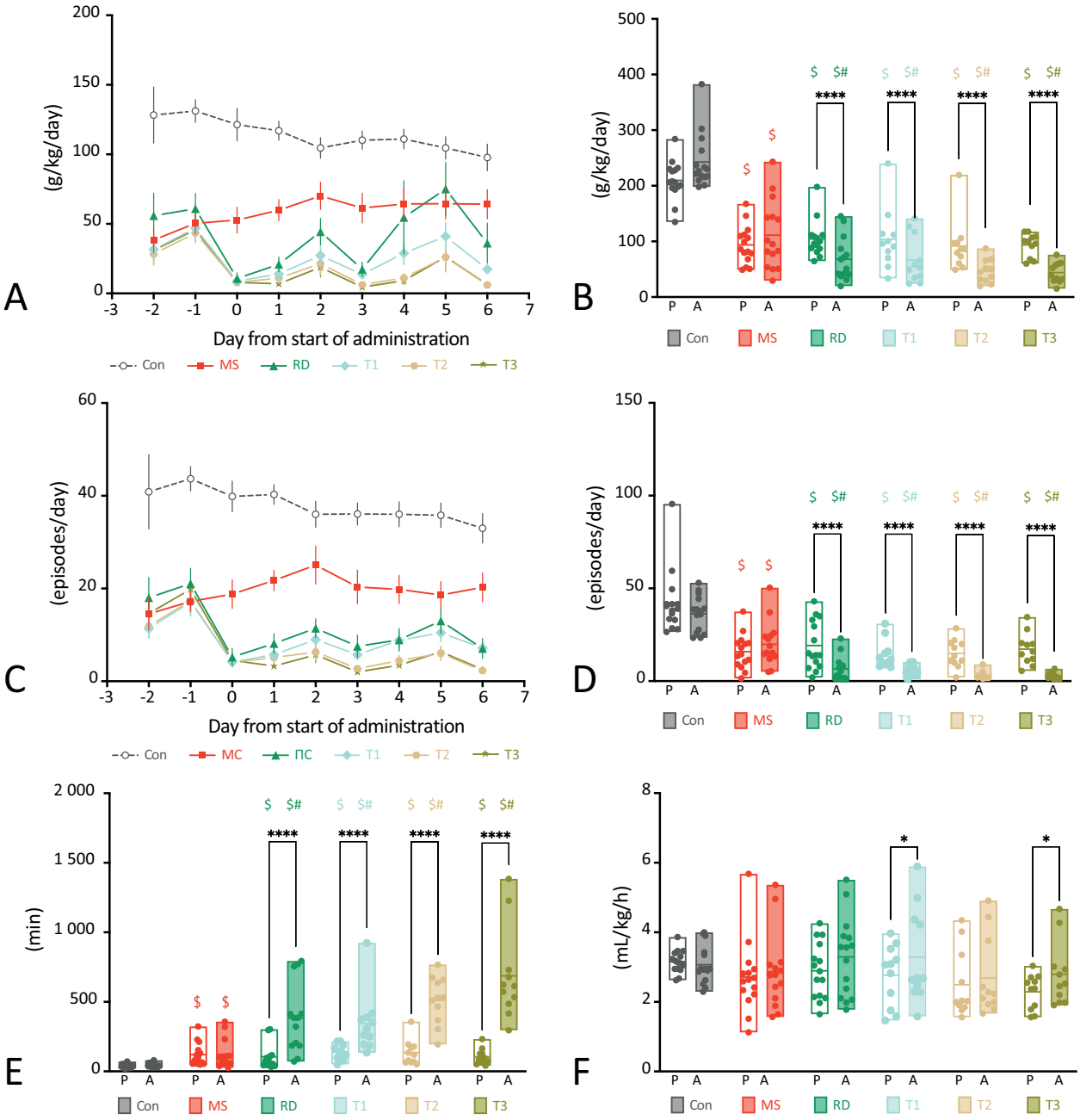

Figure 7 — Water/fructose syrup intake (A, B), number of intake episodes (C, D), duration of interval between episodes (E), and volume of water/fructose syrup intake per drinking episode during mice's stay in the PhenoMaster system.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

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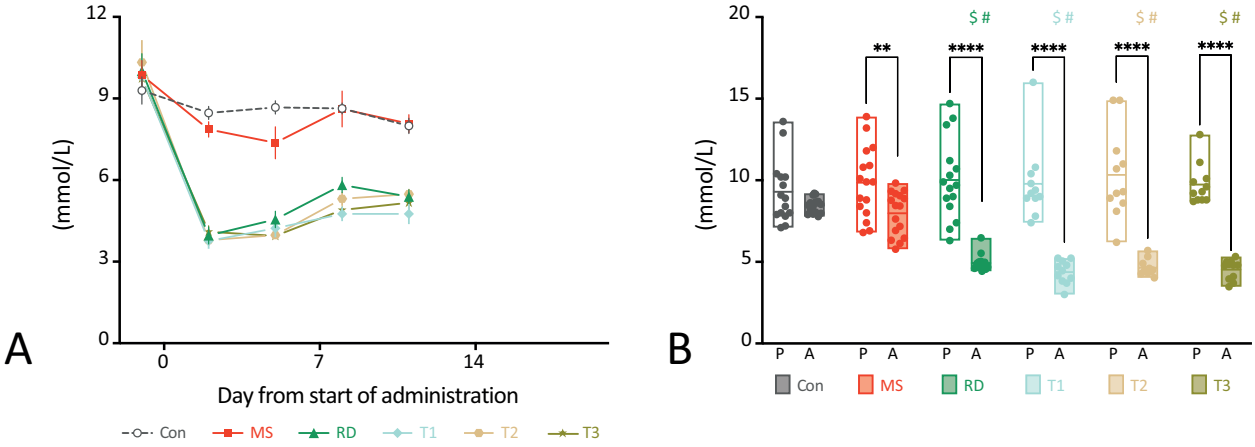

Figure 8 — Blood glucose in mice during their stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

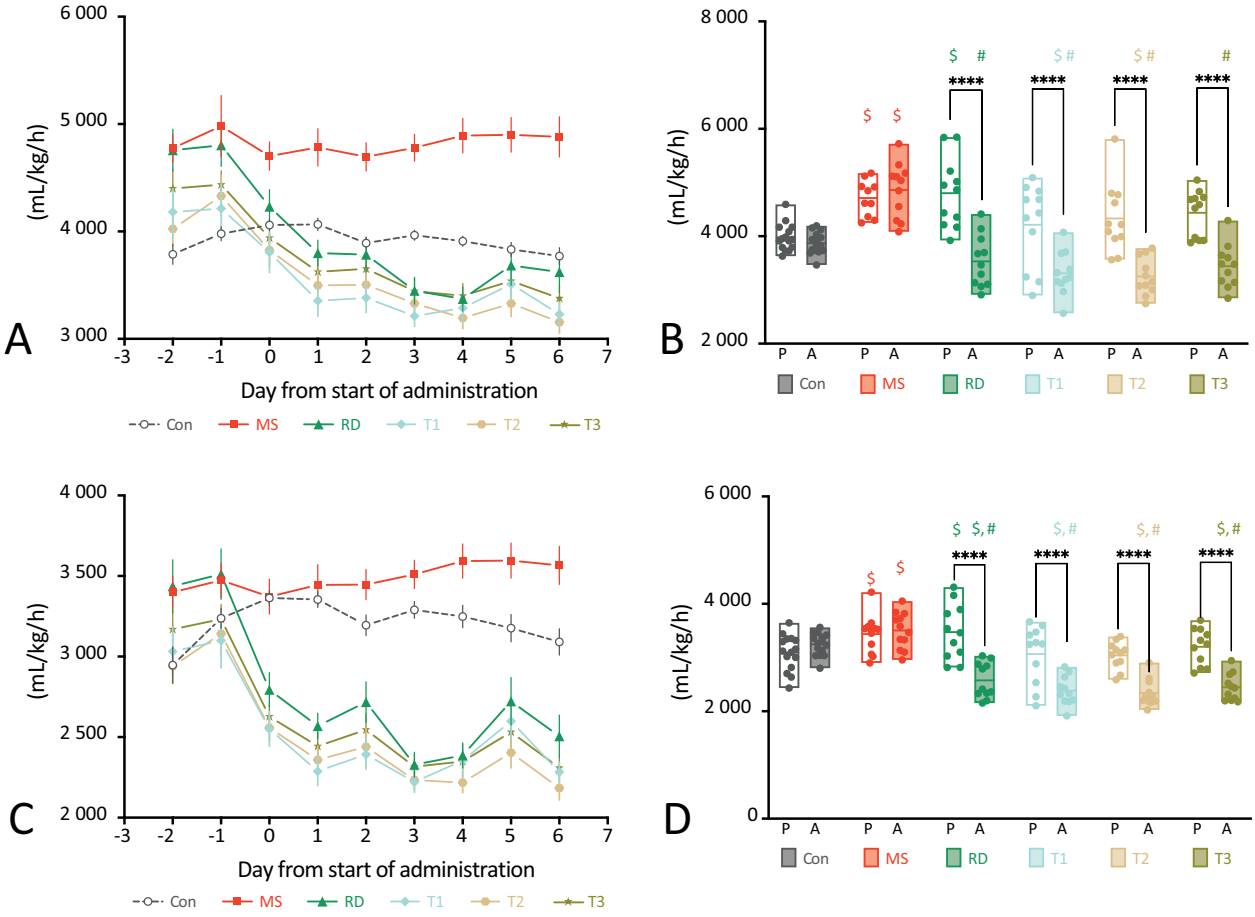

Figure 9 — Oxygen consumption (A, B) and carbon dioxide production (C, D) during mice's stay in the PhenoMaster system.
Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

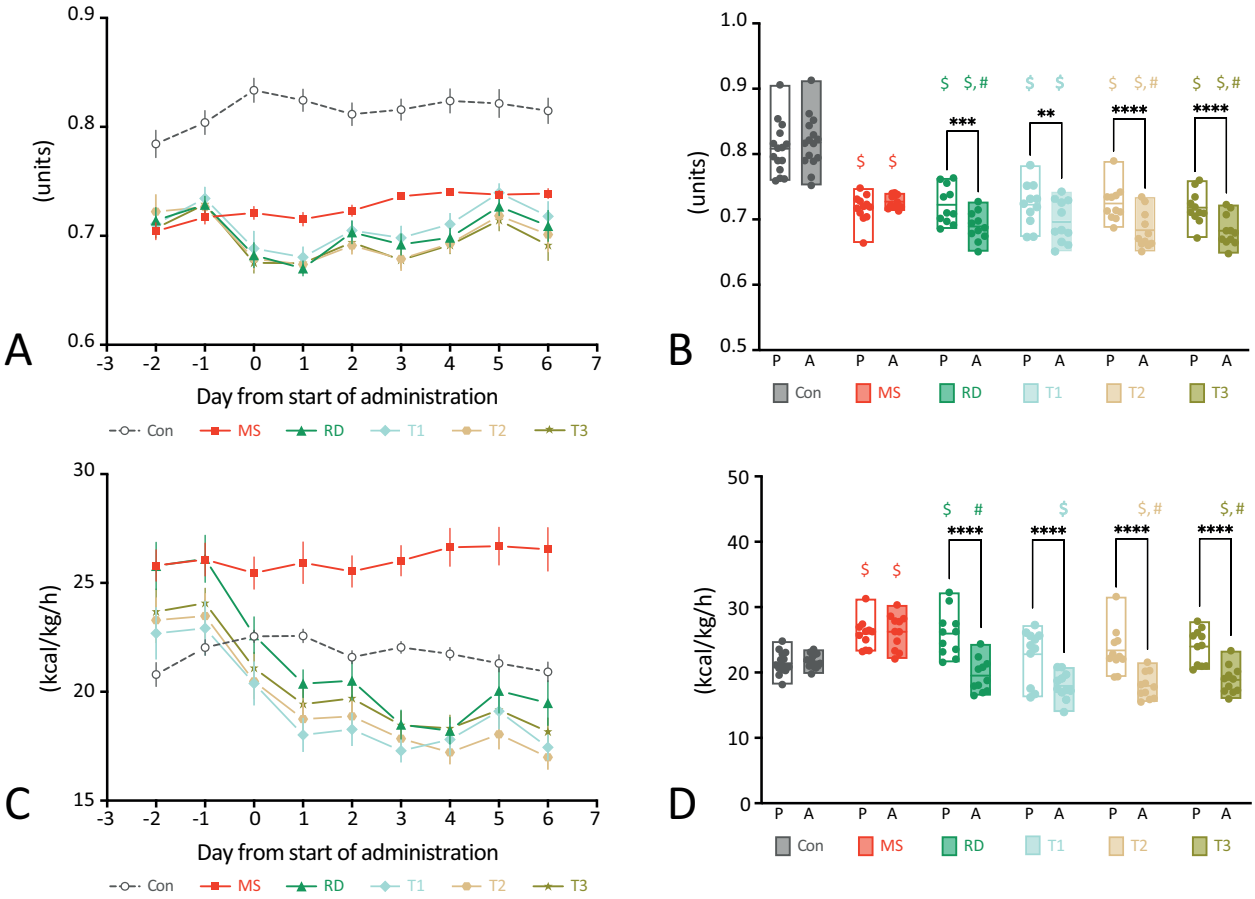

Figure 10 — Respiratory quotient (A, B) and heat production (C, D) during mice's stay in the PhenoMaster system.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

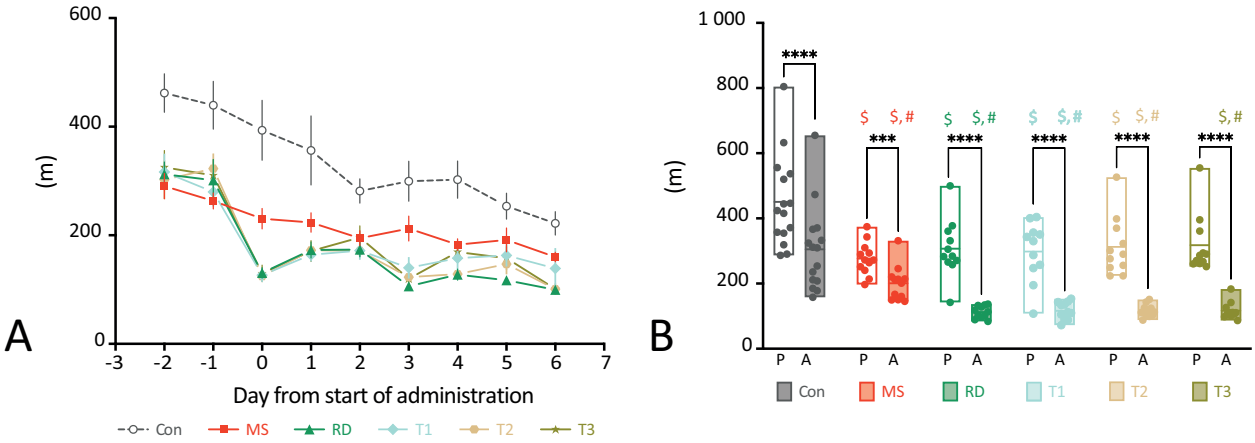

Figure 11 — Dynamics of locomotor activity (A) and its comparative analysis (B) before and during mice's stay in the PhenoMaster system.

Note: * — $p < 0.05$; ** — $p < 0.01$; *** — $p < 0.001$; **** — $p < 0.0001$; ns — not significant, Sidak's test; $ — significant difference relative to group K; # — significant difference relative to group MS, Sidak's test; P — prior to dosing; A — after dosing.

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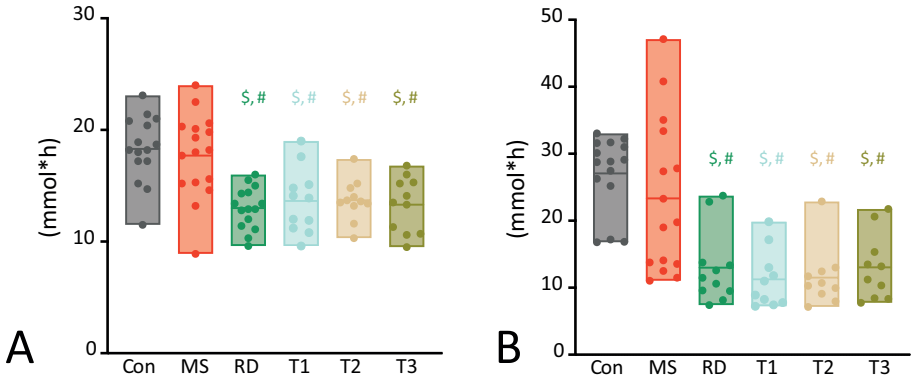

Figure 12 — Area under the curve of blood glucose concentration in mice during the glucose tolerance test (A) and insulin sensitivity test (B).
Note: $ — $p < 0.05$ vs. group K; # — $p < 0.05$ vs. group MS, Sidak's test.

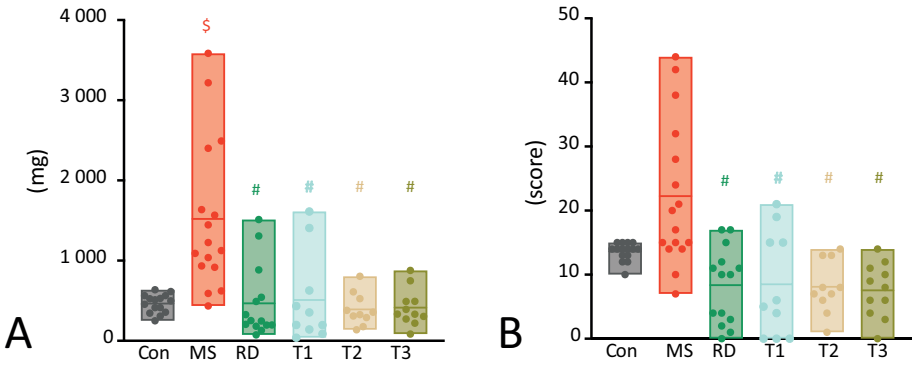

Figure 13 — Visceral fat mass (A) and fat depot severity (B) in experimental animals.
Note: $ — $p < 0.05$ vs. group K; # — $p < 0.05$ vs. group MS, Sidak's test.

Effect of tirzepatide drugs on feeding behavior

As shown in Figure 5, feed intake sharply decreased in animals receiving tirzepatide compared to the control group and the MS group, regardless of the type of administered drug: RD or T1–T3. The trend towards decreased feed intake was most pronounced immediately after drug administration and faded with repeated administrations (Fig. 5A). On average, for the first three tirzepatide administrations, the decrease in feed intake was 44 ± 10 %, 44 ± 9%, 51 ± 10%, and 60 ± 5% for the comparison drug, T1, T2, and T3, respectively (Fig. 5B). Overall, under the action of tirzepatide, feed intake was lower than in animals with untreated MS or control individuals.

We also analyzed the number of feeding episodes and the amount of food consumed per meal (Fig. 6). The amount of food consumed per feeding episode remained relatively stable during the observation period (Fig. 6A, B). A slight increase in food consumed per episode presumably reflects the adaptation of mice to using the unfamiliar feeders of the PhenoMaster system. The reduction in food intake was due to a sharp decrease in the number of feeding episodes (Fig. 6C), which was also reflected in the increase in time intervals between meals (Fig. 6D).

Water/fructose syrup intake during the observation period in PhenoMaster is shown in Figure 7. The response to the start of tirzepatide drug administration was similar to changes in food intake: fructose syrup consumption sharply decreased (Fig. 7A, B) due to a decrease in the frequency of syrup intake (Fig. 7C) and an increase in intervals between drinking (Figure 7D, E), but not a decrease in the volume of fluid consumed per drinking episode (Fig. 7F). No significant differences in drinking behavior parameters were found between animals receiving the comparison drug and the studied drugs.

Thus, it can be concluded that the studied tirzepatide drugs significantly reduced feed and fructose syrup intake in mice with MS. Mounjaro® reduced feed intake by 1.5–2.2 times. For Tirzetta® drugs, a trend towards a greater reduction in feed intake was observed — by 1.9–2.5 times. The change in daily caloric intake was expressed as a decrease in the frequency of feeding and drinking episodes.

Effect of tirzepatide drugs on blood glucose levels

Blood glucose levels were determined during the period of drug administration. Measurements were taken the day after administration. The obtained data are presented in Figure 8. Before substance administration, blood glucose concentration (non-fasting) in mice of all groups was similar (Fig. 8A). After substance administration, blood glucose in groups K and MS decreased slightly and did not differ between groups. In mice of groups RD, T1, T2, and T3, blood glucose sharply decreased after the start of tirzepatide administration. There were no differences in blood glucose concentration between animals in these groups. The glucose reduction was 48 ± 3 % in mice receiving tirzepatide as part of the comparison drug (Mounjaro®) and 53 ± 4 %, 52 ± 4 %, and 53 ± 2 % in mice receiving the studied tirzepatide drugs (Tirzetta®) T1, T2, and T3, respectively (Fig. 8B).

Effect of tirzepatide drugs on lipolysis level

Oxygen consumption in animals fed a high-fat diet and fructose syrup was predictably higher than in control animals on a standard feed and water. In MS group animals, oxygen consumption remained relatively stable throughout the observation period in PhenoMaster. In groups RD, T1, T2, and T3, after the start of tirzepatide administration, there was a gradual decrease in oxygen consumption to values lower than before administration in mice of the MS group and even the K group (Fig. 9A, B). The decrease in oxygen consumption was 26 ± 1 % in mice receiving the comparison drug, and 20 ± 1 %, 24 ± 2 %, and 22 ± 2 % in animals of groups T1, T2, and T3, respectively.

Carbon dioxide production was initially similar in animals of all groups. After the start of tirzepatide administration, CO_2 production in mice of groups RD, T1, T2, and T3 decreased by 21–26 % (Fig. 9C, D).

The respiratory quotient was 0.81, which correlates well with the indicators of animals on a standard diet consisting mainly of carbohydrates with a smaller proportion of protein and fat. In mice fed a “fatty” diet, the respiratory quotient was significantly lower, reflecting the utilization of fats primarily. After the start of tirzepatide administration as part of the studied drugs or RD, a further decrease in the respiratory quotient was observed, indicating an increase in the proportion of fats in the substrates utilized during respiration, presumably related to lipolysis (Fig. 10A, B). Similar patterns were found when analyzing animal heat production (Fig. 10C, D).

Effect of tirzepatide drugs on locomotor activity in mice

Locomotor activity of mice was recorded in the PhenoMaster system from day 6 to day 15 of the experiment, inclusive (two days before and 8 days after substance administration, d_6–d_{15}).

Over 10 days of observation, locomotor activity gradually decreased as animals became accustomed to the new conditions. Initially, all animals fed a “fatty” diet were less active than mice on a regular diet. Within 24 hours after tirzepatide administration as part of RD or the studied drugs T1, T2, and T3, there was a decrease in mouse locomotor activity (Fig. 11). This effect was equally pronounced for all tirzepatide drugs. Thus, it can be concluded that the decrease in body weight with tirzepatide intake is not mediated by increased locomotor activity.

Effect of tirzepatide drugs on glucose tolerance and insulin sensitivity

Based on the results of the loading tests, it was concluded that tirzepatide drugs improved glucose tolerance and insulin sensitivity in mice with metabolic syndrome (Fig. 12A, B).

During testing at the end of the experiment, intragastric administration of 2 g/kg glucose caused a similar rise in blood glucose concentration in control animals and mice with untreated MS, which is likely due to the loss of BW in MS mice as a result of numerous experimental manipulations. In groups RD, T1, T2, and T3, the rise in blood glucose was significantly less pronounced. For example, in mice receiving Mounjaro®, the area under the blood glucose concentration curve was 27 ± 3 % lower than in mice with untreated MS, and in mice of groups T1, T2, and T3, it was 23 ± 5 %, 23 ± 3 %, and 25 ± 4 %, respectively (Fig. 12A).

In mice receiving Mounjaro®, the area under the blood glucose concentration curve was 44 ± 7 % lower than in mice with untreated MS, and in mice of groups T1, T2, and T3, it was 52 ± 6 %, 51 ± 6 %, and 44 ± 7 %, respectively (Fig. 12B).

Thus, administration of tirzepatide drugs, both original and generic, equally improved insulin sensitivity and glucose tolerance in mice with metabolic syndrome.

Effect of tirzepatide drugs on visceral fat mass reduction

Visceral fat mass in mice with induced MS exceeded the values for control group mice on a normal diet. Administration of tirzepatide drugs led to a reduction in visceral fat mass by 69 ± 8 % in mice of group RD and by 67 ± 12 %, 74 ± 4 %, and

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73 ± 5 % in mice receiving drugs T1, T2, and T3, respectively (Fig. 13A). Similar results were obtained during visual assessment of subcutaneous and abdominal fat depot severity in mice (Fig. 13B).

Changes in mass caused by tirzepatide administration were detected for the heart, lungs, liver, salivary glands, spleen, epididymis, accessory glands, and gastrocnemius muscle (Fig. 14).

Pancreas mass was reduced in all MS mice; however, tirzepatide administration did not significantly affect this parameter.

Changes in mass were observed for several organs, but not in all experimental groups. The masses of the brain, thymus, and adrenal glands did not change depending on the induction of metabolic syndrome and tirzepatide administration.

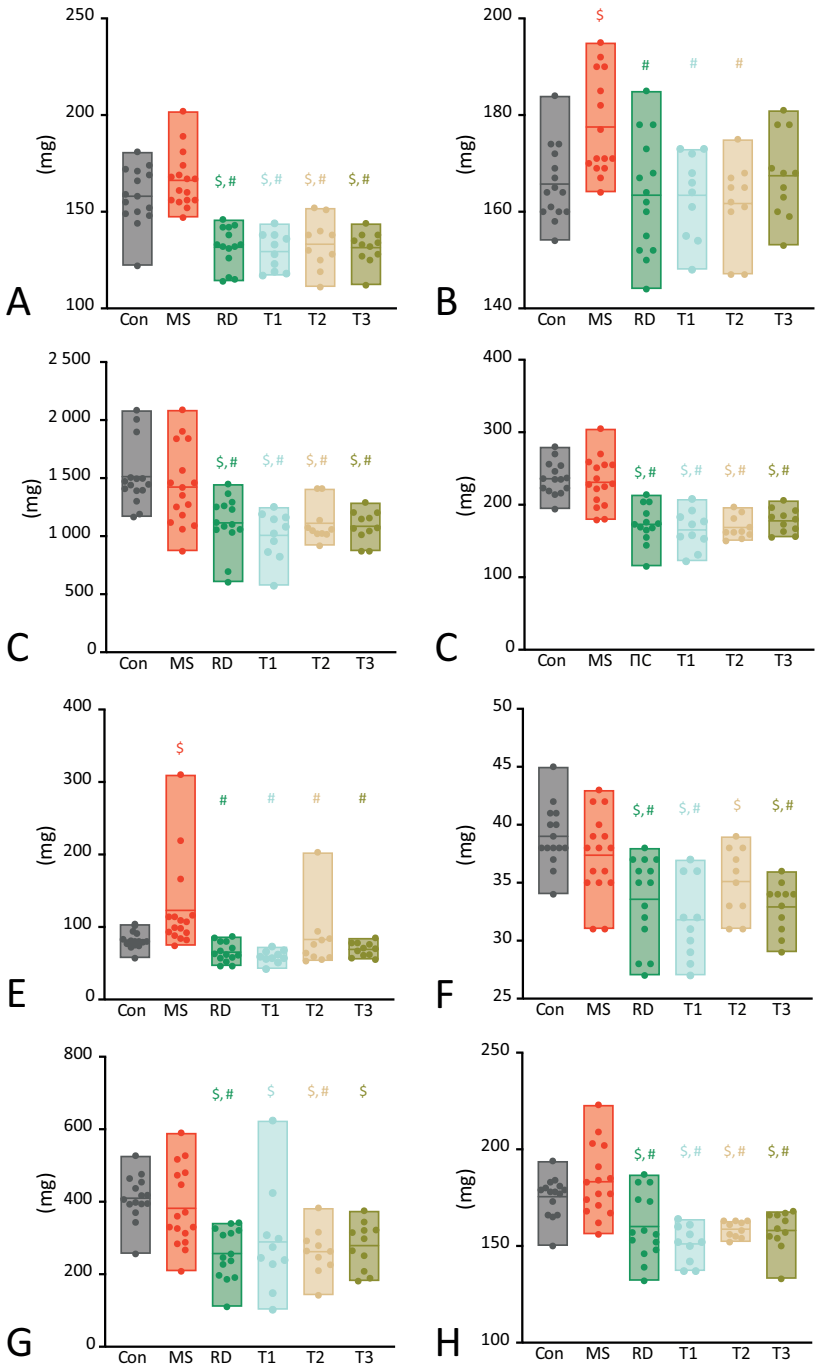

Figure 14 — Mass of the heart (A), lungs (B), liver (C), salivary glands (D), spleen (E), epididymis (F), accessory glands (G), and gastrocnemius muscle (H) in experimental animals.
Note: $ — p <0.05 vs. group K; # — p < 0.05 vs. group MS, Sidak's test.

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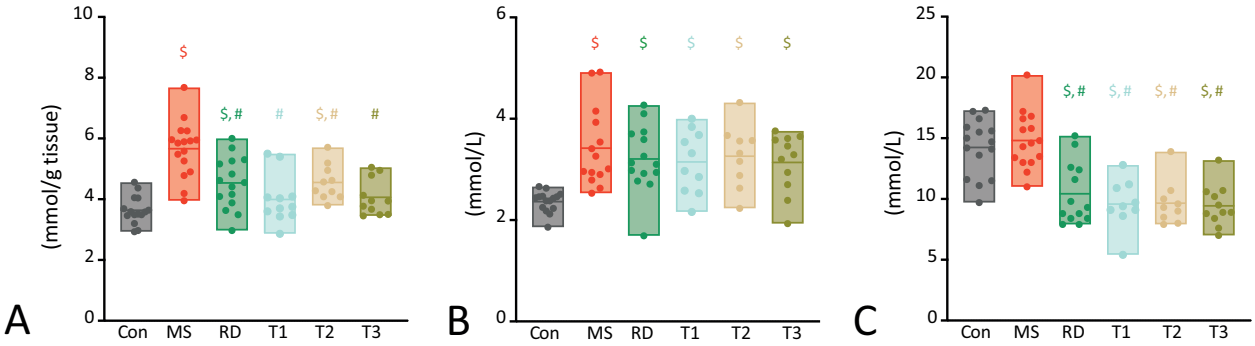

Figure 15 — Triglyceride content in the liver (A), cholesterol (B), and serum glucose (C) in experimental animals.

Note: $ — $p < 0.05$ vs. group K; # — $p < 0.05$ vs. group MS, Sidak's test.

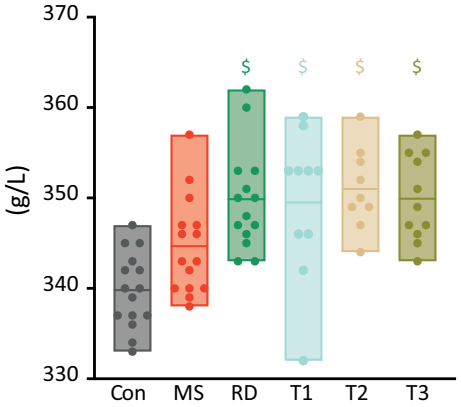

Figure 16 — Average hemoglobin content in the erythrocyte mass of experimental animals.

Note: $ — p < 0.05 vs. group K.

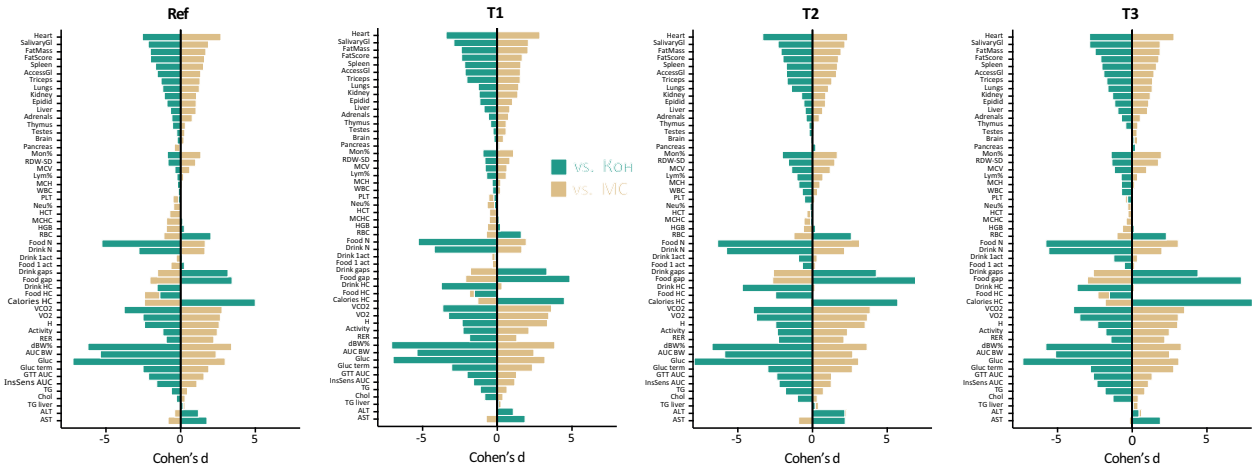

Figure 17 — Effect magnitudes of the studied drugs, T1, T2, T3, PS versus the control group and the group of mice with untreated metabolic syndrome, grouped by semantic blocks.

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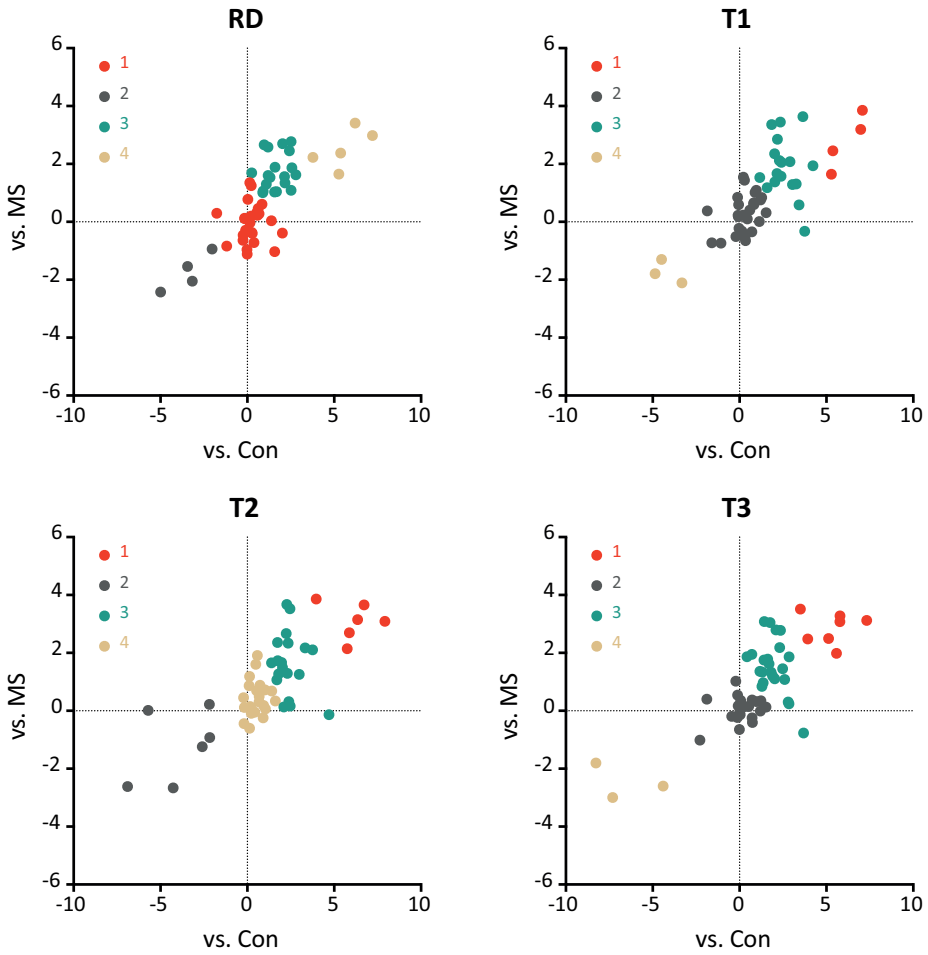

Figure 18 —Effect magnitudes (Cohen's d) of the studied drugs, T1, T2, and T3, and the comparison drug versus the control group (Con) and the group of mice with untreated metabolic syndrome (MS), grouped by clusters.

Effect of tirzepatide drugs on liver triglyceride content

Liver triglyceride content in mice with untreated MS was 56 ± 6 % higher than in control individuals receiving standard feed (Fig. 15A). In the livers of mice receiving tirzepatide, triglyceride content was lower than in mice with untreated MS by 20 ± 4 %, 30 ± 4 %, 20 ± 4 %, and 28 ± 3 % for groups RD, T1, T2, and T3, respectively. Liver triglyceride content did not differ between mice receiving different tirzepatide drugs.

Serum triglyceride concentration did not differ significantly between experimental groups of mice. Serum cholesterol was elevated in all mice with induced MS but did not differ between mice receiving tirzepatide and placebo, which serves as a marker of drug safety (Fig. 15B). Glucose concentration in mice receiving tirzepatide was lower than in individuals with MS receiving placebo and did not differ depending on the tirzepatide drug used (Fig. 17C). Thus, tirzepatide demonstrated pronounced efficacy in normalizing hepatic steatosis and hyperglycemia, along with a good safety profile regarding blood lipid content, suggesting that tirzepatide is compatible with hypocholesterolemic drugs.

Additionally, to assess the toxic effect of tirzepatide on the liver, ALT and AST concentrations were measured in mouse serum. No significant effect of MS and tirzepatide on these parameters was found.

Effect of tirzepatide drugs on hematological parameters

The study results revealed a significant difference between the control and experimental groups in hemoglobin content in the erythrocyte mass (Fig. 16).

Other hematological parameters did not differ significantly between the animal groups.

Comparative analysis of drug effect magnitudes

Figure 17 shows the effect magnitudes of the studied drugs (T1, T2, T3, RD) in comparison with the control and untreated MS groups.

For each of the 53 parameters, two types of comparisons were calculated:

1) relative to control (vs. Con) — drug effect on

healthy animals (reflects impact on a healthy organism, potential side effects);

2) relative to untreated animals with metabolic syndrome (vs. MS), reflecting efficacy. The full data matrix contained (53 parameters) × (4 groups: RD, T1, T2, T3) × (2 comparison types) = 424 Cohen's d values.

Effect coefficient values were chosen arbitrarily, prioritizing efficacy (70 %). It should be noted that modeling CS changes with different weight values for the indicators used in its calculation (in increments of 0.01) showed that the choice of drug (T1, T2, or T3) was independent of the weight values.

Differences in calculated metrics did not reach statistical significance based on one-way and multifactorial analysis of variance. Bootstrap analysis results are in good agreement with ANOVA results (Table 3).

As an alternative method for comparing data, the structure of drug effects (structure of Cohen's d values) on the studied indicators was assessed. Clustering of effects in a two-dimensional space (d vs. Con, d vs. MS) is shown in Figure 18. Each of the 53 parameters is represented as a point in a two-dimensional coordinate space (d_vs_Con, d_vs_MS). Algorithm: random selection of 4 initial centroids, iterative assignment of points to the nearest centroid, and recalculation of centroids as the mean of current clusters until convergence (parameters in R: nstart = 30, iter.max = 100, ensuring a global optimum).

When comparing the profiles of effects in this space, as well as based on the results of topological analysis of the effect matrix and the space of three statistical difference metrics between the studied drugs (T1, T2, T3) and the comparison drug (PS), no differences were found.

Thus, in terms of in vivo effects, Tirzetta® and Mounjaro® drugs are bioequivalent.

DISCUSSION

This study conducted a comprehensive comparative evaluation of the efficacy of three batches of the generic drug Tirzetta® (T1, T2, T3) and the reference drug Mounjaro® (RD) in a mouse model of MS. The study covered a wide range of indicators of energy metabolism, morphofunctional parameters, and biochemical characteristics.

The most pronounced effect of all tirzepatide drugs was a significant reduction in BW [8–10]. The dynamics of BW change showed a progressive decrease, starting from the first day of drug administration. By day 18 of the experiment, BW reduction was 25.9 ± 1.1 % for Mounjaro® and up to 28.2 ± 1.1 % for Tirzetta®. It is important to note that BW reduction was mediated by lipolysis activation and fat mass loss without signs of emaciation or deterioration of the animals' general condition, indicating the physiological nature of this process. Such a mechanism of action is a unique feature of tirzepatide compared to GLP-1 agonists, which are characterized by a pronounced decrease in muscle mass, requiring dietary adjustments and increased physical activity [8–10].

The results of feeding behavior analysis revealed that the reduction in BW was due to a substantial decrease in the intake of both standard feed and fructose syrup. These changes were observed equally for Tirzetta® and Mounjaro®.

The results of indirect calorimetry are of particular significance, providing a complete picture of the metabolic changes underlying the reduction in BW [11]. Oxygen consumption decreased in all groups receiving tirzepatide: by 26 ± 1 % for Mounjaro® and up to 24 ± 2 % in Tirzetta® groups.

Similar dynamics were observed for carbon dioxide production. The most informative indicator was the decrease in the respiratory quotient from 0.73 in the untreated group to 0.68–0.69 in all treatment groups, indicating a shift in energy metabolism towards lipolysis [12]. These data fully correlate with the decrease in fat depot mass: visual and instrumental assessments showed a significant reduction in fat accumulation in all studied locations in animals receiving tirzepatide compared to the untreated MS group. Statistically significant differences between Mounjaro® and Tirzetta® drugs were absent.

A comprehensive assessment of glycemic status using various methodological approaches demonstrated high consistency of results. In vivo measurements of blood glucose concentration over time revealed a pronounced hypoglycemic effect of all tirzepatide drugs, achieving normoglycemia by the end of the observation period. It should be noted that under Tirzetta® intake, the hypoglycemic effect was more pronounced. Glucose concentration reduction was 48 ± 3 % for Mounjaro® and 53 ± 4 % for Tirzetta®. The glucose tolerance test demonstrated a significant improvement in glucose tolerance in all groups receiving tirzepatide, with normalization of glucose utilization kinetics. The area under the glucose concentration curve was comparable for Mounjaro® and Tirzetta®. The insulin sensitivity test revealed restoration of insulin tolerance equally for Mounjaro® and Tirzetta®. Terminal glucose concentration measurements fully confirmed the in vivo monitoring data, showing a decrease in glycemia in all treatment groups without intergroup differences.

Biochemical analysis of liver tissue revealed a pronounced hypolipidemic effect of all tirzepatide drugs. Triglyceride concentration decreased from 5.66 ± 0.23 to 4.54 ± 0.22 mmol/g for Mounjaro® and to 4.55 ± 0.19 mmol/g for Tirzetta®, indicating

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correction of hepatic steatosis. The activity of liver transaminases (AST, ALT) remained within physiological limits in all treatment groups, confirming the absence of hepatotoxic effects and good tolerability of all studied drugs.

Hematological parameters showed no significant changes in any of the tirzepatide-receiving groups. The number of erythrocytes, leukocytes, platelets, hemoglobin level, and hematocrit remained within reference values, confirming the absence of systemic toxic effects and good tolerability of all studied drugs. Our data are supported by several preclinical studies of tirzepatide, which, in addition to weight loss, show a positive trend in increased glucose tolerance [13, 14].

Morphometric analysis of internal organs showed that changes in their absolute mass were primarily due to a decrease in adipose tissue [15, 16], rather than direct drug effects on the organs.

The study by J.O.A. Bittencourt et al. (2025) also investigated the therapeutic potential of tirzepatide in a mouse model combining obesity and type 2 diabetes mellitus [17]. For 4 established groups, a high-fat and sucrose diet was administered for 12 weeks. Animal therapy involved tirzepatide administration (10 nmol/kg/day) for 4 weeks. In mice of 2 experimental groups (obesity+T2DM), BW increased 1.3-fold compared to the control group. Tirzepatide normalized BW and reduced relative BW by 25 %. Histological and molecular analyses showed that tirzepatide reversed the whitening of brown adipose tissue, restored the morphology of multilocular adipocytes, and increased the expression of key thermogenic markers. Another study by T. Ma et al. (2025) on flying squirrels, comparing the effects of semaglutide, tirzepatide, and physiological saline, also confirms this. Both studied drugs showed similar effects—it was found that both semaglutide and tirzepatide increased insulin sensitivity, improved metabolism, and promoted weight loss [18].

The obtained results demonstrate the high efficacy of Tirzetta® and Mounjaro® drugs in correcting the main manifestations of MS. The mechanism of action includes reduced appetite and food intake, activation of lipolysis with a shift in energy metabolism towards fat oxidation, improved glycemic control and insulin sensitivity, and normalization of lipid profile [19, 20]. The observed effects were equally pronounced for Tirzetta® and Mounjaro® drugs, indicating their bioequivalence.

Previously, we showed the equivalence of physicochemical properties and biological activity of Tirzetta® and Mounjaro® [5]. It should be noted that according to the results of the physicochemical property study, Tirzetta® contains 4.2 times fewer impurities than Mounjaro®, which suggests greater safety for Tirzetta®. It is necessary to consider that the treatment of type 2 diabetes and obesity is long-term. Moreover, taking such drugs may become lifelong [21]. Organic impurities, such as phenol and benzyl alcohol, can accumulate in the body during long-term therapy, potentially leading to toxicity [22].

As a result of additional analysis of integral effect magnitudes (Cohen's d), performed on the entire set of parameters, an aggregated assessment was obtained based on a composite index including parameters of efficacy, safety, and selectivity, which allowed not only quantitative comparison of the structural similarity of profiles but also identification of characteristic differences at the level of effects not visible in traditional significance testing.

Comparison of drug effect magnitudes allows for quantitative assessment of therapeutic efficacy, safety, and dose-dependency in the target organism. Metrics RE (relative efficacy), SS (safety assessment), Sel (selectivity), and CS (composite score), calculated based on Cohen's d, provide a standardized multifactorial assessment of drugs in in vivo studies. They allow ranking compounds by a combination of therapeutic effects, toxicity, and specificity [23].

This approach solves the problem of subjectivity in comparing drug effects by translating differences into a universal scale of standard deviations [24]. This is particularly relevant in in vivo studies where analytes (e.g., tumor growth or biomarkers) have different units of measurement and variances. Without standardization, p-value only shows statistical significance, without considering the magnitude of the effect. Thus, a drug may be significantly better by one criterion, but in practice, this difference, although statistically significant, is still small and has no therapeutic benefit [24, 25]. When analyzing the effect magnitudes of Tirzetta® and Mounjaro® s, they were found to be equivalent—differences in effect magnitudes did not reach statistical significance (MANOVA $p = 0.977$; bootstrap analysis $p > 0.05$).

Study Limitations

Although the use of multiple methodological approaches ensures a high degree of reliability of the study results, it is necessary to note several limitations that should be considered when interpreting the results. For instance, experimental animal models have species-specific metabolic characteristics that can influence the pharmacokinetic and pharmacodynamic parameters of drugs [26]. Nevertheless, the combination of in vitro, in vivo, and physicochemical analysis methods provides a comprehensive characterization of the drugs and high reliability of conclusions about drugs bioequivalence, meeting current regulatory requirements.

CONCLUSION

Based on the results of the comprehensive study, it has been established that the drug Tirzetta® (manufacturer: LLC "PROMED RUS", Russia) does not differ from the reference drug Mounjaro® (manufacturer: Eli Lilly, USA) in all studied indicators of efficacy and safety. At the same time, the drugs demonstrated a favorable safety profile without signs of toxic effects. No statistically significant differences were found between Tirzetta® batches either. All studied drugs demonstrated comparable hypophagic effects with body weight reduction of 26–28 %, pronounced hypoglycemic properties with a decrease in blood glucose concentration of 48–53 %, a positive impact on lipid metabolism, and improved glucose tolerance and insulin sensitivity. Tirzepatide promoted lipolysis and preferential reduction of body fat mass, confirming its targeted efficacy. Such selective reduction of the lipid component is particularly important for physiological weight loss, minimizes the risk of sarcopenia, and preserves functional muscle tissue—a key factor for long-term metabolic improvement and quality of life.

Thus, Tirzetta® can be considered a therapeutic analog of Mounjaro® drug.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHORS' CONTRIBUTION

Victoria S. Scherbakova, Kira Ya. Zaslavskaya, Petr A. Bely — conceptualization, data curation, formal analysis, writing—review & editing; Alexander A. Andreev-Andrievskiy, Sofya V. Drugova, Mikhail A. Mashkin — conceptualization, investigation, formal analysis, visualization; Ksenia N. Koryanova, Ekaterina S. Mishchenko, Larisa I. Shcherbakova, Irina N. Dyakova, Polina A. Podlesnaya, Yuri G. Kazaishvili — conceptualization, investigation, formal analysis, visualization, writing—original draft. All the authors confirm their authorship compliance with the ICMJE international criteria (all the authors made a significant contribution to the conceptualization, conduct of the study and preparation of the article, read and approved the final version before publication).

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