Obesity Facts

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Real-World Comparison of Short-Term Adverse Events, Treatment Persistence, and Efficacy of Semaglutide and Tirzepatide: A Nationwide Multicenter Study

Short running title: Real-World Safety and Efficacy of Semaglutide and Tirzepatide

Sema Hepşen[1], Cem Haymana[2], Gizem Ertepe Küçükgöde[1], Büşra Özcan[3], Burak Özbaş[4], Arzu Or Koca[4], Berna İmge Aydoğan[5], Çiğdem Tura Bahadır[6], Emre Durcan[7], Volkan Yumuk[7], Bora Toros[8], Ziynet Alphan Üç[8], Çağatay Emir Önder[9], Zuhal Karaca Karagöz[10], Mehmet Aşık[11], Yusuf Öztürk[12], Muhammet Kocabaş[13], Melia Karaköse[13], Hayri Bostan[14], Sinem Kıyıcı[15], Serpil Salman[16,54], Dilek Gogas Yavuz[17], Yağmur Göksoy Solak[17], Osman Onur Daloğlu[15], Mehmet Ali Eren[18], Şahin Doğanay[18], Mehmet Güven[19], Gizem Ilgın Kaplan[20], Mustafa Cesur[5], Eda Demir Önal[21], Sibel Ertek Yalçın[22], Kemal Ağbaht[23], Elif Melis Baloğlu Akyol[20], Selin Genç[24], Özge Özer[25], Yasin Şimşek[26], Ömercan Topaloğlu[27], Fettah Acıbucu[28], Mehmet Emin Bozdoğan[28], Barış Karagün[28], Rıfat Emral[29], Sinem Başak Tan[29], Yahya Erdem İnce[30], Gamze Akkuş[30], Güven Barış Cansu[31], Mehmet Akif Saltabaş[26], Bekir Çakır[32,55], Gülsüm Karaahmetli[32], Samet Alkan[33], Mustafa Demirpençe[33], Işılay Taşkaldıran[9], Seher Tanrıkulu[34], Emre Bozkırlı[35], Seda Turgut[36], Didem Dereli Akdeniz[37], Arif Cengiz Gültekin[38], Ethem Turgay Cerit[38], Tülay Omma[39], Bülent Can[34], Hüseyin Soylu[40], Yusuf Emre Uzun[36], Süleyman Hilmi İpekçi[41], Özge Telci Çaklılı[42], Mehmet Çağrı Ünal[43], Gülşah Elbüken[44], Buket Büşra İçin[44], Yusuf Kır[2], Adnan Batman[45], Sedat Can Güney[46], Banu Ertürk[47], Pınar Akhanlı[48], Merve Çatak[49], Ayşe Kargılı Çarlıoğlu[50], Sakine Güzel Esen[51], Hakan Doğruel[48], İsmail Yıldız[52], Kübra Özsoy[53], İbrahim Demirci[5], Erman Çakal[1], Fahri Bayram[53], Alper Sönmez[5]

1 Department of Endocrinology and Metabolism, Ankara Etlik City Hospital, Ankara, Türkiye
2 Department of Endocrinology and Metabolism, Gülhane Training and Research Hospital, Ankara, Türkiye
3 Department of Endocrinology and Metabolism, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Türkiye
4 Department of Endocrinology and Metabolism, Abdurrahman Yurtaslan Training and Research Hospital, Ankara, Türkiye
5 Department of Endocrinology and Metabolism, Ankara Güven Hospital, Ankara, Türkiye
6 Department of Endocrinology and Metabolism, Ankara TOBB ETU University Hospital, Ankara, Türkiye
7 Department of Endocrinology and Metabolism, Istanbul University-Cerrahpaşa, Cerrahpaşa Faculty of Medicine, İstanbul, Türkiye
8 Department of Endocrinology and Metabolism, Uşak University, Faculty of Medicine, Uşak, Türkiye
9 Department of Endocrinology and Metabolism, Ankara Training and Research Hospital, Ankara, Türkiye
10 Department of Endocrinology and Metabolism, Elazığ Fethi Sekin City Hospital, Elazığ, Türkiye
11 Private Practice, Muğla, Türkiye
12 Department of Endocrinology and Metabolism, Sakarya Training and Research Hospital, Sakarya, Türkiye
13 Department of Endocrinology and Metabolism, Necmettin Erbakan University, Faculty of Medicine, Konya, Türkiye
14 Department of Endocrinology and Metabolism, Çanakkale Mehmet Akif Ersoy State Hospital, Çanakkale, Türkiye
15 Department of Endocrinology and Metabolism, Bursa Yüksek İhtisas Training and Research Hospital, Bursa, Türkiye
16 Private Practice, İstanbul, Türkiye
17 Department of Endocrinology and Metabolism, Marmara University, Faculty of Medicine, İstanbul, Türkiye
18 Department of Endocrinology and Metabolism, Ankara Batıkent Medicalpark Hospital, Ankara, Türkiye
19 Department of Endocrinology and Metabolism, Diyarbakır Gazi Yaşargil Training and Research Hospital, Diyarbakır, Türkiye
20 Department of Endocrinology and Metabolism, Gaziantep City Hospital, Gaziantep, Türkiye
21 Department of Endocrinology and Metabolism, Kocaeli Medicalpark Hospital, Kocaeli, Türkiye
22 Department of Endocrinology and Metabolism, Lösante Hospital, Ankara, Türkiye
23 Department of Endocrinology and Metabolism, İskenderun Gelisim Hospital, Hatay, Türkiye
24 Department of Endocrinology and Metabolism, Konya City Hospital, Konya, Türkiye
25 Department of Endocrinology and Metabolism, İzmir University of Economics, Medical Point Hospital, İzmir, Türkiye
26 Department of Endocrinology and Metabolism, Kayseri City Hospital, Kayseri, Türkiye

[27] Department of Endocrinology and Metabolism, Zonguldak Bülent Ecevit University, Faculty of Medicine, Zonguldak, Türkiye
[28] Department of Endocrinology and Metabolism, Adana City Hospital, Adana, Türkiye
[29] Department of Endocrinology and Metabolism, Ankara University, Faculty of Medicine, Ankara, Türkiye
[30] Department of Endocrinology and Metabolism, Çukurova University, Faculty of Medicine, Adana, Türkiye
[31] Department of Endocrinology and Metabolism, Kütahya Health Sciences University, Kütahya, Türkiye
[32] Department of Endocrinology and Metabolism, Ankara Bilkent City Hospital, Ankara, Türkiye
[33] Department of Endocrinology and Metabolism, İzmir City Hospital, İzmir, Türkiye
[34] Department of Endocrinology and Metabolism, Acıbadem Ataşehir Hospital, İstanbul, Türkiye
[35] Department of Endocrinology and Metabolism, Adana Acıbadem Hospital, Adana, Türkiye
[36] Department of Endocrinology and Metabolism, Ulus Liv Hospital, İstanbul, Türkiye
[37] Private Practice, İzmir, Türkiye
[38] Department of Endocrinology and Metabolism, Gazi University Faculty of Medicine, Ankara, Türkiye
[39] Department of Endocrinology and Metabolism, Lokman Hekim Akay Hospital, Ankara, Türkiye
[40] Department of Endocrinology and Metabolism, Batman Medical Point Hospital, Batman, Ankara
[41] Department of Endocrinology and Metabolism, İstanbul Hisar Hospital, İstanbul, Türkiye
[42] Department of Endocrinology and Metabolism, Kocaeli City Hospital, Kocaeli, Türkiye
[43] Department of Endocrinology and Metabolism, Kastamonu Training and Research Hospital, Kastamonu, Türkiye
[44] Department of Endocrinology and Metabolism, Tekirdağ Namık Kemal University, Faculty of Medicine, Tekirdağ, Türkiye
[45] Department of Endocrinology and Metabolism, Koç University Hospital, İstanbul, Türkiye
[46] Department of Endocrinology and Metabolism, İzmir Bakırçay University Çiğli Training and Research Hospital, İzmir, Türkiye
[47] Department of Endocrinology and Metabolism, Bilecik Training and Research Hospital, Bilecik, Türkiye
[48] Department of Endocrinology and Metabolism, Antalya City Hospital, Ankara, Türkiye
[49] Department of Endocrinology and Metabolism, Tokat Gaziosmanpaşa University, Faculty of Medicine, Tokat, Türkiye
[50] Private Practice, Ankara, Türkiye
[51] Department of Endocrinology and Metabolism, Hitit University Erol Olçok Training and Research Hospital, Çorum, Türkiye
[52] Department of Endocrinology and Metabolism, Çorlu Vatan Hospital, Tekirdağ, Türkiye
[53] Department of Endocrinology and Metabolism, Erciyes University, Faculty of Medicine, Kayseri, Türkiye
[54] Department of Endocrinology and Metabolism, İstanbul Health and Technology University, Faculty of Medicine, İstanbul, Türkiye
[55] Department of Endocrinology and Metabolism, Ankara Yıldırım Beyazıt University, Faculty of Medicine, Ankara, Türkiye

Author for Correspondence:

Sema Hepşen, M.D.

Adress: Halil Sezai Erkut Street, Yenimahalle, Ankara
Email: semahepsen@gmail.com
Orcid ID: https://orcid.org/0000-0002-8375-7409

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Abstract

Introduction: Real-world data directly comparing the safety, tolerability, and effectiveness of semaglutide and tirzepatide in patients with obesity remain limited. This nationwide multicenter observational study compared short-term adverse events, treatment discontinuation, body weight loss (BWL), and metabolic outcomes between the two treatments.

Methods: This study included 2,549 patients with obesity treated with semaglutide (n=1,434) or tirzepatide (n=1,115). Adverse events, including time to onset, dose at occurrence, and related discontinuation, were evaluated. Changes in BWL and metabolic parameters up to 6 months were assessed. Subgroup analyses were performed in patients with and without type 2 diabetes mellitus (T2DM).

Results: At least one adverse event occurred in 50.9% in the semaglutide group and 51.0% in the tirzepatide group (p=0.524), with gastrointestinal events the most frequently reported. Overall adverse event rates were comparable between groups; however, musculoskeletal and allergic reactions were more common in the tirzepatide group. The onset of gastrointestinal, neuropsychiatric, musculoskeletal symptoms, and hypoglycemia occurred earlier in the tirzepatide group. Discontinuation due to adverse events was similar between groups, except for pancreatic events, which were more frequent in the semaglutide group (p=0.006). Tirzepatide was associated with greater early BWL at all time points. At 6 months, median percentage BWL was 12.6% with semaglutide and 14.4% with tirzepatide. HbA1c reductions were comparable between groups in patients with T2DM.

Conclusion: In real-world clinical practice, semaglutide and tirzepatide show similar short-term tolerability and treatment persistence, although tirzepatide is associated with a higher incidence of musculoskeletal and allergic reactions and greater early BWL.

Introduction

Obesity is a chronic disease with a rapidly increasing global prevalence and substantial cardiometabolic consequences [1]. A holistic consideration of obesity, including its comorbidities and associated health consequences, is essential for the effective management of this complex condition and for determining the most appropriate individualized treatment approach [2]. In this context, pharmacological therapy with glucagon like peptide-1 (GLP-1) analogues has assumed an increasingly pivotal role in obesity treatment, particularly when lifestyle-based strategies fail to achieve adequate weight reduction. Within these treatment options, semaglutide is a selective GLP-1 receptor agonist, whereas tirzepatide acts as a dual agonist of the GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, targeting multiple central and peripheral pathways involved in appetite regulation and energy balance, and both are administered via once-weekly subcutaneous injection [3].

The primary objective of these treatments is to reduce total body weight and, consequently, to improve body composition, metabolic profile, and obesity-associated comorbidities [4]. Evidence from randomized clinical trials indicates that both treatments are significantly effective for weight management in patients with obesity, with

and without type 2 diabetes mellitus (T2DM) [5–8]. Real-world studies have also confirmed clinically meaningful body weight loss (BWL) and metabolic improvements in patients treated with semaglutide and tirzepatide [9–11]. Although comparisons from randomized controlled trials and meta-analyses have shown greater BWL with tirzepatide than with semaglutide, real-world comparative analyses of these two widely used GLP-1 analogues remain limited [12–16].

These agents are also associated with various adverse effects, predominantly gastrointestinal symptoms such as nausea, vomiting, dyspepsia, and diarrhea [17]. Beyond these well-known effects, neuropsychiatric, dermatological, renal, and hepatobiliary events have also been reported [18,19]. However, despite their widespread and growing use, important gaps remain in the comprehensive characterization of adverse events, particularly regarding their spectrum, timing of onset, dose dependency, and real-world management strategies. Additionally, several factors may limit treatment persistence with these medications in real-world practice, including adverse effects and financial barriers, particularly given that these treatments are generally not covered by health insurance [20].

This real-world study aimed to compare the short-term adverse event profiles, patterns of treatment discontinuation, and therapeutic effectiveness of semaglutide and tirzepatide within a nationwide multicenter cohort.

Material and Methods

Study Design and Patient Population

This multicenter observational cohort study included patients from 53 endocrinology units across 24 cities throughout Türkiye. The study was approved by the Ethics Committee of Ankara Etlik City Hospital and was conducted in accordance with the principles of the Declaration of Helsinki (Approval number: AEŞH-BADEK2-2025-500 Date: 02/09/2025). Institutional approval for the use of patient data was obtained from all participating hospitals and clinics.

Patients aged ≥18 years with a body mass index (BMI) ≥30 kg/m², or a BMI ≥27 kg/m² with at least one weight-related comorbidity (such as hypertension, prediabetes, T2DM, or dyslipidemia), who initiated treatment with semaglutide or tirzepatide between April 2025 and November 2025 were evaluated for inclusion in the study. Patients were excluded if they had type 1 diabetes mellitus; had used another GLP-1 receptor agonist or other anti-obesity medications (e.g., orlistat) within the previous 3 months; had a history of bariatric surgery; were younger than 18 years; had a GFR <30 mL/min; were pregnant or breastfeeding; had advanced liver disease or hepatic failure; or had a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia type 2 (MEN2).

Patient and Treatment Characteristics

Baseline characteristics, including age, sex, baseline body weight, BMI, comorbidities, and chronic medication use, were recorded. Dyslipidemia was defined as LDL cholesterol ≥100 mg/dL, triglycerides ≥150 mg/dL, HDL cholesterol <40 mg/dL in men and <50 mg/dL in women, or the use of lipid-lowering therapy [21]. BMI was classified as overweight (25.0–29.9 kg/m²) or obesity (≥30.0 kg/m²), with obesity further subclassified as class I (30.0–34.9 kg/m²), class II (35.0–39.9 kg/m²), and class III (≥40.0 kg/m²) [22]. Dose escalation for all patients was performed in accordance with the recommended monthly dose-titration schedule for each medication. The maximum tolerated dose and the total duration of treatment for each patient were recorded. Patients who discontinued treatment due to adverse events before 12 weeks were excluded from follow-up analyses. All remaining patients had a minimum follow-up of 3 months and were followed for up to 6 months.

Adverse Event Profile

Patients who met the inclusion criteria and had initiated semaglutide or tirzepatide treatment within the specified study period were assessed for adverse events during follow-up visits. Adverse events were evaluated in detail and categorized as gastrointestinal, hepatobiliary, pancreatic, neuropsychiatric, musculoskeletal, dermatological, allergic, urogenital, renal, ophthalmic, hypoglycemic, and cardiovascular. Pancreatic adverse events were categorized as acute pancreatitis and asymptomatic elevations in pancreatic enzyme levels ≥2× the upper limit of normal (ULN). Symptomatic hypoglycemia was defined as hypoglycemic symptoms with a blood glucose level <70 mg/dL, and severe hypoglycemia as an episode requiring external assistance [23]. For each adverse event, the time to onset following treatment initiation, the dose at occurrence, and whether the event resulted in treatment discontinuation were assessed.

Body Weight Loss Outcomes
Patients' body weight measurements were recorded at each monthly clinic visit, up to a maximum follow-up period of 6 months. Monthly BWL was calculated in kilograms and as a percentage of total body weight separately for patients with T2DM and those with obesity. In addition, for each month, the numbers of patients achieving 5%, 10%, and 15% loss of total body weight were calculated for the overall cohort.

Glucose and Lipid Parameters Outcomes
Fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), total cholesterol, triglycerides, LDL-C, and HDL-C levels were recorded at treatment initiation. These glucose and lipid parameters were also evaluated at the 3rd and 6th months of treatment.

Statistical Analysis
Normality of continuous variables was assessed using the Kolmogorov–Smirnov and Shapiro–Wilk tests. Categorical variables, including the proportions of patients achieving 5%, 10%, and 15% body weight loss, were compared between the semaglutide and tirzepatide groups using the chi-square test or Fisher's exact test when chi-square assumptions were violated due to low expected cell counts. Comparisons of normally distributed continuous variables between groups were performed using the Student's t-test, whereas changes in body weight expressed in kilograms and percentages, as well as changes in laboratory parameters from baseline to the 3rd and 6th months, were analyzed using the Mann–Whitney U test. Categorical variables are presented as numbers and percentages. Normally distributed continuous variables are expressed as mean ± standard deviation. Non-normally distributed treatment-related variables and body weight changes are presented as medians with minimum and maximum values, whereas non-normally distributed laboratory parameters are reported as medians with interquartile ranges (IQR, 25th–75th percentiles). A two-sided p value < 0.05 was considered statistically significant for all analyses.

Results
Patient and Treatment Characteristics
A total of 2,549 patients were evaluated, including 1,434 patients in the semaglutide group and 1,115 patients in the tirzepatide group. Patients in the semaglutide group had a higher median age and a greater female predominance, while BMI values were comparable between the two treatment groups (p< 0.001, p= 0.005, and p= 0.991; respectively). The prevalence of comorbidities, including T2DM, prediabetes, hypertension, dyslipidemia, atherosclerotic cardiovascular disease (ASCVD), and chronic kidney disease was higher in the semaglutide group compared with the tirzepatide group. Baseline characteristics, the distribution of obesity categories, comorbidity rates, and diabetic microvascular complications are presented in Table 1. The medications used by patients in both groups are shown in Supplementary Table 1.
The median treatment duration was 16 (1–24) weeks in the semaglutide group and 12 (1–24) weeks in the tirzepatide group. The median dose was 1 (0.25–2.4) mg in the semaglutide group and 5 (0.25–15) mg in the tirzepatide group.

Treatment Discontinuation
Treatment was discontinued due to unplanned pregnancy in one patient in the semaglutide group at week 5 and in one patient in the tirzepatide group at week 12. The number of patients who discontinued treatment due to adverse events within first 12 weeks was 97 (6.8%) in the semaglutide group and 78 (7.0%) in the tirzepatide group (p= 0.819). Overall, treatment discontinuation due to adverse events occurred in 154 patients (10.7%) in the semaglutide group and 106 patients (9.5%) in the tirzepatide group (p= 0.308). Drug discontinuation reasons for both groups within and after 12 weeks of treatment are presented in Figure 1.

Adverse Event Profile
The number of patients experiencing at least one adverse event was 730 (50.9%) in the semaglutide group and 569 (51.0%) in the tirzepatide group (p= 0.524). The most frequently observed adverse events were gastrointestinal complaints, occurring in 673 (47.0%) patients in the semaglutide group and 507 (45.5%) patients in the tirzepatide group, with similar rates between the two groups (p= 0.471). Nausea and vomiting were the

most common gastrointestinal adverse events, followed by dyspepsia and abdominal pain. The median dose at the initiation of gastrointestinal adverse events was 0.5 mg in the semaglutide group and 2.5 mg in the tirzepatide group. The median time to onset of gastrointestinal symptoms was earlier in the tirzepatide group at 7 (1–165) days compared with 10 (1–210) days in the semaglutide group (p= 0.002).
The second most common adverse event profile was neuropsychiatric symptoms, with similar rates observed between the semaglutide and tirzepatide groups (p= 0.118). The median dose at the onset of these adverse events was 0.5 mg in the semaglutide group and 2.5 mg in the tirzepatide group. Fatigue and malaise were the most frequently reported neuropsychiatric adverse events in both groups, followed by headache and negative mood changes. The median time to onset of neuropsychiatric symptoms was 30 (1–100) days in the tirzepatide group and 32 (1–182) days in the semaglutide group, occurring earlier in the tirzepatide group (p= 0.01).
The rates and time to onset of hepatobiliary adverse events, including cholecystitis, cholelithiasis, and elevations in liver enzymes, as well as pancreatic adverse events, including acute pancreatitis and asymptomatic elevated amylase and lipase levels, were similar between the groups.
Similarly, the rates of symptomatic and severe hypoglycemia were similar between the semaglutide and tirzepatide groups; however, the median time to onset of these events was shorter in the tirzepatide group (p= 0.029).
The rates and time to onset of cardiovascular, renal, ophthalmic, urogenital, and dermatological adverse events, excluding dermatitis, were similar between the two groups. The incidence of dermatitis was higher in patients treated with tirzepatide compared with those receiving semaglutide (p= 0.016). Musculoskeletal and allergic adverse events were more frequent in the tirzepatide group than in the semaglutide group (p< 0.001 and p= 0.028, respectively). The time to onset of musculoskeletal adverse events was earlier in the tirzepatide group (p= 0.001).
Across all mild and severe adverse events, excluding pancreatic events, treatment discontinuation rates were similar between the two groups. The discontinuation rate due to pancreatic events was higher in the semaglutide group, with 9 patients (0.6%), whereas no discontinuations were observed in the tirzepatide group (p= 0.006).
The analyses of the adverse event profile are detailed in Table 2.

Body Weight Loss

In the entire cohort, median BWL in kilograms was greater in the tirzepatide group at each monthly time point up to 6 months (p< 0.001 for all comparisons). Median BWL percentages were higher in the tirzepatide group at each monthly time point up to 5 months (p< 0.001 for all comparisons) but were comparable between the groups at the 6th month (p= 0.116). Among patients with obesity without T2DM, both absolute BWL (kg) and percentage BWL were consistently greater in the tirzepatide group at all endpoints throughout the 6-month follow-up period (p< 0.05 for all comparisons). Among patients with T2DM and obesity, BWL in kilograms was greater in the tirzepatide group up to the 5th month, whereas percentage BWL remained greater up to the 6th month; thereafter, the comparisons between the groups were comparable. Comparative data on BWL in kilograms and percentages for the entire cohort, patients with obesity and T2DM, and patients with obesity without T2DM are presented in Supplementary Tables 2, 3, and 4, respectively. Figure 2 illustrates monthly BWL percentages up to 6 months in the overall cohort, as well as in patients with obesity with and without T2DM.
In the overall cohort, during the 1st month of treatment, the proportion of patients achieving 5% BWL was significantly higher in the tirzepatide group than in the semaglutide group, whereas the proportion of patients achieving 10% BWL was similar between the groups. In the 2nd, 3rd, and 4th months, the proportions of patients achieving 5%, 10%, and 15% BWL were significantly higher in the tirzepatide group. By the 5th month, the proportion of patients achieving 5% BWL was comparable between the groups, and by the 6th month, the proportions of patients achieving 5%, 10%, and 15% BWL were similar between the two groups. The numbers of patients achieving 5%, 10%, and 15% BWL over 6 months are presented in Table 3.

Glucose and Lipid Parameters

At baseline, median FPG, HbA1c, and triglyceride levels were higher in the semaglutide group than in the tirzepatide group (p< 0.001, p< 0.001, and p= 0.022, respectively). Baseline total cholesterol, HDL-C, and LDL-C levels were comparable between the two groups. At the 6th month, the median reductions in FPG and LDL-C were greater in the semaglutide group than in the tirzepatide group (p= 0.006 and p= 0.036, respectively). A modest increase in HDL-C levels was observed in the semaglutide group at the 3rd and 6th months compared

with the tirzepatide group (p= 0.03 and p= 0.029, respectively). No significant differences were observed between the groups in other glucose and lipid parameters at the 3rd and 6th month endpoints. The changes in these parameters at the specified endpoints are presented in Table 4.

The HbA1c Analysis of Patients with Diabetes Mellitus

At baseline, the median HbA1c levels were 7.4 (6.6–8.6) % in patients using semaglutide and 7.2 (6.5–8.3) % in those using tirzepatide (p= 0.045). The median reduction in HbA1c at the 3rd month was −0.5 (−1.1, −0.3) % in the semaglutide group and −0.7 (−1.1, −0.4) % in the tirzepatide group. At the 6th month, the median HbA1c reduction was −0.9 (−1.6, −0.5) % in the semaglutide group and −0.8 (−3.8, 0.61) % in the tirzepatide group. Among patients with T2DM, there was no significant difference in the reduction of HbA1c levels between the semaglutide and tirzepatide groups at the 3rd and 6th months (p= 0.084 and p= 0.356, respectively).

Discussion

This multicenter observational study suggested that, except for a higher incidence of musculoskeletal symptoms and allergic reactions in the tirzepatide group, the short-term adverse event profiles of semaglutide and tirzepatide were largely similar. Treatment discontinuation due to adverse events did not differ between the two groups, supporting comparable short-term tolerability in real-world clinical practice. BWL and the proportions of patients achieving target BWL were higher in the tirzepatide group compared with the semaglutide group in the short-term use.

GLP-1 analogue treatment is associated with a range of adverse effects, predominantly gastrointestinal, including nausea, vomiting, dyspepsia, constipation, and diarrhea [24]. To date, only a limited number of studies have directly compared the safety and adverse event profiles of semaglutide and tirzepatide, with available data primarily derived from meta-analyses of randomized controlled trials. Moreover, there remains a gap in the literature regarding detailed analyses of adverse event characteristics, timing, dose-related associations, and discontinuation rates attributable to specific adverse events. Gastrointestinal side effects are the most well-known adverse events and represent the most important limitation of treatment associated with GLP-1 analogs [25,26]. A recent large meta-analysis including 48 randomized controlled trials demonstrated that the overall incidence of gastrointestinal adverse effects associated with GLP-1 analogue treatment was 11.6%, with nausea being the most common symptom (21.5%), followed by diarrhea, vomiting, dyspepsia, and constipation [25]. Our findings are consistent with the existing literature, with nausea being the most common gastrointestinal adverse effect, occurring at a similar incidence in patients treated with semaglutide (25%) and tirzepatide (23%). The second most frequently reported gastrointestinal adverse effect in our cohort was dyspepsia, followed by constipation and diarrhea. In line with this large meta-analysis, diarrhea was observed slightly more frequently in the tirzepatide group, whereas constipation was marginally more common in the semaglutide group; however, these differences did not reach statistical significance. The median time to onset of gastrointestinal adverse effects was shorter in the tirzepatide group at 7 days compared with 10 days in the semaglutide group. Other less frequently reported gastrointestinal adverse events in our cohort included halitosis and altered taste sensitivity, each with an incidence of less than 1%.

Although some pharmacovigilance studies have raised alerts regarding acute pancreatitis risk with GLP-1 analogue treatment, available evidence suggests that the risk of acute pancreatitis and severe gastrointestinal or hepatobiliary adverse events remains very low with these agents [24,27–29]. A recent meta-analysis demonstrated that the incidence of severe gastrointestinal adverse events, including acute pancreatitis, biliary disease, bowel obstruction, gastroparesis, and severe constipation, was comparable among patients with T2DM using GLP-1 analogues, including semaglutide and tirzepatide [26]. In the present study, hepatobiliary and pancreatic events were evaluated separately, and rates of cholecystitis, cholelithiasis, liver enzyme elevations <3× and ≥3× the ULN, time to onset, and discontinuation due to these events were all very low (<1%) and comparable between semaglutide and tirzepatide. No cases of acute pancreatitis were observed in the tirzepatide group, whereas one patient in the semaglutide group experienced acute pancreatitis during the second week after treatment initiation. Asymptomatic elevations in amylase and lipase levels were comparable between the two groups. Treatment discontinuation due to pancreatic events was more frequent in the semaglutide group. However, these findings should be interpreted with caution. Only one patient in the semaglutide group developed acute pancreatitis, whereas the remaining pancreatic events consisted of asymptomatic elevations in pancreatic enzymes, which may reflect biochemical abnormalities rather than clinically significant pancreatic disease.

Data regarding neuropsychiatric events associated with GLP-1 analogue treatment are conflicting. While some studies suggest potential beneficial effects on psychiatric outcomes, others have raised concerns about an increased risk of psychiatric adverse events, such as negative mood changes, depression, and suicidal ideation, as well as neurological complaints including dizziness, tremor, dysgeusia, parosmia, and allodynia [30–32]. Although the exact relationship and underlying mechanisms are not yet fully understood, these complaints warrant close monitoring [32]. In the present cohort, fatigue and malaise were the most common symptoms in this category, with an incidence of 7.6% in the semaglutide group and 6.6% in the tirzepatide group, followed by headache, negative mood changes, vertigo, insomnia, and neuropathic symptoms at progressively lower frequencies. The median time to onset of neuropsychiatric symptoms was earlier in the tirzepatide group at 30 days compared with 32 days in the semaglutide group. Consistent with our findings, a recent pharmacovigilance analysis of neurological adverse events reported a median onset time of 31 days [32].

In the present cohort, musculoskeletal complaints, including arthralgia and myalgia, were observed in 2.0% of patients treated with semaglutide and 4.5% of those treated with tirzepatide. These events were more frequent and occurred slightly earlier in the tirzepatide group compared with the semaglutide group. To our knowledge, this is the first real-world comparative study to report a significantly higher incidence of musculoskeletal adverse events with tirzepatide compared with semaglutide. The more rapid and pronounced weight loss achieved with tirzepatide may lead to greater absolute reduction in lean body mass and altered biomechanical loading on muscles and joints during the early treatment phase [33]. Additionally, several factors that may influence musculoskeletal complaints, such as vitamin D status and patients' daily exercise routines, were not available in this study and may have affected the interpretation of these findings. However, despite the expected beneficial effects of weight loss and the potential anti-inflammatory effects of GLP-1 analogue therapy on articular symptoms, emerging concerns regarding reduced lean mass and altered muscle performance associated with these agents also highlight an important gap in the current literature [34]. Consistent with the existing literature indicating that hypoglycemia rates are very low with semaglutide and tirzepatide and are typically associated with concomitant use of other hypoglycemic agents or higher doses of GLP-1 analogue therapy, we observed low and comparable hypoglycemia rates in both groups. Notably, hypoglycemic events occurred earlier in patients treated with tirzepatide compared with those receiving semaglutide [35,36]. Cardiovascular adverse effects, including bradycardia, tachycardia, and blood pressure changes, as well as renal events and urogenital complaints such as menstrual irregularities and impotence, were observed at very low rates in our cohort and were comparable between the two treatment agents.

Hypersensitivity reactions associated with GLP-1 analogue therapy, including local allergic reactions, urticaria, and anaphylaxis, are generally considered to occur at a very low risk; however, comparative data across different GLP-1 analogues remain limited [37,38]. A recent retrospective study evaluating dermatological adverse reactions associated with GLP-1 analogue therapies identified eczema, pruritus, drug eruptions, hyperhidrosis, and alopecia as the five most common reactions [39]. The study reported a higher overall risk with exenatide and further observed that semaglutide was more frequently associated with these events compared with tirzepatide. Local allergic reactions were seen more frequent in tirzepatide in our cohort with an incidence of 1.2% versus 0.4% in semaglutide, likewise dermatitis is slightly higher than semaglutide with a rate of 0.9%. In Türkiye, tirzepatide is currently available in vial form rather than as a prefilled pen, which requires patients to use separate needles for injection. This variability could partially contribute to the higher incidence of local injection-site reactions observed with tirzepatide in our cohort, although a causal relationship cannot be established. Ophthalmic events, including progression of diabetic retinopathy and non-arteritic anterior ischemic optic neuropathy (NAION), represent among the most concerning potential adverse effects of semaglutide and tirzepatide, with conflicting findings reported in the literature [40,41]. In the present study, two patients in the semaglutide group experienced progression of diabetic retinopathy, leading to treatment discontinuation.

In real-world obesity management, both semaglutide and tirzepatide are associated with treatment discontinuation in approximately half of patients within 6–12 months [20]. Discontinuation is driven predominantly by financial barriers, access limitations, and gastrointestinal adverse effects [20,25]. According to the meta-analysis by Kagassa et al., the discontinuation rate due to adverse effects was 7.3% for the maximally tolerated dose of semaglutide and 5.6% for the maximally tolerated dose of tirzepatide [13]. Real-world evidence indicates that discontinuation due to adverse effects occurred in 8.1% of patients treated with semaglutide in a Canadian cohort and in 14.6% of patients receiving semaglutide or tirzepatide in a study from United States [42,43]. In our cohort, discontinuation due to adverse events occurred in 10.7% of patients treated with

semaglutide and 9.5% of those treated with tirzepatide. Overall, these findings suggest that the rates of treatment discontinuation due to adverse events were comparable between the semaglutide and tirzepatide groups, supporting the notion that short-term tolerability of the two treatments is largely similar in real-world clinical practice. The second most common reason for treatment discontinuation was drug cost. Beyond treatment discontinuation, the maximum tolerated doses of these drugs in real-world practice remain lower than those reported in randomized controlled trials [44]. A descriptive cohort study using the Veradigm database reported a 6-month treatment persistence rate of 54.2% among patients treated with tirzepatide, with 5 mg being the most commonly prescribed dose [44]. These findings suggest that dose-escalation practices in real-world settings are more conservative and progress more slowly than those observed in randomized controlled trials. Consistent with these findings, in our study the median dose within the first 6 months of treatment was 1 mg for semaglutide and 5 mg for tirzepatide.

Overall, the results indicate that both semaglutide and tirzepatide lead to substantial BWL in randomized controlled trials as well as in real-world studies; however, BWL reductions observed in real-world practice tend to be modestly lower than those reported in randomized controlled trials [20,45]. Real-world studies have reported weight loss of approximately 13–16% with semaglutide, with generally greater responses observed in individuals without T2DM compared with those with T2DM [9,10]. The short-term effectiveness of tirzepatide was evaluated in a recent 6-month real-world study of patients with obesity without T2DM, in which treatment with tirzepatide 5 mg resulted in a 7.3% reduction in body weight from baseline [11].

Direct comparative data on the efficacy of semaglutide and tirzepatide mainly derive from meta-analyses of randomized controlled trials, with only a limited number of comparative real-world analyses available, which have demonstrated higher efficacy of tirzepatide compared with semaglutide [12,46]. Meta-analytic data across varying doses suggest that tirzepatide may achieve weight reductions of approximately 15–20%, whereas semaglutide is generally associated with weight loss in the range of 11–14% [13]. Real-world studies have shown similar trends, with a substantial proportion of patients achieving clinically meaningful weight loss [15,16]. In our cohort, patients with obesity without T2DM achieved greater weight loss with tirzepatide compared with semaglutide (15.6% vs. 13.4%), while among those with T2DM, the corresponding reductions were 11.3% and 10.6%, respectively, over a 6-month treatment period. Overall, 75% of patients in the tirzepatide group and 73% in the semaglutide group achieved at least a 10% reduction in BWL from baseline. These findings are consistent with previously reported real-world data, supporting lower BWL reductions in patients with T2DM compared with those without T2DM. Our findings confirmed greater BWL reduction in the tirzepatide group compared with the semaglutide group up to 5 months of treatment. The comparable results observed at 6 months in our cohort may be attributable to a declining number of patients who persisted with treatment over time. Additionally, the observed overall superiority of tirzepatide over semaglutide may have been influenced by the higher prevalence of metabolic abnormalities, including T2DM and dyslipidemia, in the semaglutide group. However, subgroup analyses stratified by T2DM status showed that tirzepatide continued to demonstrate greater efficacy, particularly in the early phase of treatment, suggesting that baseline differences did not fully explain the observed treatment effect.

Beyond its established effects on weight management, GLP-1 analogue therapy is associated with significant metabolic improvements. Randomized controlled trials have demonstrated substantial reductions in HbA1c, with tirzepatide achieving approximately 1.9–2.1% and semaglutide approximately 1.5–1.6% [47,48]. In real-world settings, HbA1c reductions tend to be more modest, likely reflecting differences in patient characteristics, adherence, and dosing strategies [16]. Consistent with these findings, HbA1c reductions in our cohort were comparable between treatment groups, with decreases of 0.9% with semaglutide and 0.8% with tirzepatide over 6 months. In addition to glycemic effects, GLP-1–based therapies have been associated with improvements in lipid profiles [9]. In the overall cohort, semaglutide was associated with a modest reduction in FPG and LDL-C levels, along with a modest increase in HDL-C, compared with tirzepatide. This difference may be attributed to the higher prevalence of comorbidities, including T2DM, dyslipidemia, and ASCVD, among patients receiving semaglutide in our cohort.

This study has several notable strengths. It provides large-scale, multicenter real-world comparative data on semaglutide and tirzepatide derived from routine clinical practice, thereby complementing evidence from randomized controlled trials. A major strength is the systematic assessment of a broad range of adverse events, together with their associated drug dose, time to onset, and discontinuation rates for each adverse event category. This comprehensive evaluation of safety outcomes, including treatment persistence and tolerability,

contributes to a detailed characterization of adverse event profiles and provides clinically relevant insights into differential treatment responses, which may inform individualized obesity management strategies. Several limitations of this study should also be acknowledged. A major limitation of this study is the relatively small number of patients who completed the 6-month follow-up, especially in the tirzepatide group. This is primarily attributable to the recent availability of tirzepatide in Türkiye since May 2025, which limited the number of patients able to complete 6 months of treatment and reach higher tirzepatide doses. Another possible explanation is that some patients in the tirzepatide group achieved their target weight loss within a shorter treatment duration, resulting in shorter follow-up periods. Notably, all patients, except those who discontinued treatment due to adverse effects, completed at least 3 months of therapy, after which a decreasing number of patients continued treatment up to 6 months. Furthermore, efficacy analyses were based on the median doses administered during the treatment period. As not all patients reached the maximum dose, the observed efficacy outcomes should be interpreted with caution. Another limitation of our study is the lack of body composition measurements, which prevented a detailed comparison of the effects of semaglutide and tirzepatide on fat mass and lean mass. Some findings, including the rate of diabetic neuropathy, which appears lower than that reported in epidemiological studies, may be influenced by underdiagnosis in routine clinical practice. Additionally, adverse events were based on patient self-reports, which may underestimate the incidence of mild or transient symptoms and are subject to reporting bias. Finally, as this study evaluated only the short-term adverse effects of these agents, prospective studies with longer follow-up over a period of at least 1 year and standardized dosing strategies are warranted to further clarify their comparative effectiveness and safety.

In conclusion, this large-scale, multicenter, real-world study demonstrated that semaglutide and tirzepatide have similar short-term tolerability and treatment persistence profiles, despite a higher incidence of musculoskeletal and allergic reactions and a slightly earlier onset of certain adverse events with tirzepatide. Tirzepatide achieved greater and more rapid body weight loss during the first five months. Comparable results at six months should be interpreted cautiously, given the limited number of patients completing longer follow-up. These findings suggest that both agents represent effective therapeutic options for obesity management, with treatment selection potentially guided by individual patient characteristics, comorbidity profiles, and tolerability considerations. Long-term comparative studies are warranted to determine whether the early efficacy advantage of tirzepatide persists and to identify predictors of response that may enable more personalized treatment strategies.

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None

Statement of Ethics

The study was approved by the Ethics Committee of Ankara Etlik City Hospital and was conducted in accordance with the principles of the Declaration of Helsinki (Approval number: AEŞH-BADEK2-2025-500 Date: 02/09/2025). The written informed consent was obtained from participants.

Conflict of Interest Statement

E.B., D.G.Y., G.A., F.A., R.E., M.C., A.O.K., B.K, and Ö.T.Ç. have received lecture honoraria from Novo Nordisk. S.H.İ., G.A., R.E., Ö.T., M.C., B.K., and A.O.K. have received lecture honoraria from Eli Lilly. S.K. has served on advisory boards for Novo Nordisk and has received lecture honoraria from Novo Nordisk, Boehringer Ingelheim, AstraZeneca, and Sanofi. S.K. has also participated as a principal investigator in clinical trials sponsored by Boehringer Ingelheim. S.S. has received lecture honoraria from Eli Lilly, Novo Nordisk, Abbott, and Roche Diagnostics. D.G.Y. and F.A. have participated as investigators in clinical trials sponsored by Novo Nordisk. R.E. has served as a coordinating investigator and D.G.Y. as an investigator in clinical trials sponsored by Eli Lilly. C.H. has received lecture honoraria from Sanofi, Novartis, and Boehringer Ingelheim. V.Y. has participated in advisory boards and received lecture honoraria from Novo Nordisk, Eli Lilly, Rhythm, and Regeneron. F.B. has participated in clinical studies and advisory board meetings sponsored by Novo Nordisk, Eli Lilly, MSD, Medtronic, Trispera, Abbott, Sanovel, Sanofi, and Novartis. A.S. has participated in advisory board meetings organized by AstraZeneca, MSD, Novartis, Eczacıbaşı, Roche Diagnostics, Daiichi-Sankyo, Eli Lilly, Novo Nordisk, Sanovel, Trispera, and Deva, and has served as an investigator in clinical trials sponsored by Novo Nordisk, Sanofi, Novartis, and AstraZeneca. Volkan Yumuk was a member of the journal's Editorial Board at the time of submission. All other authors declare that they have no conflict of interest.

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Author's contribution
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Data Availability Statement
The data that support the findings of this study are not publicly available due to privacy reasons but are available from the corresponding author (S.H.) upon request.

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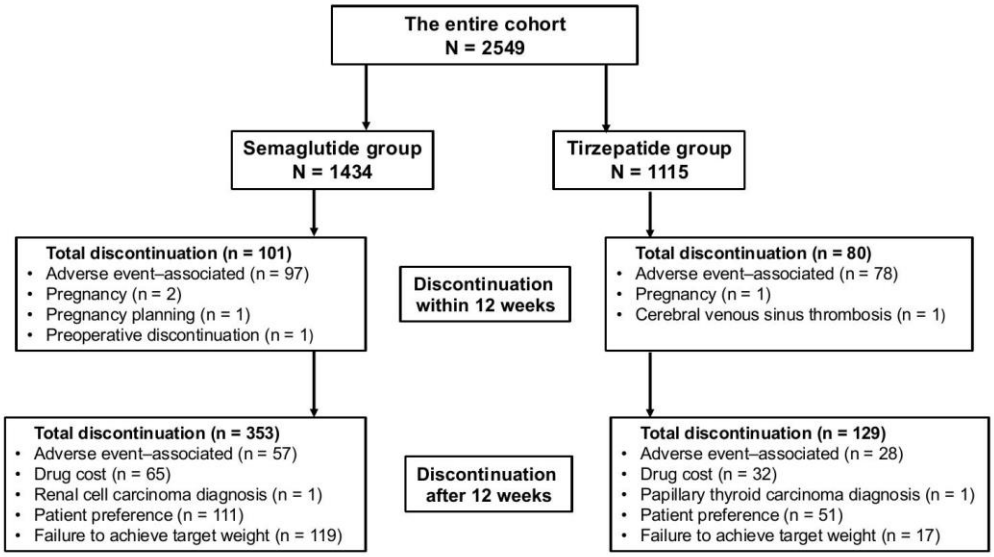
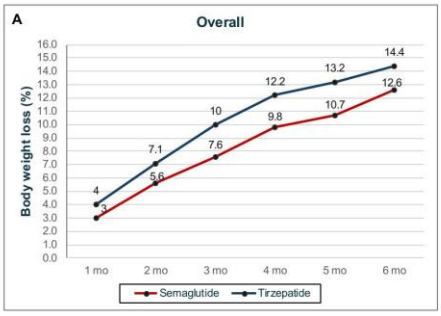
Figure Legends

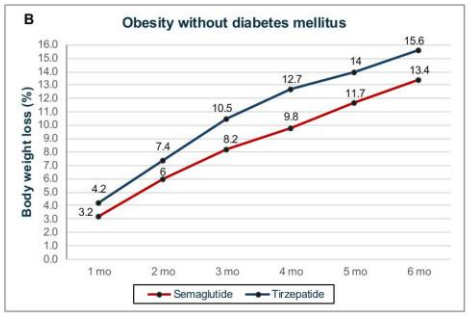
Figure 1. Distribution of reasons for treatment discontinuation within and after 12 weeks of treatment in patients receiving semaglutide and tirzepatide.

Figure 2. Monthly changes in body weight loss (%) up to 6 months in (A) the overall cohort, (B) patients with obesity and without diabetes mellitus, and (C) patients with obesity and diabetes mellitus, stratified by treatment

group. The numbers of patients at each monthly time point and the corresponding p values from monthly comparisons are provided in Supplementary Tables 2, 3, and 4, respectively.







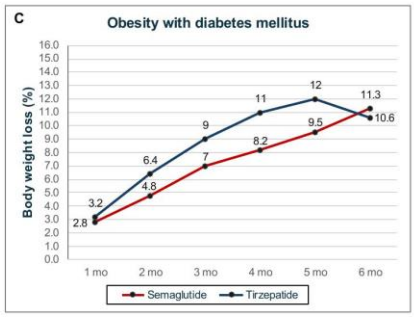


Table 1. Basal characteristics, comorbidities, and diabetic microvascular complications of the patients

	Semaglutide group (N= 1434)	**Tirzepatide group (N= 1115)**	***P* value**
Age (years)	44 ± 12.5	42 ± 11.6	**<0.001**
Sex (female), n (%)	1051 (73.3)	761 (68.3)	**0.005**
Baseline body weight (kg)	99 (56–226)	101 (64–200)	**0.025**
BMI (kg/m^2)	36.4 (27.1–76.4)	36.3 (27.1–69.0)	0.991
Obesity category, n (%)			0.536
Overweight	103 (7.2)	65 (5.8)	
Class I obesity	468 (32.6)	375 (33.6)	
Class II obesity	447 (31.2)	358 (32.1)	
Class III obesity	416 (29.0)	317 (28.4)	
Comorbidities, n (%)			
Diabetes mellitus	493 (34.4)	254 (22.8)	**<0.001**
Prediabetes	421 (53.2)	371 (46.8)	**0.034**
Hypertension	411 (28.7)	264 (23.7)	**0.005**
Dyslipidemia	841 (58.6)	582 (40.9)	**0.001**
Atherosclerotic cardiovascular disease	105 (7.3)	55 (4.9)	**0.014**
Obstructive sleep apnea	73 (5.1)	66 (5.9)	0.361
Chronic kidney disease	37 (2.6)	11 (1.0)	**0.003**
Diabetic microvascular complications			
Retinopathy			0.761
Non-proliferative	32 (6.5)	14 (5.5)	
Proliferative	5 (1.0)	1 (0.4)	
Unknown	30 (6.1)	14 (5.5)	
Nephropathy			**0.006**
Yes	82 (16.6)	45 (17.7)	
Unknown	10 (2.0)	17 (6.7)	
Neuropathy			**0.008**
Yes	58 (11.8)	29 (11.4)	
Unknown	13 (2.6)	7 (2.8)	

BMI, Body mass index.

Categorical variables are expressed as numbers and percentages, parametric variables as mean ± SD, and nonparametric variables as median (min–max).

Percentages for diabetic complications were calculated among patients with diabetes mellitus.

Table 2. Adverse event profile: Frequency, onset time, event-associated dose, and discontinuation rate due to adverse events

	Semaglutide group (N= 1434)	**Tirzepatide group (N=1115)**	***P value***
Gastrointestinal, n (%)	673 (47)	507 (45.5)	0.471
Median dose, mg	0.5 (0.25–1.7)	2.5 (2.5–12.5)	-
Time to onset, day	10 (1–210)	7 (1–165)	**0.002**
Discontinuation rate, n (%)	118 (8.2)	76 (6.8)	0.266
Nausea/vomiting	364 (25.3)	263 (23.6)	0.296
Dyspepsia/abdominal pain	249 (17.4)	165 (14.8)	0.081
Constipation	147 (10.3)	108 (9.7)	0.637
Diarrhea	112 (7.8)	92 (8.3)	0.684
Changed taste sensitivity	8 (0.6)	6 (0.5)	0.947
Halitosis	6 (0.4)	4 (0.4)	0.981
Hepatobiliary, n (%)	14 (1)	15 (1.3)	0.722
Median dose, mg	1 (0.25–1.7)	5 (2.5–10)	-
Time to onset, day	50 (2–180)	40 (2–98)	0.472
Discontinuation rate, n (%)	8 (0.6)	9 (0.8)	0.443
Cholecystitis	5 (0.3)	5 (0.4)	0.760
Cholelithiasis	1 (0.07)	1 (0.09)	0.991
≥ 3× ULN elevation in liver enzymes	3 (0.2)	3 (0.3)	0.962
<3× ULN elevation in liver enzymes	5 (0.3)	6 (0.5)	0.349
Pancreatic, n (%)	15 (1.05)	8 (0.7)	0.530
Median dose, mg	1 (0.25–1.7)	5 (2.5–7.5)	-
Time to onset, day	90 (2–212)	32 (28–90)	0.063
Discontinuation rate, n (%)	9 (0.6)	0 (0)	**0.006**
Acute pancreatitis	1(0.07)	0 (0)	0.380
Elevated amylase and lipase levels	14 (1)	8 (0.7)	0.483
Hypoglycemia, n (%)	31 (2.2)	15 (1.3)	0.270
Median dose, mg	0.5 (0.25–1.7)	5 (2.5–5)	-
Time to onset, day	40 (2–150)	30 (1–40)	**0.029**
Discontinuation rate, n (%)	3 (0.2)	0 (0)	0.261
Symptomatic	30 (2.1)	14 (1.3)	0.108
Severe	1 (0.07)	1 (0.09)	0.991
Cardiovascular, n (%)	35 (2.4)	25 (2.2)	0.743
Median dose, mg	0.5 (0.25–1.7)	5 (2.5–5)	-
Time to onset, day	33 (1–180)	35 (1–58)	0.446
Discontinuation rate, n (%)	5 (0.35)	6 (0.5)	0.549
Bradycardia	0 (0)	1 (0.09)	0.380
Increased blood pressure	1 (0.07)	4 (0.4)	0.232
Hypotension	12 (0.8)	8 (0.7)	0.741
Tachycardia	22 (1.5)	12 (1.1)	0.317
Allergic, n (%)	10 (0.7)	18 (1.6)	**0.028**
Median dose, mg	0.5 (0.25–1)	2.5 (2.5–5)	-
Time to onset, day	30 (1–95)	14 (1–61)	0.168
Discontinuation rate, n (%)	0 (0)	3 (0.3)	0.084
Local allergic reaction	6 (0.4)	13 (1.2)	**0.03**
Urticaria	4 (0.3)	5 (0.4)	0.713
Dermatological, n (%)	29 (2)	32 (2.9)	0.130
Median dose, mg	0.5 (0.5–1)	5 (2.5–10)	-
Time to onset, day	37 (10–180)	42 (1–110)	0.514
Discontinuation rate, n (%)	3 (0.2)	1 (0.09)	0.636
Hair loss	24 (1.7)	22 (2)	0.573
Dermatitis	3 (0.2)	10 (0.9)	**0.016**
Psoriasis flare	1 (0.07)	0 (0)	0.380
Facial fat loss	1 (0.07)	0 (0)	
Neuropsychiatric, n (%)	193 (13.5)	127 (11.4)	0.118
Median dose, mg	0.5 (0.25–1)	2.5 (2.5–10)	-
Time to onset, day	32 (1–182)	30 (1–100)	**0.01**
Discontinuation rate, n (%)	20 (1.4)	11 (1)	0.351
Fatigue and malaise	109 (7.6)	74 (6.6)	0.349
Headache	49 (3.4)	31 (2.8)	0.360
Negative mood change	24 (1.7)	13 (1.2)	0.288
Insomnia	2 (0.14)	3 (0.3)	0.681
***Vertigo/d**izziness*	8 (0.6)	5 (0.45)	0.982

Neuropathic symptoms	1 (0.07)	2 (0.2)	0.645
Musculoskeletal, n (%)	28 (2.0)	50 (4.5)	**<0.001**
Median dose, mg	0.5 (0.25–1.7)	5 (2.5–7.5)	-
Time to onset, day	33 (3–120)	30 (3–95)	**0.001**
Discontinuation rate, n (%)	7 (0.5)	6 (0.5)	0.861
Myalgia	26 (1.8)	39 (3.5)	**0.007**
Arthralgia	2 (0.14)	11 (1)	**0.003**
Renal, n (%)	2 (0.14)	1 (0.09)	0.667
Median dose, mg	1 (1–1)	2.5	-
Time to onset, day	77.5 (60–95)	10	-
Discontinuation rate, n (%)	2 (0.14)	1 (0.09)	0.667
<1.5 × ULN increase in creatinine	1 (0.07)	1 (0.09)	0.991
≥ 1.5 × ULN increase in creatinine	1 (0.07)	0 (0)	0.380
Electrolyte imbalance	0 (0)	1 (0.09)	0.380
Ophthalmic, n (%)	2 (0.14)	1 (0.09)	0.647
Median dose, mg	0.75 (0.5–1)	2.5	-
Time to onset, day	120 (100-140)	35	-
Discontinuation rate, n (%)	2 (0.14)	1 (0.09)	0.647
Progression of diabetic retinopathy	2 (0.14)	0 (0)	0.221
Peripapillary atrophy	0 (0)	1 (0.09)	0.380
Urogenital, n (%)	11 (0.8)	9 (0.8)	0.909
Median dose, mg	1 (0.5–1)	2.5 (2.5–5)	
Time to onset, day	30 (15–90)	40 (20–90)	0.683
Discontinuation rate, n (%)	1 (0.07)	0 (0)	0.380
Menstrual irregularities	9 (0.6)	7 (0.6)	0.812
Impotence	2 (0.14)	2 (0.2)	0.972

Percentages reflect within-group proportions. Categorical variables are expressed as n (%), and non-parametric variables are summarized as minimum to maximum values.

Table 3. Proportions of patients achieving 5%, 10%, and 15% total body weight loss among groups

	Semaglutide group	Tirzepatide group	*P* value
Month 1			
Patients, n	1275	1026	
5%	248 (19.5)	338 (32.9)	**<0.001**
10%	20 (1.6)	17 (1.7)	0.867
15%	-	-	-
Month 2			
Patients, n	1085	870	
5%	626 (57.7)	682 (78.4)	**<0.001**
10%	112 (10.3)	183 (21)	**<0.001**
15%	11 (1.0)	22 (2.5)	**0.01**
Month 3			
Patients, n	1230	978	
5%	1004 (81.6)	906 (92.6)	**<0.001**
10%	365 (29.7)	509 (52)	**<0.001**
15%	63 (5.1)	140 (14.3)	**<0.001**
Month 4			
Patients, n	624	302	
5%	576 (92.3)	290 (96.0)	**0.031**
10%	304 (48.7)	217 (72.0)	**<0.001**
15%	95 (15.2)	85 (28.1)	**<0.001**
Month 5			
Patients, n	376	91	
5%	356 (94.7)	88 (96.7)	0.592
10%	216 (57.4)	79 (86.8)	**<0.001**
15%	95 (25.3)	38 (41.8)	**0.002**
Month 6			
Patients, n	342	43	
5%	320 (93.6)	41 (95.3)	1.00
10%	249 (72.8)	32 (74.4)	0.823
15%	109 (31.9)	18 (41.9)	0.189

Proportions were calculated based on patients with available body weight data at each time points and presented as numbers a
percentages.

Table 4. The comparison of baseline and follow-up changes in laboratory parameters within all patients among treatment groups

	Semaglutide group	Tirzepatide group	*P* value
FPG, mg/dL			
BL	101 (91–124)	98 (89–110)	**<0.001**
⊿ BL–3 month	–8 (–17, –2)	–7 (–15, –2)	0.247
⊿ BL–6 month	–12 (–24, –3)	–9 (–17, –3)	**0.006**
HbA1C, %			
BL	5.9 (5.5–6.8)	5.7 (5.4–6.2)	**<0.001**
⊿ BL–3 month	–0.3 (–0.6, –0.1)	–0.3 (–0.5, –0.1)	0.169
⊿ BL–6 month	–0.5 (–0.9, –0.2)	–0.5 (–0.7, –0.2)	0.284
Total cholesterol mg/dL			
BL	203 (172–230)	200 (175–227)	0.319
⊿ BL–3 month	–15 (–35, –2)	–14 (–35, –2)	0.308
⊿ BL–6 month	–20 (–46, –3)	–17 (–37, –2)	0.146
Triglyceride, mg/dL			
BL	148 (104, 211)	139 (100, 196)	**0.022**
⊿ BL–3 month	–16 (–45, 2)	–13 (–40, 1)	0.422
⊿ BL–6 month	–23 (–62, –2)	– 22 (–60, –1)	0.869
HDL-C, mg/dL			
BL	46 (40, 54)	46 (39, 55)	0.650
⊿ BL–3 month	0.15 (–3, 3)	0 (–4.8, 3)	**0.03**
⊿ BL–6 month	1.65 (–3, 5)	0 (–5, 4)	**0.029**
LDL-C, mg/dL			
BL	124 (101, 147)	125 (103, 145)	0.929
⊿ BL–3 month	–10 (–25, –1)	–10 (–24, 1)	0.365
⊿ BL–6 month	–15 (–31, –2)	–11 (–29, 4)	**0.036**

BL, baseline; Δ, change, FPG, Fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol.
Data were presented as median and interquartile ranges (IQR 25–75).