

Preliminary Findings From a Prospective Cohort Study of Tirzepatide in Adults With Obesity and Heart Failure with Preserved Ejection Fraction: Longitudinal Effectiveness, Cardiometabolic Response, and Gastrointestinal Tolerability in Kazakhstan

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ABSTRACT

Background: Evidence describing the longitudinal effectiveness and tolerability of tirzepatide in adults with obesity and heart failure with preserved ejection fraction (HFpEF) remains limited, particularly from prospective cohorts with repeated cardiometabolic assessments. This study evaluated longitudinal changes in weight, metabolic health, and treatment-emergent symptoms during tirzepatide therapy in a Kazakhstan cohort with obesity and HFpEF.

Methods: We conducted a preliminary analysis of the tirzepatide-treated cohort enrolled at one center within a broader prospective interventional study. The present analysis included adults with obesity and HFpEF who received once-weekly tirzepatide according to a prospectively defined treatment protocol. Participants underwent scheduled assessments from baseline through Week 41. Longitudinal changes in anthropometric, metabolic, inflammatory, renal, and body composition outcomes were analyzed using linear mixed-effects models. Individual treatment-emergent symptoms were summarized descriptively, while longitudinal regression models were used for aggregated adverse-event outcomes and symptom burden. Complete-case and exploratory predictor analyses were performed as sensitivity analyses.

Results: Twenty-four participants with obesity and HFpEF contributed longitudinal observations, including 16 with mature Week-41 follow-up. Tirzepatide treatment was associated with significant reductions in body weight, BMI, waist circumference, fasting glucose, triglycerides, and selected inflammatory markers over time. Mean percentage weight loss at Week 41 was 17.2±8.1%, corresponding to 18.7±7.0 kg. Among the 16 participants with paired baseline and Week-41 measurements, all achieved ≥5% weight loss, while 87.5%, 50.0%, and 25.0% achieved ≥10%, ≥15%, and ≥20% weight loss, respectively. Gastrointestinal symptoms were reported in 25.0% of participants, with nausea

(20.8%) and vomiting (12.5%) being the most frequently recorded. No serious adverse events were observed during the study period. No statistically significant association was detected between gastrointestinal symptom occurrence or burden and longitudinal weight loss; however, these analyses were exploratory given the small number of gastrointestinal events.

Conclusions: In this preliminary analysis of a prospective tirzepatide-treated cohort of adults with obesity and HFpEF from Kazakhstan, tirzepatide was associated with substantial and sustained weight loss accompanied by favorable cardiometabolic changes. Gastrointestinal symptoms were reported in a minority of participants, although their severity was not formally graded. These findings should be interpreted within the specific clinical context of obesity with concomitant HFpEF.

Keywords: obesity; tirzepatide; GLP-1/GIP receptor agonist; longitudinal study; weight loss; cardiometabolic health; gastrointestinal adverse events

Introduction

Obesity is a chronic, relapsing, multifactorial disease that has emerged as one of the greatest public health challenges worldwide. Despite substantial advances in prevention and treatment strategies, its prevalence continues to increase across all regions and age groups, with projections indicating that more than half of the global adult population may be living with overweight or obesity by 2050 if current trends persist [1]. Excess adiposity is associated with a broad spectrum of obesity-related complications, including type 2 diabetes mellitus, cardiovascular disease, metabolic dysfunction-associated steatotic liver disease (MASLD), chronic kidney disease, obstructive sleep apnea, several obesity-associated cancers, and increased all-cause mortality, resulting in substantial healthcare expenditures and reduced life expectancy [2,3]. Importantly, even relatively modest weight reduction of approximately 5-10% of initial body weight produces clinically meaningful improvements in glycemic control, blood pressure, lipid metabolism, hepatic steatosis, and overall cardiometabolic risk [2,4]. However, lifestyle interventions based on dietary modification, increased physical activity, and behavioral therapy frequently fail to achieve durable long-term weight loss because of complex neuroendocrine adaptations that promote weight regain [5,6]. Consequently, effective and durable anti-obesity pharmacotherapy has become an important component of obesity management.

Tirzepatide is the first approved dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist developed for the treatment of obesity. By simultaneously activating both incretin pathways, tirzepatide enhances glucose-dependent insulin secretion, suppresses glucagon release, delays gastric emptying, and acts on central appetite-regulating pathways to reduce energy intake while improving insulin sensitivity and overall metabolic homeostasis [7,8]. The efficacy of tirzepatide has been demonstrated in the global phase 3 SURMOUNT clinical trial program across diverse populations with overweight and obesity. In SURMOUNT-1, once-weekly tirzepatide produced mean weight reductions approaching 20% of baseline body weight over 72 weeks, accompanied by significant improvements in waist circumference, glycemic measures, blood pressure, lipid profile, and multiple prespecified cardiometabolic risk factors [9]. Similar benefits were subsequently confirmed in adults with obesity and type 2 diabetes (SURMOUNT-2), following intensive lifestyle intervention (SURMOUNT-3), and during long-term maintenance therapy (SURMOUNT-4), demonstrating consistent and sustained weight reduction together with favorable metabolic effects across different clinical settings [10-12]. In randomized clinical trials, gastrointestinal

adverse events – including nausea, diarrhea, vomiting, and constipation – represent the most frequently reported treatment-emergent events and have generally been mild to moderate in severity, occurred predominantly during dose escalation, and rarely led to treatment discontinuation [9,12]. These randomized clinical trials established tirzepatide as one of the most effective pharmacological treatments currently available for obesity.

Although the SURMOUNT clinical trial program established the efficacy and safety of tirzepatide under rigorously controlled conditions, several important questions remain regarding its effectiveness in routine clinical practice. Randomized clinical trials typically enroll carefully selected participants according to predefined eligibility criteria, employ standardized treatment protocols, and are conducted in highly monitored settings, which may limit the generalizability of their findings to broader and more heterogeneous patient populations [13]. Furthermore, while pivotal trials primarily reported overall treatment effects at prespecified time points, comparatively limited evidence is available regarding individual longitudinal trajectories of weight loss, repeated changes in cardiometabolic and inflammatory parameters during treatment, the temporal evolution of gastrointestinal adverse events, and the relationship between symptom burden and treatment effectiveness. In addition, relatively few prospective studies have incorporated serial assessments of anthropometric, metabolic, inflammatory, renal, and body composition measures together with repeated evaluation of treatment-emergent symptoms and exploratory analyses of predictors of therapeutic response. Prospective evidence from Central Asia is particularly limited, and published longitudinal data describing the effectiveness and tolerability of tirzepatide in adults with obesity from Kazakhstan are currently lacking. These gaps limit understanding of longitudinal treatment responses to tirzepatide across geographically and clinically diverse populations.

Therefore, we conducted a prospective, single-arm, longitudinal interventional cohort study to provide preliminary evidence on the effectiveness and tolerability of tirzepatide in adults with obesity and concomitant heart failure with preserved ejection fraction (HFpEF) in Kazakhstan. Participants initiating once-weekly tirzepatide therapy underwent serial evaluations during the 40-week treatment period and at the Week-41 end-of-treatment assessment, including repeated anthropometric, clinical, metabolic, inflammatory, renal, and body composition assessments. Using a longitudinal design, we sought to characterize trajectories of weight reduction and changes in cardiometabolic health throughout treatment rather than relying solely on fixed endpoint comparisons. We also evaluated the proportion of participants achieving clinically meaningful weight-loss thresholds, described the frequency and temporal

evolution of gastrointestinal treatment-emergent symptoms, and explored baseline clinical and metabolic characteristics associated with subsequent weight-loss response. By generating prospective longitudinal data from a Central Asian cohort with obesity and HFpEF, this study aimed to complement evidence from randomized clinical trials and expand understanding of treatment response to tirzepatide in a previously underrepresented regional population.

Methods

Study design and setting

This prospective, longitudinal interventional cohort study was conducted at the Corporate Fund “University Medical Center” (UMC; Astana, Kazakhstan) as part of the broader multicenter research program “Improving Cardiovascular Disease Diagnosis and Treatment in Kazakhstan Using Metabolic Correction With GLP-1 Drugs” (NCT07303556). The parent protocol (version 1.0, October 29, 2024) prospectively defined two participating clinical centers with center-specific study populations and tirzepatide and standard-therapy groups. At UMC in Astana, the protocol enrolled adults with heart failure with preserved ejection fraction (HFpEF), defined in the protocol as a left ventricular ejection fraction $\geq 45\%$, with or without type 2 diabetes. At the participating center in Almaty, the corresponding study population comprised patients with HFpEF and concomitant type 2 diabetes. The present manuscript is restricted to the tirzepatide-treated UMC cohort and does not include the standard-therapy comparison group or participants enrolled at the Almaty center.

Tirzepatide (Mounjaro®, Eli Lilly) was administered according to the prospectively defined study protocol, with dose escalation and maintenance at the maximally tolerated dose individualized according to treatment tolerability and clinical response. The study protocol and case report forms were developed before participant enrollment, and the study was conducted in accordance with Good Clinical Practice and the Declaration of Helsinki. The study was approved by the Local Committee of Bioethics of the Corporate Fund “University Medical Center,” Kazakhstan (Protocol No. 11/2024/IIЭ dated December 12, 2024). The parent study was subsequently registered at ClinicalTrials.gov (NCT07303556); the registry record was first submitted on July 30, 2025 and first publicly posted on December 26, 2025. Thus, ClinicalTrials.gov registration occurred after participant enrollment had begun.

The present manuscript represents a preliminary analysis based on data available as of July 20, 2026. Participants were consecutively assessed for eligibility at UMC between March 3 and December 25, 2025. A total of 42 patients were screened during this period, of whom 30 met the eligibility criteria, were enrolled in the UMC tirzepatide cohort, and initiated tirzepatide treatment. The standard-therapy group specified in the broader parent protocol was separate from these 30 participants and was not included in the present preliminary analysis. At the interim database cutoff, 24 of the 30 tirzepatide-treated participants had accumulated sufficient longitudinal follow-up for inclusion in the present analysis. The remaining six participants were still undergoing treatment and had not yet accumulated sufficient follow-up for inclusion in this interim dataset.

Because enrollment was staggered, follow-up duration differed according to enrollment date. Among the 24 participants included in the longitudinal analysis, 16 had reached the Week-41 assessment window by the database cutoff, whereas eight were still undergoing treatment and had not yet reached Week 41. Thus, incomplete Week-41 follow-up reflected staggered

enrollment and administrative censoring at the interim database cutoff rather than treatment discontinuation or loss to follow-up.

Eligibility for the UMC cohort was determined according to predefined clinical and echocardiographic criteria, including HFpEF with a left ventricular ejection fraction $\geq 45\%$. Type 2 diabetes was not required for enrollment in the UMC cohort. Additional eligibility criteria included age 18–75 years, stable body weight before screening, and BMI ≥ 25 kg/m². Major exclusion criteria included type 1 diabetes, acute or exacerbated chronic pancreatitis, severe renal impairment (estimated glomerular filtration rate < 45 mL/min/1.73 m²), recent myocardial infarction or stroke, previous bariatric surgery or conditions associated with delayed gastric emptying, active hepatitis, medullary thyroid carcinoma or multiple endocrine neoplasia type 2, recent use of other weight-loss medications, and severe psychiatric illness. Eligibility was confirmed using standardized screening forms before treatment initiation. Although the protocol permitted enrollment of adults with either overweight or obesity (BMI ≥ 25 kg/m²), all participants included in the present analysis had obesity at baseline (BMI ≥ 30 kg/m²).

Treatment protocol

Participants received once-weekly subcutaneous tirzepatide according to the prospectively defined treatment protocol. Treatment was initiated at 2.5 mg once weekly, with planned escalation to 5 mg, 7.5 mg, and 10 mg according to tolerability and clinical response. The maximum dose of 10 mg once weekly was prospectively specified in the study protocol as part of a safety- and tolerability-oriented dose-escalation strategy; doses of 12.5 and 15 mg were not included. Tirzepatide was administered for a planned 40-week treatment period, with the Week-41 visit serving as the end-of-treatment assessment. Actual tirzepatide dose was recorded longitudinally at each scheduled assessment. Treatment exposure was characterized by maximum achieved dose, dose distribution at key follow-up visits, delayed or incomplete dose escalation, dose reductions, treatment interruptions, and discontinuations. Estimated cumulative prescribed exposure was calculated using the recorded weekly dose, with the most recently documented dose carried forward between scheduled assessments.

Lifestyle counseling, including recommendations regarding dietary habits and physical activity, was provided as part of individualized clinical care during follow-up. These recommendations were tailored to participants’ clinical needs rather than delivered according to a uniform, protocol-defined lifestyle intervention. Given the preliminary nature of the present analysis, the intensity, implementation, and adherence to lifestyle recommendations were not systematically quantified and were therefore not included as separate covariates in the current analyses.

Concomitant pharmacotherapy was managed according to clinical indications and was not protocol-mandated to remain unchanged during follow-up. Relevant background therapies included glucose-lowering, antihypertensive, and lipid-lowering medications. Accordingly, changes in lifestyle behaviors and concomitant therapies may have contributed to the observed changes in cardiometabolic outcomes.

Clinical assessments

Baseline demographic characteristics, anthropometric measurements, blood pressure, heart rate, laboratory biomarkers, and body composition parameters were collected before treatment initiation. Scheduled follow-up assessments were performed at baseline and approximately Weeks 2, 4, 8, 16, 28, and 41, although additional intermediate visits were recorded as

part of routine clinical care. At each visit, body weight, BMI, waist circumference (WC), blood pressure, heart rate, current tirzepatide dose, and treatment-emergent symptoms were documented.

Laboratory investigations included fasting plasma glucose, glycated hemoglobin (HbA1c), lipid profile, liver enzymes, renal function, C-reactive protein (CRP), interleukin-6 (IL-6), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and other routine biochemical parameters according to the study schedule. Carotid ultrasonography and hepatic steatosis/fibrosis assessments were also performed according to the study protocol. Body composition was assessed using a Tanita MC-780MA Body Composition Analyzer (Tanita Corp., Tokyo, Japan) employing multi-frequency segmental bioelectrical impedance analysis. Recorded parameters included body fat percentage, fat mass, muscle mass, and metabolic age. Measurements were obtained at baseline and at available follow-up assessments according to the study schedule. Carotid and hepatic imaging assessments were additionally evaluated as exploratory outcomes in participants with paired baseline and Week-41 measurements. Carotid imaging outcomes included carotid stenosis category and atherosclerosis grade, while hepatic imaging outcomes included steatosis and fibrosis grades. Because these measures were ordinal, baseline-to-Week-41 changes were evaluated using paired nonparametric analyses and are reported as median [IQR]. These imaging analyses were considered exploratory.

Outcomes

Weight reduction was prospectively specified as an efficacy outcome in the original parent-study protocol. For the present preliminary obesity-focused analysis, longitudinal percentage change in body weight from baseline during tirzepatide therapy was selected as the primary analytic outcome. Secondary efficacy outcomes included longitudinal changes in absolute body weight, BMI, waist circumference (WC), systolic and diastolic blood pressure, fasting plasma glucose, HbA1c, lipid profile (total cholesterol, LDL-C, HDL-C, and triglycerides), inflammatory biomarkers (CRP and IL-6), renal function parameters, and body composition measures, including body fat percentage, fat mass, and skeletal muscle mass. In addition, clinically meaningful weight-loss responses were evaluated according to the proportions of participants achieving $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ weight loss at Weeks 28 and 41. Safety outcomes included patient-level incidence, visit-specific prevalence, and longitudinal evolution of treatment-emergent gastrointestinal and other adverse symptoms recorded throughout the follow-up period.

Assessment of treatment-emergent symptoms

Treatment-emergent symptoms were prospectively assessed using standardized case report forms and structured questioning at predefined follow-up time points. Specifically, symptoms were assessed at 15 scheduled post-baseline treatment/safety contacts at Weeks 1–11, 16, 20, 24, and 28, yielding 360 observations among the 24 participants. These assessments were scheduled irrespective of symptom occurrence and included more frequent monitoring during the early treatment and dose-escalation period; they did not represent symptom-driven visits. Participants were asked whether any adverse events had occurred following tirzepatide administration, including during the early post-dose period and subsequent follow-up intervals. Adverse events could additionally be identified through spontaneous patient reporting or clinical examination.

Symptoms of interest included nausea, vomiting, diarrhea, constipation, abdominal pain, decreased appetite, belching,

headache, dizziness, and other patient-reported adverse events. Multiple symptoms could be recorded during the same assessment. Participants who developed adverse events underwent additional clinical evaluation as clinically indicated; however, these clinically indicated evaluations were not included as additional observations in the 360-observation longitudinal dataset. Formal severity grading using a standardized adverse-event grading system was not incorporated into the case report form; therefore, the present analysis focuses on the occurrence and longitudinal frequency of reported symptoms rather than their graded severity. Serious adverse events, treatment interruptions, and treatment discontinuations were additionally reviewed from the available study records. Individual gastrointestinal symptoms were summarized descriptively, while the total number of concurrent gastrointestinal symptoms was evaluated as a measure of gastrointestinal symptom burden in longitudinal analyses.

Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation (SD) for approximately normally distributed data or median with interquartile range (IQR) for skewed distributions. Categorical variables are summarized as counts and percentages. Normality was assessed using visual inspection of histograms and Q-Q plots together with the Shapiro-Wilk test.

Longitudinal changes in continuous outcomes were evaluated using linear mixed-effects models including study visit as a categorical fixed effect and participant-specific random intercepts to account for within-subject correlation. Models were fitted using restricted maximum likelihood (REML) and included all available repeated measurements without imputation, assuming data were missing at random. Estimated marginal means with 95% confidence intervals were calculated for each visit, and pairwise comparisons with baseline were adjusted for multiple testing using the Holm method. Degrees of freedom were estimated using the Kenward–Roger approximation.

Clinically meaningful weight-loss responses were evaluated among participants with paired baseline and Week 28 or Week 41 body-weight measurements. The proportions of participants achieving $\geq 5\%$, $\geq 10\%$, $\geq 15\%$, and $\geq 20\%$ weight loss from baseline were calculated together with Wilson 95% confidence intervals. Individual treatment responses at Week 41 were visualized using waterfall plots.

Treatment-emergent symptoms were summarized as patient-level incidence and visit-specific prevalence. Individual gastrointestinal symptoms were infrequent and were therefore summarized descriptively rather than evaluated using symptom-specific mixed-effects or GEE models. Longitudinal inferential analyses were restricted to aggregated adverse-event outcomes with sufficient outcome variation. Associations between current tirzepatide dose, treatment duration, and aggregated adverse-event outcomes were evaluated using mixed-effects logistic regression, with generalized estimating equations (GEE) using an exchangeable correlation structure performed as sensitivity analyses. Gastrointestinal symptom burden was additionally analyzed using mixed-effects Poisson regression and cumulative link mixed models for ordinal symptom-burden categories. Associations between gastrointestinal symptom occurrence or burden and longitudinal percentage weight loss were evaluated using mixed-effects regression models adjusted for treatment duration. Participant-specific random intercepts were included in mixed-effects models as appropriate.

Sensitivity analyses were performed using participants with paired baseline and Week 41 measurements. Continuous outcomes were compared using paired t-tests or Wilcoxon

signed-rank tests, as appropriate according to data distribution. P values for multiple comparisons were adjusted using the Holm method.

Exploratory analyses were performed to examine associations between selected baseline characteristics and percentage weight loss at Week 41. Separate linear regression models were fitted for each baseline variable after standardization of continuous variables to one standard deviation and were adjusted for cumulative tirzepatide exposure. P values were adjusted using the Benjamini-Hochberg false discovery rate procedure. Given the small number of participants with mature Week-41 follow-up, these analyses were considered strictly exploratory and hypothesis-generating and were not intended to establish independent predictors of treatment response.

All statistical analyses were performed using R (version 4.5.1, R Foundation for Statistical Computing, Vienna, Austria). Longitudinal analyses were conducted using the lme4, lmerTest, emmeans, ordinal, and geepack packages, with data management and visualization performed using the tidyverse and ggplot2 packages.

Results

Study population and follow-up

A total of 24 participants were included in the longitudinal analysis. Baseline demographic, clinical, metabolic, and body composition characteristics are summarized in Table 1.

The cohort consisted predominantly of women (58.3%), with a mean age of 43.5 years. All participants had obesity, including 20.8% with class I, 50.0% with class II, and 29.2% with class III obesity.

Hypertension was present in 14 participants (58.3%), hepatic steatosis/steatohepatosis in 11 (45.8%), dyslipidemia or dyslipoproteinemia in 6 (25.0%), atrial fibrillation in 5 (20.8%), and ischemic heart disease in 2 (8.3%). Three participants (12.5%) had documented prediabetes or impaired glucose tolerance. At baseline, 10 participants (41.7%) were receiving statin therapy and 11 (45.8%) were receiving antihypertensive medication. Three participants (12.5%) were receiving metformin. Lifestyle management was documented in 19 participants (79.2%), including dietary interventions in 15 (62.5%), walking in 9 (37.5%), and structured training or fitness activities in 10 (41.7%).

Markers of obesity demonstrated substantial adiposity at study entry. Body composition analysis showed a high mean body fat percentage and fat mass, consistent with severe obesity, while muscle mass was preserved. More than half of participants had advanced hepatic steatosis (grade 3, 54.2%), whereas hepatic fibrosis was absent in 54.2% of the cohort. Carotid ultrasonography demonstrated evidence of atherosclerosis in half of the participants, with 8.3% exhibiting $\geq 50\%$ carotid stenosis. According to NASCET criteria, 45.8% of participants had measurable carotid stenosis.

Baseline metabolic profiling showed generally preserved glycemic control, with a mean HbA1c of $5.69 \pm 0.40\%$, although fasting glucose values ranged from normal to diabetic levels (97.6 ± 17.3 mg/dL). Lipid concentrations were consistent with a population at increased cardiometabolic risk. The median triglyceride concentration was 139.2 mg/dL (IQR, 95.2–215.0), while mean total cholesterol, HDL cholesterol, and LDL cholesterol were 197.0 ± 57.8 mg/dL, 53.0 ± 9.8 mg/dL, and 128.5 ± 46.8 mg/dL, respectively. Mean apolipoprotein B was 0.89 ± 0.22 .

Baseline renal function (mean eGFR= 105.6 ± 16.0 mL/min/1.73 m²) was preserved. Inflammatory biomarkers showed

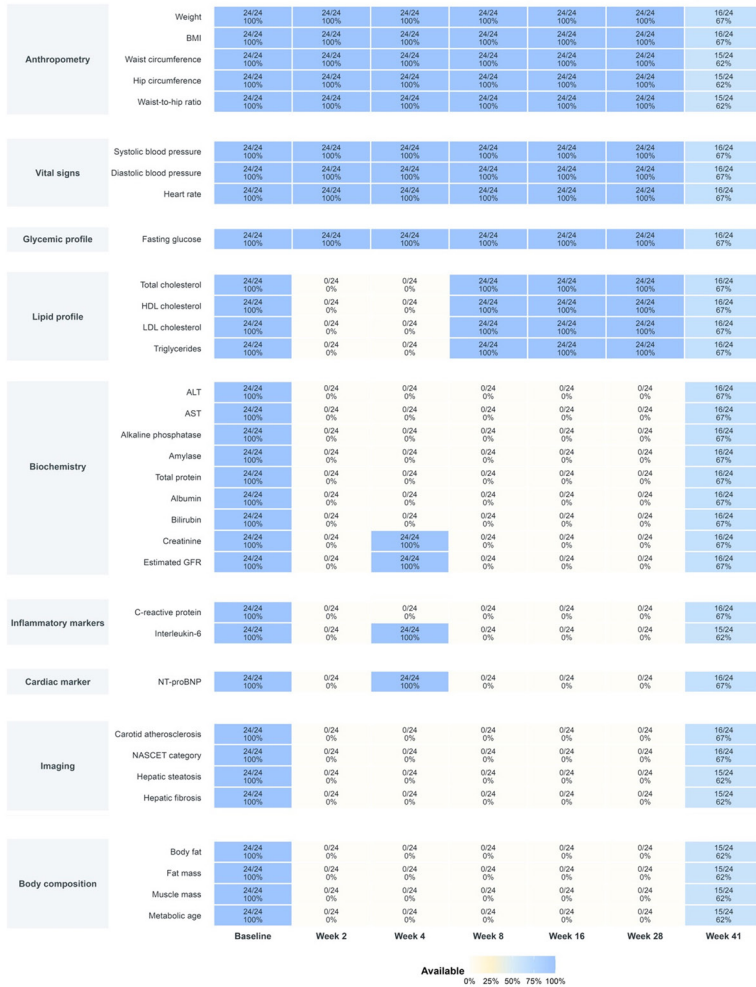
Table 1

Baseline characteristics of the study population (N=24)

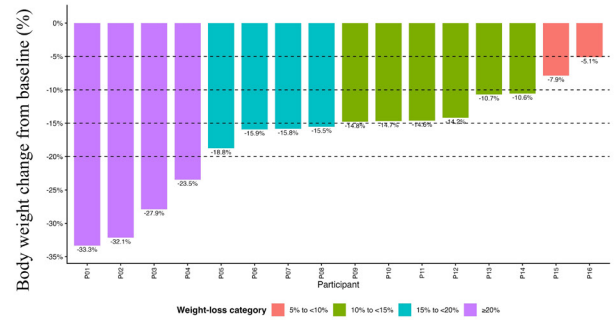
Characteristic	n (%) / M $\pm$ SD
<i>Demographic characteristics</i>	
Age	43.5 $\pm$ 12.2
Sex	
Male	10 (41.7%)
Female	14 (58.3%)
<i>Anthropometric characteristics</i>	
Weight, kg	111.6 $\pm$ 22.4
BMI, kg/m ²	38.4 $\pm$ 5.0
Obesity class	
Class I obesity	5 (20.8%)
Class II obesity	12 (50.0%)
Class III obesity	7 (29.2%)
Waist circumference, cm	115.4 $\pm$ 14.0
Hip circumference, cm	123.4 $\pm$ 9.3
<i>Cardiometabolic characteristics and comorbidities</i>	
Blood pressure $\geq 140/90$ mmHg at baseline	7 (29.2%)
Arterial hypertension	14 (58.3%)
Hepatic steatosis/steatohepatosis	11 (45.8%)
Dyslipidemia/dyslipoproteinemia	6 (25.0%)
Atrial fibrillation	5 (20.8%)
Ischemic heart disease	2 (8.3%)
Chronic kidney disease	1 (4.2%)
Prediabetes/impaired glucose tolerance	3 (12.5%)
<i>Concomitant pharmacotherapy</i>	
Statins	10 (41.7%)
Antihypertensive therapy	11 (45.8%)
Metformin	3 (12.5%)
Antiplatelet therapy	4 (16.7%)
Anticoagulant therapy	4 (16.7%)
<i>Lifestyle management</i>	
Any documented lifestyle intervention	19 (79.2%)
Dietary modification	15 (62.5%)
Walking	9 (37.5%)
Exercise/fitness training	10 (41.7%)
<i>Imaging and instrumental assessments</i>	
Carotid atherosclerosis	
No atherosclerosis	12 (50.0%)
Stenosis <50%	10 (41.7%)
Stenosis $\geq 50\%$	2 (8.3%)
Carotid stenosis by NASCET	
No stenosis	13 (54.2%)
1-29%	5 (20.8%)
30-49%	6 (25.0%)
Hepatic steatosis grade	
Grade 0	2 (8.3%)
Grade 1	4 (16.7%)
Grade 2	5 (20.8%)
Grade 3	13 (54.2%)
Hepatic fibrosis grade	
Grade 0	13 (54.2%)
Grade 1	4 (16.7%)
Grade 2	4 (16.7%)
Grade 3	3 (12.5%)
<i>Body composition</i>	
Body fat, %	41.6 $\pm$ 6.3
Fat mass, kg	46.2 $\pm$ 13.2
Muscle mass, kg	61.1 $\pm$ 12.4
Metabolic age, years	58.2 $\pm$ 11.9

Note: Data are presented as mean $\pm$ standard deviation (SD) or n (%), as appropriate. Comorbidities and concomitant pharmacotherapy were determined from baseline clinical records. Comorbidity, medication, and lifestyle-management categories are not mutually exclusive; therefore, percentages within these sections may sum to >100%. Abbreviations: BMI, body mass index; NASCET, North American Symptomatic Carotid Endarterectomy Trial; SD, standard deviation.

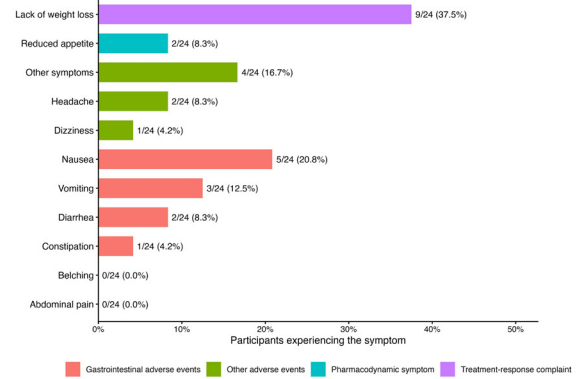
A. Data availability across study visits



B. Individual percentage weight change at Week 41 (N=16)



C. Patient-level incidence of treatment-emergent symptoms



D. Weekly prevalence of treatment-emergent symptoms

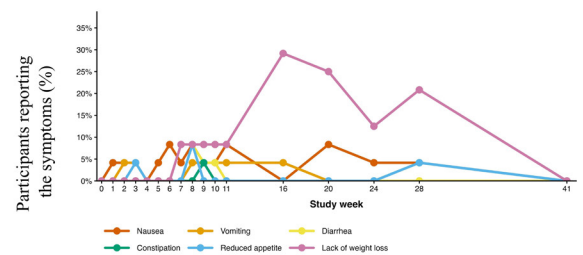


Figure 1 – Study overview, clinical efficacy, and treatment-emergent symptoms during tirzepatide therapy

(A) Data availability across scheduled study visits for each study variable. Cell shading represents the proportion of participants with available measurements at each visit, with the number and percentage of available observations shown within each cell. Imaging variables were assessed at baseline and Week 41 and were not included as repeated longitudinal outcomes. (B) Waterfall plot showing individual percentage change in body weight from baseline to Week 41 among participants with paired measurements (N=16). Dashed horizontal lines indicate clinically relevant weight-loss thresholds of 5%, 10%, 15%, and 20%. Bar colors indicate the corresponding weight-loss category. (C) Patient-level incidence of treatment-emergent symptoms, defined as the proportion of participants reporting each symptom at least once during follow-up. Symptoms are grouped as gastrointestinal adverse events, other adverse events, pharmacodynamic symptoms, or treatment-response complaints, as indicated by the color coding. Multiple symptoms could be reported by the same participant. (D) Visit-specific prevalence of selected treatment-emergent symptoms during follow-up. Percentages were calculated using the number of participants assessed at each visit as the denominator; therefore, denominators varied according to visit availability. Treatment-emergent symptoms were prospectively recorded at scheduled study visits using standardized case report forms; symptom severity was not formally graded. Lack of weight loss was classified as a treatment-response complaint rather than an adverse event. BMI, body mass index; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NASCET, North American Symptomatic Carotid Endarterectomy Trial.

right-skewed distributions: median CRP was 0.29 mg/L (IQR, 0.18-1.04), median IL-6 was 2.53 pg/mL (IQR, 1.50-4.20), and median NT-proBNP was 33.69 pg/mL (IQR, 18.37-63.70). Longitudinal follow-up was complete through Week 28 for all 24 participants. At the database cutoff of July 20, 2026, 16 participants (66.7%) had reached the Week-41 follow-up window and had paired baseline and Week-41 body-weight measurements. The remaining 8 participants (33.3%) had not yet reached Week 41 because of staggered enrollment. No participants had discontinued treatment or were lost to follow-up. Thus, the smaller sample size at Week 41 reflected administrative censoring related to the timing of the interim database cutoff rather than attrition. For outcomes other than

body weight, Week-41 data were available for 15-16 participants depending on the scheduled assessment and data availability (Figure 1A). Primary longitudinal mixed-effects analyses included all available repeated observations without imputation. Week-41 descriptive and complete-case analyses were restricted to participants with paired baseline and Week-41 measurements for the relevant outcome. All 24 participants initiated tirzepatide at 2.5 mg once weekly and subsequently underwent protocol-guided dose escalation. By Week 16, 22 participants (91.7%) had reached 10 mg, whereas two (8.3%) remained at 7.5 mg. At Week 28, 22 participants (91.7%) were receiving 10 mg, one (4.2%) was receiving 7.5 mg, and one (4.2%) was receiving 2.5 mg. Among

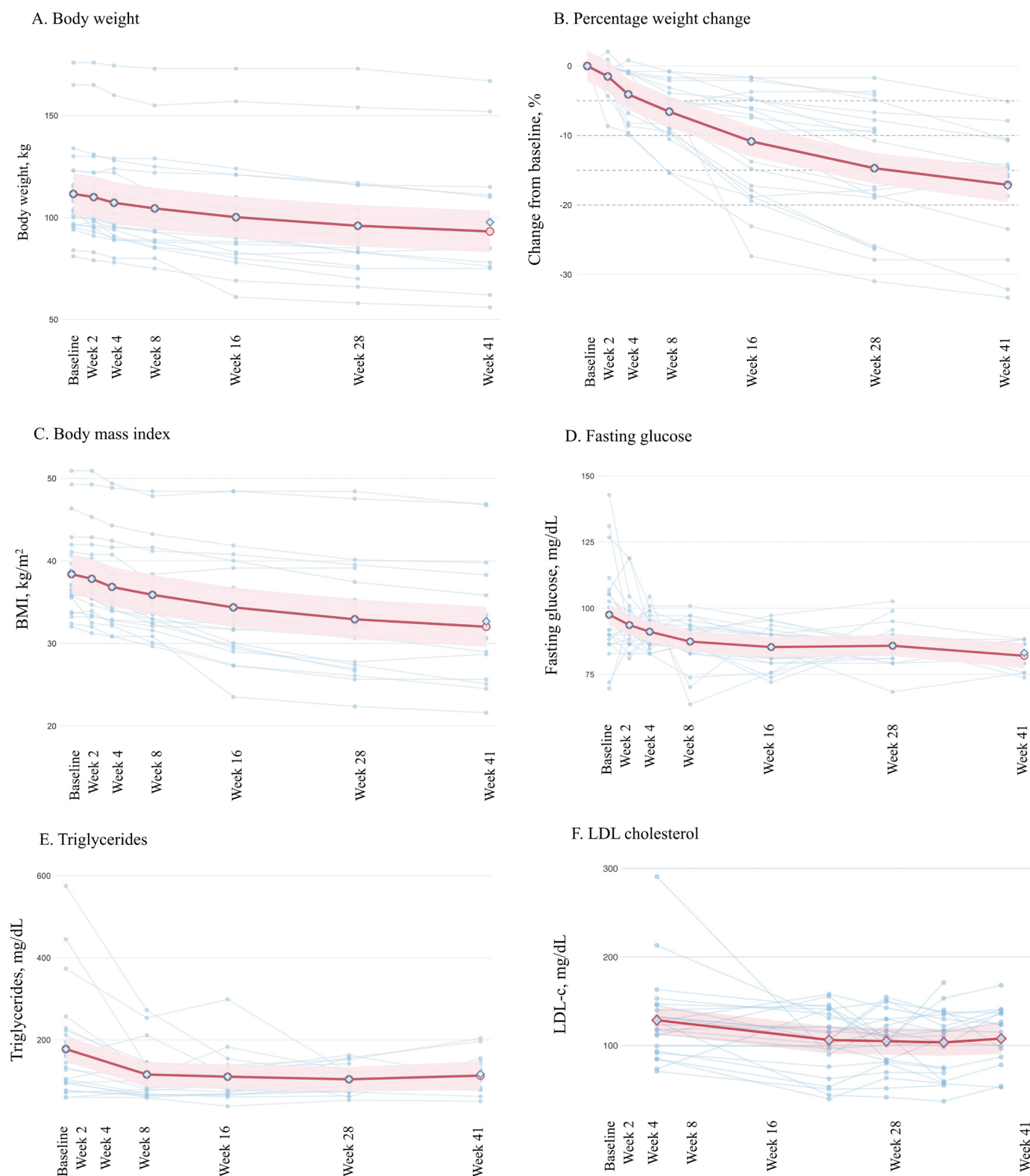


Figure 2 – Longitudinal changes in anthropometric and metabolic outcomes during tirzepatide therapy

(A) Body weight. (B) Percentage change in body weight from baseline. (C) Body mass index (BMI). (D) Fasting glucose. (E) Triglycerides. (F) Low-density lipoprotein cholesterol (LDL-C). Solid red lines represent model-estimated mean trajectories, with shaded areas indicating 95%CI. Individual participant trajectories are shown as light blue lines. Analyses were based on all available longitudinal observations using linear mixed-effects models; therefore, estimates account for repeated measurements and missing follow-up data under the missing-at-random assumption. Outcome-specific sample sizes varied across visits according to data availability.

the 16 participants with mature Week-41 follow-up, the final treatment dose recorded at Week 40 was 10 mg in 12 participants (75.0%), 7.5 mg in three (18.8%), and 2.5 mg in one (6.3%); Week 41 represented the end-of-treatment follow-up assessment rather than an additional treatment week. The maximum achieved

dose was 10 mg in 22 participants (91.7%) and 7.5 mg in two (8.3%). One participant underwent a documented dose reduction from 7.5 mg to 2.5 mg between Weeks 24 and 28. No treatment interruptions or discontinuations due to gastrointestinal adverse events were documented; however, the available data did not

Table 2 Observed values for primary and key secondary outcomes

Outcome	Baseline	Week 2	Week 4	Week 8	Week 16	Week 28	Week 41
Body weight, kg	111.6±22.4 (n=24)	110.0±22.9 (n=24)	107.2±23.1 (n=24)	104.5±23.0 (n=24)	100.2±25.4 (n=24)	96.0±25.8 (n=24)	97.7±29.4 (n=16)
Body weight change from baseline, %	-	-1.5±2.1 (n=24)	-4.1±3.0 (n=24)	-6.6±3.9 (n=24)	-10.9±7.3 (n=24)	-14.7±8.4 (n=24)	-17.2±8.1 (n=16)
BMI, kg/m ²	38.4±5.0 (n=24)	37.8±5.2 (n=24)	36.9±5.2 (n=24)	35.9±5.2 (n=24)	34.4±6.2 (n=24)	32.9±6.5 (n=24)	32.7±7.4 (n=16)
WC, cm	115.4±14.0 (n=24)	113.2±13.0 (n=24)	111.7±16.1 (n=24)	111.5±15.0 (n=24)	107.5±16.7 (n=24)	103.9±19.2 (n=24)	100.2±17.1 (n=15)
Fasting glucose, mg/dL	97.6±17.3 (n=24)	93.7±9.7 (n=24)	91.2±6.1 (n=24)	87.4±8.7 (n=24)	85.4±7.3 (n=24)	85.8±7.0 (n=24)	83.2±5.1 (n=16)
Triglycerides, mg/dL	139.1 [95.2-215.0] (n=24)	Not available	Not available	105.0 [73.5-131.6] (n=24)	110.2 [73.1-128.5] (n=24)	102.8 [75.7-122.3] (n=24)	109.6 [82.8-143.1] (n=16)

Note: Values are observed mean±SD or median [Q1-Q3], with available n in every cell. No imputation was performed.

permit definitive attribution of delayed dose escalation or dose reduction to specific adverse events. Estimated cumulative prescribed tirzepatide exposure through Week 28 was 209.6±9.9 mg (median 212.5 mg; range, 175.0–212.5 mg).

Observed longitudinal changes

Observed values demonstrated a progressive reduction in body weight throughout follow-up (Table 2, Figure 2). Mean body weight decreased from 111.6±22.4 kg at baseline to 97.7±29.4 kg at Week 41 among participants with available follow-up, corresponding to an observed mean body weight reduction of 17.2±8.1% from baseline.

Similarly, mean BMI decreased from 38.4±5.0 to 32.7±7.4 kg/m², while WC decreased from 115.4±14.0 to 100.2±17.1 cm. Progressive reductions in systolic and diastolic blood pressure were also observed over time.

Fasting glucose declined steadily from 97.6±17.3 mg/dL at baseline to 83.2±5.1 mg/dL at Week 41. Lipid concentrations generally decreased during follow-up. Median triglyceride concentrations declined from 139.1 mg/dL (IQR 95.2-215.0) at baseline to 109.6 mg/dL (IQR 82.8-143.2) at Week 41. Mean total cholesterol decreased from 197.0±57.8 mg/dL at baseline to 161.6±40.1 mg/dL at Week 28, before increasing to 181.1±39.6 mg/dL at Week 41. Similarly, mean LDL-C decreased from 128.5±46.8 mg/dL at baseline to 103.4±35.6 mg/dL at Week 28 and subsequently increased to 113.6±32.8 mg/dL at Week 41. Mean HDL-C showed a more modest reduction, from 53.0±9.8

mg/dL at baseline to 46.9±9.3 mg/dL at Week 28 and 48.4±14.6 mg/dL at Week 41. The number of available observations remained complete through Week 28 and decreased to 15–16 participants at Week 41.

Model-estimated longitudinal changes

Linear mixed-effects models demonstrated significant longitudinal improvements in the primary efficacy outcome and most key secondary outcomes (Table 3). The overall effect of visit was highly significant for percentage body weight change (F=57.6, p<0.001), body weight (F=70.8, p<0.001), body mass index (F=66.9, p<0.001), waist circumference (F=40.5, p<0.001), and fasting glucose (F=8.1, p<0.001). Significant longitudinal effects were also observed for total cholesterol (F=6.10, p<0.001), HDL cholesterol (F=3.83, p=0.006), LDL cholesterol (F=4.14, p=0.004), and triglycerides (F=7.30, p<0.001). The overall longitudinal effect was not statistically significant for systolic blood pressure (p=0.074).

Estimated percentage body weight reduction increased progressively throughout treatment. Compared with baseline, the reduction was not statistically significant at Week 2 (-1.5%, adjusted p=0.191), but became significant from Week 4 onwards (all adjusted p<0.001). By Week 41, the model-estimated reduction reached 17.1% (95% CI 14.5-19.7). Likewise, estimated body weight decreased by 18.4 kg (95% CI 15.9-20.9) at Week 41, with statistically significant reductions observed from Week 4 onwards.

Table 3 Model-estimated longitudinal changes in primary and key secondary outcomes

Domain	Outcome	Overall F statistic	Overall P value	First significant visit*	Week 41 estimated change from baseline (95% CI)
Weight response	Percentage body weight change	57.6	<0.001	Week 4	-17.1% (-19.7 to -14.5)
	Body weight	70.8	<0.001	Week 4	-18.4 kg (-20.9 to -15.9)
Anthropometry	Body mass index	66.9	<0.001	Week 4	-6.4 kg/m ² (-7.3 to -5.5)
	WC	40.5	<0.001	Week 4	-15.9 cm (-18.5 to -13.3)
Vital signs	SBP	2.0	0.074	Week 28	-9.4 mmHg (-16.8 to -2.1)
Glycemic profile	Fasting glucose	8.1	<0.001	Week 4	-15.6 mg/dL (-21.2 to -9.9)
	Total cholesterol	6.10	<0.001	Week 8	-20.8 mg/dL (-40.8 to -0.9)
Lipid profile	HDL cholesterol	3.83	0.006	Week 8	-4.9 mg/dL (-9.3 to -0.5)
	LDL cholesterol	4.14	0.004	Week 8	-20.8 mg/dL (-37.5 to -4.0)
	Triglycerides	7.30	<0.001	Week 8	-64.8 mg/dL (-101.2 to -28.3)

Note: *First post-baseline visit remaining statistically significant after Holm adjustment. Lipid estimates are presented as model-estimated absolute mean differences from baseline with 95% confidence intervals. P values for post-baseline comparisons with baseline were adjusted using the Holm method.

BMI and WC demonstrated marked longitudinal improvements throughout follow-up. Estimated BMI decreased by 6.4 kg/m² (95% CI 5.5-7.3), while WC decreased by 15.9 cm (95% CI 13.3-18.5) at Week 41. For both outcomes, statistically significant reductions were observed from Week 4 after Holm adjustment.

Systolic blood pressure showed a gradual numerical decline during treatment, reaching an estimated reduction of 9.4 mmHg (95% CI 2.1-16.8) at Week 41. Although several individual post-baseline comparisons reached nominal statistical significance, the overall longitudinal effect of visit was not statistically significant (p=0.074).

Fasting glucose declined progressively over time. Significant reductions became evident at Week 4 and persisted throughout follow-up, reaching 15.6 mg/dL (95% CI 9.9-21.2) below baseline at Week 41. The overall longitudinal effect of visit was statistically significant (p<0.001).

Significant longitudinal changes were observed across all evaluated lipid parameters. Total cholesterol decreased significantly from baseline at Week 8 (estimated mean difference, -33.5 mg/dL; Holm-adjusted p<0.001), with reductions maintained at Week 16 and Week 28. At Week 41, the estimated reduction was smaller but remained statistically significant (-20.8 mg/dL; adjusted p=0.041). LDL-C showed a similar pattern, with significant reductions from Week 8 onward. The largest estimated reduction was observed at Week 28 (-25.1 mg/dL; adjusted p=0.004), while LDL-C remained below baseline at Week 41 (-20.8 mg/dL; adjusted p=0.015). HDL-C decreased modestly during follow-up, with significant reductions at Week 8 (-6.6 mg/dL; adjusted p=0.004), Week 16 (-5.1 mg/dL; adjusted p=0.020), Week 28 (-6.1 mg/dL; adjusted p=0.007), and Week 41 (-4.9 mg/dL; adjusted p=0.028). Triglyceride concentrations also decreased significantly from Week 8 onward, with the largest estimated reduction at Week 28 (-73.7 mg/dL; adjusted p<0.001) and a sustained reduction at Week 41 (-64.8 mg/dL; adjusted p<0.001).

Clinically relevant weight-loss response

Clinically meaningful weight loss was already evident by Week 28 and became more pronounced among participants with mature Week-41 follow-up. At Week 28, mean percentage weight loss was 14.7±8.4%, corresponding to a mean reduction of 15.6±8.2 kg from baseline. A weight reduction of at least 5% was achieved by 20 of 24 participants (83.3%), while 15 of 24 (62.5%), 11 of 24 (45.8%), and 5 of 24 (20.8%) achieved reductions of at least 10%, 15%, and 20%, respectively.

Among the 16 participants with paired baseline and Week-41 measurements (Figure 1B), mean body weight decreased from 116.4±25.6 kg to 97.7±29.4 kg, corresponding to a mean reduction of 18.7±7.0 kg and a mean percentage weight loss of 17.2±8.1%. The median percentage weight loss was 15.1% (IQR, 13.3-19.9%). All 16 participants achieved at least 5% weight loss, 14 of 16 achieved at least 10% (87.5%), 8 of 16 achieved at least 15% (50.0%), and 4 of 16 achieved at least 20% (25.0%).

When participants were classified into mutually exclusive Week-41 response categories, none had less than 5% weight loss. Two participants (12.5%) achieved 5% to <10% weight loss, 6 (37.5%) achieved 10% to <15%, 4 (25.0%) achieved 15% to <20%, and 4 (25.0%) achieved at least 20% weight loss. These findings indicate that clinically meaningful weight reduction was observed in all participants with mature Week-41 follow-up, although the magnitude of response varied across the cohort.

Treatment-emergent symptoms, gastrointestinal tolerability, and their relationship with weight loss

Across the 24 participants, 15 (62.5%) reported at least one treatment-emergent adverse event, while 6 (25.0%) experienced at least one gastrointestinal adverse event. Nausea was the most frequent gastrointestinal event, occurring in 5 participants (20.8%), followed by vomiting in 3 (12.5%), diarrhea in 2 (8.3%), and constipation in 1 (4.2%). No participants reported abdominal pain or belching. Among non-gastrointestinal events, other symptoms were reported by 4 participants (16.7%), headache by 2 (8.3%), and dizziness by 1 (4.2%). Reduced appetite, considered an expected pharmacodynamic effect rather than a conventional adverse event, was reported by 2 participants (8.3%). Perceived lack of weight loss was the most frequently recorded treatment-response complaint, affecting 9 participants (37.5%) (Figure 1C). No serious adverse events were observed during the study period.

Weekly symptom profiles demonstrated that gastrointestinal adverse events were generally infrequent and intermittent throughout follow-up (Figure 1D). Nausea and vomiting occurred predominantly during the early and intermediate phases of treatment, with prevalence at individual visits generally remaining below 10%. Reduced appetite was uncommon and sporadic. In contrast, reports of perceived lack of weight loss became more frequent after treatment initiation, peaked around Week 16, and gradually declined thereafter.

Longitudinal mixed-effects logistic regression based on 360 post-baseline observations from 24 participants demonstrated no evidence that increasing tirzepatide dose or treatment duration was associated with a higher likelihood of aggregated gastrointestinal or overall adverse-event outcomes (Table 4). For any gastrointestinal adverse event, the odds ratio per 2.5-mg dose increase was 1.61 (p=0.315), while the odds ratio per four-week increase in treatment duration was 0.83 (p=0.479). Likewise, neither dose nor treatment duration was associated with the occurrence of any adverse event (dose: OR, 1.21; p=0.627; time: OR, 0.99; p=0.944). Individual gastrointestinal symptoms were infrequent and were therefore summarized descriptively rather than evaluated using symptom-specific regression models.

Sensitivity analyses using generalized estimating equations produced consistent results, with no significant associations

Table 4 Treatment-emergent symptoms and longitudinal safety analyses during tirzepatide therapy (N=24)

Outcome	Patients n (%)	Mixed-effects model		GEE	
		OR (95% CI)	P value	OR (95% CI)	P value
Any adverse event	15 (62.5)	1.21 (0.57-2.57)	0.627	1.12 (0.58-2.20)	0.732
Any GI adverse event	6 (25.0)	1.61 (0.64-4.06)	0.315	1.36 (0.57-3.28)	0.489
Lack of weight loss†	9 (37.5)	18.22 (3.50-94.87)	<0.001	4.38 (1.53-12.56)	0.006

Note: Odds ratios represent the change in odds per 2.5-mg increase in tirzepatide dose. Analyses were based on 360 scheduled post-baseline observations from 24 participants (15 assessments per participant at Weeks 1–11, 16, 20, 24, and 28). Individual gastrointestinal symptoms were infrequent and were therefore summarized descriptively rather than evaluated using symptom-specific regression models. †Lack of weight loss was considered a treatment-response complaint rather than an adverse event. OR, odds ratio; CI, confidence interval; GEE, generalized estimating equation.

between tirzepatide dose or treatment duration and the aggregated gastrointestinal or overall adverse-event outcomes. The only significant finding involved perceived lack of weight loss, which demonstrated a positive association with increasing dose in both the mixed-effects model (OR, 18.22; $p<0.001$) and the GEE analysis (OR, 4.38; $p=0.006$). As this variable represents a subjective assessment of treatment response rather than a treatment-emergent adverse event, it was interpreted separately from the safety analyses.

To explore whether gastrointestinal symptoms influenced treatment efficacy, longitudinal mixed-effects models evaluated the relationship between symptom occurrence and percentage weight loss (Table 5). Weight loss progressed significantly throughout follow-up, with an adjusted reduction of 1.61 percentage points per four treatment weeks ($p<0.001$). However, neither the presence of any concurrent gastrointestinal symptom (adjusted mean difference, -0.08 percentage points; $p=0.964$) nor increasing gastrointestinal symptom burden (0.06 percentage points per additional symptom; $p=0.960$) was associated with greater weight loss after adjustment for treatment duration.

Table 5 Longitudinal associations between gastrointestinal symptoms, weight loss, and gastrointestinal symptom burden during tirzepatide therapy

Outcome	Predictor	Effect estimate (95% CI)	P value
Percentage weight change from baseline	Treatment duration (per 4 weeks)	-1.61 percentage points (-1.83 to -1.39)	<0.001
	Any concurrent gastrointestinal symptom	-0.08 percentage points (-3.51 to 3.36)	0.964
	GI symptom burden (per additional symptom)	0.06 percentage points (-2.31 to 2.43)	0.960
Number of concurrent GI symptoms	Tirzepatide dose (per 2.5-mg increase)	Rate ratio 1.62 (0.82 to 3.17)	0.163
	Treatment duration (per 4 weeks)	Rate ratio 0.80 (0.54 to 1.19)	0.268
Higher GI symptom burden category	Tirzepatide dose (per 2.5-mg increase)	Common OR 1.76 (0.70 to 4.43)	0.228
	Treatment duration (per 4 weeks)	Common OR 0.78 (0.47 to 1.29)	0.332

Note: Ordinal mixed-effects model comparing higher gastrointestinal symptom burden categories (0 symptoms, 1 symptom, ≥ 2 symptoms).

Similarly, mixed-effects count and ordinal regression models demonstrated no significant association between tirzepatide dose or treatment duration and overall gastrointestinal symptom burden. In the count model, the rate ratio per 2.5-mg dose increase was 1.62 ($p=0.163$), while the rate ratio per four-week increase in treatment duration was 0.80 ($p=0.268$). Comparable results were obtained using the ordinal mixed model (dose: common OR, 1.76; $p=0.228$; time: common OR, 0.78; $p=0.332$).

An exploratory participant-level analysis suggested that participants who experienced at least one gastrointestinal symptom during follow-up exhibited a steeper estimated weight-loss trajectory than those without gastrointestinal symptoms (interaction estimate, -0.84 percentage points per four weeks; $p<0.001$). Because gastrointestinal-symptom status was defined using post-baseline information, this analysis was considered exploratory and should not be interpreted as evidence that gastrointestinal symptoms mediated greater weight loss.

Overall, these findings indicate that treatment-emergent gastrointestinal symptoms were reported in a minority of

participants and were generally intermittent during follow-up. No statistically significant associations were detected between gastrointestinal symptom occurrence or burden and longitudinal weight-loss outcomes. However, given the small number of gastrointestinal events and limited sample size, these analyses should be considered exploratory and do not exclude a possible relationship between gastrointestinal tolerability and treatment response. Because symptom severity was not formally graded, these findings should be interpreted as describing the frequency and temporal pattern of reported gastrointestinal symptoms rather than their clinical severity.

Complete-case sensitivity analyses

Complete-case analyses were performed in participants with paired baseline and Week 41 measurements ($n=15-16$ depending on the outcome) to assess the robustness of the primary longitudinal findings (Table 6). The direction and magnitude of the observed changes were consistent with the primary mixed-effects analyses.

Significant improvements were observed across all major anthropometric measures. Body weight (Holm-adjusted $p=0.012$), BMI (adjusted $p<0.001$), WC (adjusted $p=0.018$), and HC (adjusted $p<0.001$) all decreased significantly in paired analyses and remained significant after Holm correction. In contrast, the waist-to-hip ratio did not change significantly after multiple-comparison adjustment.

Both systolic and diastolic blood pressure showed numerical reductions of approximately 11 mmHg between baseline and Week 41. Nominal statistical significance was observed in paired analyses; however, these differences did not remain significant after Holm correction, consistent with the absence of a significant overall longitudinal effect in the mixed-effects models. Fasting glucose decreased by 19.9 ± 21.2 mg/dL, remaining statistically significant after correction for multiple comparisons (Holm-adjusted $p=0.048$).

In the complete-case analysis, triglycerides decreased by 64.4 ± 95.0 mg/dL from baseline to Week 41 (raw $p=0.016$), whereas LDL-C showed a smaller nominal reduction (median change, -8.5 mg/dL; raw $p=0.049$). Total cholesterol and HDL-C did not differ significantly between baseline and Week 41 (raw $p=0.063$ and $p=0.089$, respectively). None of the four lipid outcomes remained statistically significant after Holm correction for multiple comparisons.

C-reactive protein decreased significantly from baseline to Week 41 and remained significant after Holm adjustment (Holm-adjusted $p=0.048$). IL-6 did not change significantly. NT-proBNP demonstrated a nominal increase during follow-up, although statistical significance was not retained after multiple-comparison adjustment.

Among biochemical markers, ALT, AST, and amylase demonstrated significant nominal changes; however, only the reduction in AST remained significant after Holm correction (Holm-adjusted $p=0.020$). No significant changes were observed in alkaline phosphatase, total protein, albumin, bilirubin, creatinine, or estimated glomerular filtration rate.

Exploratory paired analyses showed no statistically significant baseline-to-Week-41 changes in carotid stenosis category, atherosclerosis grade, hepatic steatosis grade, or hepatic fibrosis grade after correction for multiple comparisons (Table 6).

In contrast, body composition improved substantially. Body fat percentage decreased by 6.5 ± 4.5 percentage points, fat mass by 12.7 ± 5.8 kg, and muscle mass by 4.7 ± 2.3 kg (all Holm-adjusted $p\leq 0.002$). Metabolic age demonstrated a numerical reduction but did not reach statistical significance after adjustment for multiple testing.

Table 6

Complete-case sensitivity analyses of baseline-to-Week 41 changes

Outcome	Paired n	Baseline	Week 41	Change	95% CI / IQR	P-Value	Holm-adjusted P
Body weight, kg	16	112.5 [102.5-124.8]	94.0 [77.5-110.2]	-18.0 [-19.0 to -15.2]	-19.0 to -15.5	<0.001	0.012
BMI, kg/mw	16	39.1±5.7	32.7±7.4	-6.4±2.5	-7.8 to -5.1	<0.001	<0.001
WC, cm	15	115.0 [107.5-128.0]	100.0 [86.0-110.5]	-14.0 [-23.5 to -12.0]	-24.0 to -12.0	<0.001	0.018
HC, cm	15	123.7±8.7	107.7±8.9	-16.1±9.0	-21.0 to -11.1	<0.001	<0.001
Waist-to-hip ratio	15	0.95±0.10	0.91±0.12	-0.04±0.09	-0.09 to 0.01	0.088	1.000
SBP, mmHg	16	124.4±17.1	113.4±7.5	-10.9±14.6	-18.7 to -3.1	0.009	0.201
DBP, mmHg	16	81.9±13.3	70.6±7.7	-11.2±13.6	-18.5 to -4.0	0.005	0.110
HR, beats/min	16	76.0±13.4	69.2±6.0	-6.8±11.5	-13.0 to -0.7	0.032	0.542
Fasting glucose, mg/dL	16	103.1±18.4	83.2±5.1	-19.9±21.2	-31.2 to -8.6	0.002	0.048
Total cholesterol, mg/dL	16	196.6 [190.8-216.4]	188.9 [155.5-210.8]	-8.1 [-31.6 to 4.6]	-22.6 to 4.1	0.063	0.877
HDL cholesterol, mg/dL	16	54.4±10.8	48.4±14.6	-6.0±13.2	-13.0 to 1.0	0.089	1.000
LDL cholesterol, mg/dL	16	129.5 [116.6-145.7]	123.7 [94.2-137.2]	-8.5 [-37.4 to -4.4]	-32.0 to -4.7	0.049	0.791
Triglycerides, mg/dL	16	181.4±109.2	117.0±44.0	-64.4±95.0	-115.0 to -13.8	0.016	0.321
C-reactive protein, mg/L	16	0.46 [0.17-1.40]	0.17 [0.07-0.81]	-0.29 [-0.56 to -0.06]	-0.53 to -0.06	0.002	0.048
Interleukin-6, pg/mL	15	4.19±2.79	4.86±1.78	0.67±3.04	-1.02 to 2.35	0.409	1.000
NT-proBNP, pg/mL	16	30.9 [18.3-57.8]	41.3 [30.4-130.9]	23.0 [-3.5 to 66.7]	-2.1 to 54.2	0.017	0.330
ALT, U/L	16	28.8 [21.0-45.7]	21.1 [13.7-30.7]	-6.6 [-16.8 to -1.2]	-23.1 to -2.4	0.013	0.274
AST, U/L	16	25.2 [19.6-34.1]	18.1 [14.7-21.5]	-6.1 [-13.5 to -1.6]	-14.0 to -1.7	<0.001	0.020
Alkaline phosphatase, U/L	16	93.8±24.3	87.1±23.3	-6.7±18.8	-16.7 to 3.3	0.174	1.000
Amylase, U/L	16	22.9 [17.1-28.3]	26.1 [22.7-38.0]	3.6 [0.8-6.5]	1.1 to 6.5	0.017	0.330
Total protein	16	7.46±0.52	7.21±0.35	-0.25±0.54	-0.54 to 0.04	0.082	1.000
Albumin	16	4.41±0.33	4.35±0.23	-0.06±0.26	-0.20 to 0.09	0.413	1.000
Bilirubin	16	0.52 [0.47-0.79]	0.58 [0.50-0.73]	0.04 [-0.03 to 0.18]	-0.05 to 0.21	0.233	1.000
Creatinine	16	0.82 [0.71-0.90]	0.84 [0.70-1.03]	0.02 [-0.03 to 0.05]	-0.03 to 0.05	0.187	1.000
eGFR, mL/min/1.73 m ²	16	106.6 [102.5-113.5]	107.0 [98.2-114.3]	0.6 [-4.2 to 2.2]	-4.2 to 2.1	0.691	1.000
Carotid stenosis category	16	0.0 [0.0 to 1.0]	0.0 [0.0 to 1.0]	0.0 [-1.0 to 0.0]	-1.0 to 0.0	0.317	1.000
Atherosclerosis grade	16	0.0 [0.0 to 1.0]	1.0 [0.0 to 1.0]	0.0 [0.0 to 1.0]	0.0 to 1.0	0.763	1.000
Hepatic steatosis grade	15	3.0 [1.5 to 3.0]	1.0 [0.0 to 3.0]	0.0 [-2.0 to 0.0]	-2.0 to 0.0	0.102	1.000
Hepatic fibrosis grade	15	1.0 [0.0 to 2.0]	0.0 [0.0 to 1.5]	0.0 [-1.0 to 0.0]	-1.0 to 0.0	0.096	1.000
Body fat, %	15	40.9±6.5	34.4±8.6	-6.5±4.5	-9.0 to -4.0	<0.001	0.002
Fat mass, kg	15	45.7±12.2	33.1±14.2	-12.7±5.8	-15.9 to -9.5	<0.001	<0.001
Muscle mass, kg	15	62.4±12.6	57.7±13.4	-4.7±2.3	-6.0 to -3.5	<0.001	<0.001
Metabolic age, years	15	58.0 [49.5-63.0]	47.0 [41.0-58.0]	0.0 [-9.0 to 1.0]	-6.0 to 1.0	0.057	0.861

Note. P values were obtained using paired t tests or Wilcoxon signed-rank tests, as appropriate. Ordinal outcomes are presented as median [IQR]. Nominal P values are shown together with Holm-adjusted P values accounting for multiple comparisons across the complete-case outcomes.

Overall, the complete-case analyses were generally consistent with the principal findings of the mixed-effects models, demonstrating substantial improvements in body weight, adiposity, glycemic control, and body composition among participants with mature Week-41 follow-up.

Exploratory associations with Week-41 weight loss

Exploratory analyses among participants with mature Week-41 follow-up suggested an association between greater baseline WC and a smaller percentage weight loss at Week 41. Each 1-SD higher baseline WC (approximately 14.8 cm) was associated with 5.10 percentage points less weight loss (95% CI, 2.60–7.59; nominal $p<0.001$), and the association remained statistically significant after Benjamini-Hochberg correction (adjusted $p=0.027$). However, given the small number of participants with Week-41 data, this analysis was considered hypothesis-generating and should not be interpreted as establishing an independent predictor of treatment response. Higher baseline BMI, waist-to-hip ratio, fat mass, muscle mass, and fibrosis grade 3 showed nominal associations with smaller weight loss, but these associations did not remain significant after correction for multiple comparisons. Baseline inflammatory and cardiometabolic biomarkers, including IL-6, CRP, HbA1c,

fasting glucose, and lipid measures, were not significantly associated with Week-41 weight loss.

Discussion

In this prospective longitudinal interventional cohort of adults with obesity and concomitant HFpEF treated with tirzepatide according to a predefined treatment protocol, we observed four principal findings. First, among the 16 participants with mature Week-41 follow-up, mean weight reduction was 17.2%, and all achieved $\geq 5\%$ weight loss. Second, treatment was accompanied by favorable changes in anthropometric and metabolic measures, CRP, and body composition. Third, gastrointestinal symptoms were reported in a minority of participants and were not significantly associated with treatment duration, current tirzepatide dose, or concurrent longitudinal weight-loss outcomes. Collectively, these findings complement evidence from randomized clinical trials by providing prospective longitudinal treatment data from a Central Asian population that remains underrepresented in the published tirzepatide literature.

Weight-loss efficacy

The magnitude of weight loss observed in our cohort is consistent with the efficacy reported in the SURMOUNT clinical trial program. Participants with mature Week-41 follow-up achieved a mean weight reduction of 17.2%, with all 16 participants attaining $\geq 5\%$ weight loss and 14 of 16 attaining $\geq 10\%$ weight loss. In SURMOUNT-1, participants receiving the highest tirzepatide dose achieved a mean weight reduction of 20.9% after 72 weeks, with 89% achieving $\geq 5\%$ and 57% achieving $\geq 20\%$ weight loss [9]. Similarly, SURMOUNT-3 and SURMOUNT-4 demonstrated sustained and progressive weight reduction with continued treatment, whereas treatment discontinuation resulted in substantial weight regain, emphasizing the importance of ongoing therapy [11,12]. Although direct comparisons should be interpreted cautiously because of differences in follow-up duration, participant characteristics, and dose titration, our findings suggest that substantial weight loss can occur during the first year of tirzepatide treatment under the protocol used in the present cohort.

Our results are also broadly consistent with emerging real-world studies reporting mean weight reductions of approximately 13-18% during the first year of tirzepatide therapy [13,14]. Differences in study design, population characteristics, treatment persistence, dose-escalation strategies, and follow-up duration limit direct comparisons across randomized trials, observational studies, and the present interventional cohort. The favorable outcomes observed in our cohort may partly reflect prospective follow-up with scheduled assessments that facilitated individualized dose optimization and treatment adherence. Clinically, the high proportion of participants achieving weight loss exceeding 10% and 15% is important because these thresholds are associated with meaningful improvements in obesity-related complications, including glycemic control, cardiometabolic risk, metabolic dysfunction-associated steatotic liver disease, and quality of life [2,3].

Cardiometabolic improvements

Beyond weight reduction, tirzepatide treatment was associated with broad improvements in cardiometabolic health. Fasting glucose declined progressively despite near-normal baseline HbA1c concentrations, suggesting that the metabolic effects of tirzepatide extend beyond patients with overt dysglycemia. This observation is consistent with the complementary actions of dual GIP/GLP-1 receptor agonism on insulin sensitivity, glucose-dependent insulin secretion, glucagon suppression, and hepatic glucose production and agrees with findings from the SURMOUNT program [9,10,15,16].

Lipid parameters demonstrated a heterogeneous but predominantly favorable longitudinal pattern. Total cholesterol, LDL-C, and triglycerides decreased significantly from Week 8 onward, with the largest reductions generally observed during the intermediate treatment period and partial attenuation of the reductions in total and LDL cholesterol by Week 41. In contrast, HDL-C showed a modest but statistically significant decrease during follow-up, with partial recovery toward baseline by Week 41. Thus, the lipid response was characterized primarily by reductions in atherogenic lipid measures and triglycerides rather than a uniform improvement across all lipid fractions. Similar reductions in triglycerides and LDL-C have been reported in randomized tirzepatide trials [8-10,17]. However, given the small single-arm cohort and the use of concomitant lipid-lowering therapy in a substantial proportion of participants, the observed lipid changes cannot be attributed exclusively to tirzepatide.

We also observed a significant reduction in CRP, supporting the concept that sustained weight loss attenuates obesity-related systemic inflammation. This finding is consistent with evidence from lifestyle and pharmacological weight-loss interventions demonstrating that CRP decreases in parallel with improvements in adiposity and metabolic health [13,18,19]. In contrast, IL-6 remained unchanged, which is biologically plausible given its multiple tissue sources and substantial biological variability, particularly in relatively small cohorts [20]. Accordingly, CRP appears to represent a more robust marker of the anti-inflammatory effects of tirzepatide than individual circulating cytokines [19].

Body composition analyses demonstrated that weight loss was primarily driven by reductions in adipose tissue, with smaller decreases in skeletal muscle mass. This pattern closely resembles findings from the SURMOUNT-1 body composition substudy, which showed that approximately three-quarters of tirzepatide-induced weight loss resulted from fat mass reduction and one-quarter from lean mass loss [21]. Similar body composition changes occur with lifestyle, pharmacological, and bariatric weight-loss interventions and likely represent physiological adaptation rather than treatment-induced muscle impairment [22]. Nevertheless, preserving skeletal muscle remains an important therapeutic goal, supporting current recommendations to combine incretin-based pharmacotherapy with adequate dietary protein intake and resistance exercise [23].

Gastrointestinal tolerability

Gastrointestinal tolerability is a key determinant of long-term adherence to incretin-based therapies. In our cohort, gastrointestinal symptoms were reported in a minority of participants and were generally intermittent during follow-up, with nausea and vomiting being the most frequently reported symptoms. Symptom prevalence remained low throughout follow-up and did not increase over time. Because symptom severity was not formally graded, our findings characterize the frequency and temporal pattern of reported gastrointestinal symptoms rather than their clinical severity. In the SURMOUNT trials, gastrointestinal adverse events were generally mild to moderate in severity, occurred predominantly during dose escalation, and rarely led to treatment discontinuation [9,12]. Similar patterns of gastrointestinal adverse events have been reported in real-world studies [13].

A notable strength of our study was the prospective longitudinal evaluation of gastrointestinal symptom burden. Mixed-effects and generalized estimating equation analyses did not detect statistically significant associations between symptom burden and tirzepatide dose, treatment duration, or weight-loss trajectory. However, given the small number of gastrointestinal events and the limited sample size, these findings should be interpreted cautiously and do not exclude a possible relationship between gastrointestinal tolerability and treatment response. From a mechanistic perspective, the weight-lowering effects of tirzepatide are mediated through integrated neuroendocrine mechanisms involving appetite regulation, satiety, gastric emptying, and energy balance [7,24,25], suggesting that persistent gastrointestinal symptoms are not necessarily required for its therapeutic effects. Nevertheless, the present cohort was not sufficiently powered to establish whether the presence or absence of gastrointestinal symptoms influences the magnitude of weight-loss response, and this relationship warrants evaluation in larger prospective cohorts.

Exploratory predictors of weight-loss response

Exploratory analyses identified baseline waist circumference as the only clinical characteristic associated with a smaller percentage weight-loss response after adjustment for cumulative tirzepatide exposure. Although this finding should be interpreted cautiously, it is biologically plausible because waist circumference reflects visceral adiposity, which is closely linked to insulin resistance, adipose tissue dysfunction, and metabolic heterogeneity [26,27]. Individual variability in response to incretin-based therapy is likely influenced by multiple biological pathways, including insulin sensitivity, appetite regulation, and energy expenditure [28]. No significant associations were observed for baseline glycemic, lipid, or inflammatory biomarkers after correction for multiple testing, suggesting that routinely available clinical variables alone have limited predictive value. Given the exploratory design, small number of participants with mature Week-41 follow-up, and evaluation of multiple candidate predictors, the observed association between greater baseline WC and smaller percentage weight loss should be considered hypothesis-generating. The estimate may be susceptible to model instability and should not be interpreted as establishing the clinical predictive value of baseline WC. Confirmation in larger, adequately powered prospective cohorts is required.

Clinical implications

The present findings have several potential clinical implications for the management of adults with obesity. First, within the present prospectively treated cohort, tirzepatide was associated with clinically meaningful weight loss approaching 15-20% during the first year of treatment, accompanied by favorable changes in cardiometabolic risk factors and body composition. Second, treatment-emergent gastrointestinal symptoms were reported in a minority of participants and were generally intermittent during follow-up. Gastrointestinal symptom occurrence was not significantly associated with increasing tirzepatide dose or treatment duration and was not associated with longitudinal weight-loss outcomes. Because symptom severity was not formally graded, these findings describe the frequency and temporal pattern of reported gastrointestinal symptoms rather than their clinical severity. Second, treatment-emergent gastrointestinal symptoms were reported in a minority of participants and were generally intermittent during follow-up. No statistically significant associations were detected between gastrointestinal symptom occurrence and tirzepatide dose, treatment duration, or longitudinal weight-loss outcomes. However, given the small number of gastrointestinal events, these findings should be interpreted cautiously and do not establish that gastrointestinal symptoms are unrelated to treatment response. Because symptom severity was not formally graded, these findings primarily describe the frequency and temporal pattern of reported gastrointestinal symptoms rather than their clinical severity. Third, our findings suggest that serial monitoring of anthropometric measures, metabolic biomarkers, and treatment-emergent symptoms throughout therapy may facilitate timely assessment of treatment response and individualized dose optimization. Such longitudinal follow-up may be particularly valuable in settings where region-specific prospective evidence remains limited and the clinical implementation of incretin-based therapies is expanding. In this context, prospective longitudinal data from Central Asia complement evidence from randomized clinical trials and contribute to the growing body of region-specific evidence on incretin-based obesity treatment [29,30].

Strengths and Limitations

This study has several important strengths. Its prospective design with repeated standardized assessments allowed comprehensive evaluation of longitudinal changes in anthropometric measures, metabolic biomarkers, inflammatory markers, body composition, and gastrointestinal tolerability throughout the 40-week treatment period and at the Week-41 assessment. The use of linear mixed-effects models enabled efficient analysis of repeated measurements while accounting for within-participant correlation and incomplete follow-up. Complete-case analyses were generally directionally consistent with the primary longitudinal findings, although several secondary outcomes, particularly lipid parameters, did not remain significant after correction for multiple comparisons. In addition, our prospective longitudinal assessment of gastrointestinal symptom burden and exploratory analyses of predictors of weight-loss response provided additional information beyond endpoint-based assessments of treatment response. To our knowledge, this represents one of the first prospective longitudinal cohorts evaluating the effectiveness and tolerability of tirzepatide in adults with obesity and concomitant HFpEF from Kazakhstan and the Central Asian region. Importantly, all participants in the present UMC cohort had concomitant HFpEF as required by the parent study protocol. Accordingly, the cohort should not be considered representative of an unselected population of adults with obesity, and the magnitude and pattern of treatment response observed here may not be directly generalizable to individuals with obesity without HFpEF. Mature Week-41 follow-up was available for only 16 of 24 participants; therefore, the Week-41 weight-loss estimates and categorical response rates are based on this subgroup and may be susceptible to selection bias, even though incomplete Week-41 follow-up primarily reflected staggered enrollment and the administrative data cutoff rather than treatment discontinuation or loss to follow-up. Body composition measurements were performed in a limited subgroup, and the absence of a control group precludes causal inference. Furthermore, although tirzepatide treatment followed a prospectively defined dose-escalation protocol, maintenance dosing was individualized according to tolerability and clinical response. In addition, 41.7% of participants were receiving statin therapy at baseline, and longitudinal changes in lipid-lowering therapy were not systematically captured. Therefore, the independent contribution of concomitant lipid-lowering pharmacotherapy to the observed changes in lipid parameters cannot be determined. The broader study protocol included a standard-therapy comparison group; however, the present preliminary analysis was restricted to the tirzepatide-treated cohort and therefore does not include comparative analyses between treatment groups. Consequently, the present findings should be interpreted as within-group longitudinal changes, and comparative effectiveness or causal treatment effects cannot be established from this preliminary report.

Conclusion

In this prospective longitudinal interventional cohort of adults with obesity and concomitant HFpEF, tirzepatide treatment was associated with substantial and sustained weight loss, accompanied by favorable longitudinal changes in cardiometabolic parameters, selected markers of systemic inflammation, and body composition. Gastrointestinal symptoms were reported in a minority of participants, and no statistically significant associations with treatment duration, dose escalation, or weight-loss trajectory were detected; however, the small

number of gastrointestinal events and absence of formal severity grading limit definitive conclusions regarding gastrointestinal tolerability and its relationship with treatment response. Repeated longitudinal assessments further demonstrated the value of prospective monitoring for characterizing treatment response beyond single endpoint evaluations. Overall, these findings provide preliminary prospective longitudinal data on tirzepatide treatment in adults with obesity and HFpEF from Kazakhstan and the Central Asian region and complement the predominantly trial-based evidence available from other populations. Larger multicenter prospective studies, including more diverse obesity populations with and without HFpEF, are warranted to confirm these preliminary observations and further define long-term effectiveness, safety, and predictors of response.

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