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ORIGINAL RESEARCH

Persistence-Dependent Effectiveness of Tirzepatide on the Cardio-Metabolic-Kidney Syndrome Outcomes in Obesity: Real-World Evidence from the United Arab Emirates

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ABSTRACT

Introduction: Tirzepatide has been associated with significant reductions in body weight in randomized clinical trials. However, real-world evidence evaluating the multisystemic effects of tirzepatide across the cardio-metabolic-kidney (CKM) continuum remains limited. The aim of this study was to assess the real-world persistence-driven cumulative benefits of tirzepatide beyond weight reduction in adults with obesity but without type 2 diabetes mellitus (T2DM).

Methods: This single-center observational cohort study evaluated in the United Arab Emirates adults with obesity (body mass index [BMI] ≥ 30 kg/m^2) treated with tirzepatide. Participants were stratified by treatment persistence: ≤ 1 year (short-term) and > 1 year (long-term). Anthropometric, glycemic, lipid, hepatic, and renal outcomes were assessed at baseline and follow-up.

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Results: One hundred participants (25 women; mean age 37.6 ± 10.0 years; baseline BMI 35.0 [33.0–39.0] kg/m^2) were included. Median weight reduction was − 8.1% in the short-term group and − 22.6% in the long-term group ($p < 0.001$). 62% of long-term treated individuals achieved > 15% weight loss versus 20% among short-term users. Significant between-group differences were observed in BMI (− 8.3% vs. − 19.1%), waist circumference (− 4.0% vs. − 9.2%), and glycated hemoglobin (HbA1c) (− 5.0% vs. − 7.2%). Total cholesterol decreased by − 10.1% vs. − 18.7% ($p = 0.005$), low-density lipoprotein cholesterol (LDL-C) by − 9.6% vs. − 30.5% ($p < 0.001$), and triglycerides by − 11.2% vs. − 32.5% ($p < 0.001$). Liver enzymes, aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) declined by − 11.3% and − 13.2%, respectively, in long term group with no significant improvement in short term group (between-groups p values for both liver enzymes < 0.05). Serum creatinine declined significantly in the long-term group (− 6.6%, $p < 0.001$), estimated glomerular filtration rate (eGFR) increasing by + 3.2% ($p = 0.001$), and blood urea nitrogen (BUN) decreasing by − 7.8% ($p = 0.006$) while microalbuminuria showed no meaningful changes. Weight loss correlated with improvements in LDL-C, triglycerides, and SGOT, and inversely with high-density lipoprotein cholesterol (HDL-C) changes.

Conclusions: Tirzepatide showed greater cumulative benefits across CKM syndrome outcomes during the second treatment year, highlighting the need to overcome adherence barriers in real-world settings.

Keywords: Tirzepatide; Treatment; Obesity; Cardio-metabolic-kidney syndrome; Real-world evidence

Key Summary Points

Why carry out this study?

To assess the real-world persistence-dependent effects of tirzepatide beyond weight reduction in adults with obesity but without T2DM.

What was the hypothesis of the study?

We hypothesized that tirzepatide's benefits in adults with obesity were stronger with a longer duration of treatment. Therefore patients were stratified by treatment persistence.

What was learned from the study?

Tirzepatide showed cumulative benefits across cardio-metabolic-kidney syndrome outcomes when administered in both short- and long-term.

Yet, we found greater tirzepatide benefits during the second treatment year.

We therefore highlight the need to overcome adherence barriers in real-world settings.

INTRODUCTION

Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptor agonist, is the most potent pharmacologic therapy currently approved for chronic obesity management, demonstrating superior weight-loss efficacy compared with semaglutide, the single GLP-1 receptor agonist [1]. Obesity is commonly associated with multisystemic complications, conceptualized as cardio-metabolic-kidney (CKM) syndrome, encompassing metabolic, hepatic, and renal dysfunctions.

In the pivotal SURMOUNT-1 trial, mean body weight reduction reached − 20.9% after 72 weeks with tirzepatide 15 mg, and this effect was sustained during its 36-week

open-label extension phase [2, 3]. Prolonged tirzepatide treatment produced durable cardiometabolic benefits, including reductions in waist circumference (– 17 to 19%), systolic blood pressure (– 6 to 8 mmHg), and glycated hemoglobin (HbA1c) (– 0.6% to – 0.9%). Hepatic biomarkers improved substantially, with alanine and aspartate aminotransferase levels decreasing by ~ 20–30%. Adherence and persistence within SURMOUNT trials were high, with discontinuation due to adverse events remaining below 7% over up to 88 weeks of treatment [4].

In contrast to the 83–88% adherence observed in clinical trials over 66–88 weeks, real-world adherence to anti-obesity pharmacotherapy declines to 33–50% at 1 year and approximately 15% at 2 years [5]. In a large retrospective real-world U.S. cohort derived from Optum Market Clarity database, which integrates electronic health records and insurance claims, only about 55% of adults with obesity without type 2 diabetes mellitus (T2DM). remained persistent on tirzepatide treatment at 6 months [6]. In another real-world U.S. study using Veradigm's Network electronic health record database, just over half of adults with obesity without T2DM (54%) remained persistent on tirzepatide after 6 months [7].

Real world Evidence on persistence-dependent multisystemic outcomes of anti-obesity pharmacotherapy, beyond weight reduction, encompassing CKM syndrome's domains, remains scarce. Therefore, we aimed to evaluate the real-world effectiveness of tirzepatide in adults with obesity without T2DM, focusing on the relevant components of the CKM syndrome among participants with short-term (≤ 1 year) versus long-term (> 1 year) treatment persistence.

METHODS

Study Design and Setting

This was a longitudinal observational cohort study conducted at a tertiary high-volume metabolic and obesity management center in UAE (RAK Medical and Health Sciences University, RAK Hospital). Data were collected from electronic medical records between December 2024 and March 2025. The study adhered to the principles of the Declaration of Helsinki and was approved on September 5, 2024, by the institutional ethical committee of the RAK Hospital, Ras Al Khaimah (protocol n. RAKMHSU-HEC-86-2023/24-F-M). All participants provided written informed consent for participation and for the use of anonymized data for research purposes.

Study Population

Eligible participants were adults aged 18 years or older with a diagnosis of obesity (body mass index [BMI] ≥ 30 kg/m^2) who initiated tirzepatide treatment for weight management. Participants were included if they had no diagnosis of T2DM at baseline, defined as an HbA1c < 6.5% and no use of glucose-lowering medications, and if they had at least one follow-up visit occurring 12 weeks or more after treatment initiation. Patients were excluded if they had received another GLP-1 receptor agonist, GIP receptor agonist, or dual incretin therapy within 6 months prior to starting tirzepatide, or if they had any of the following: pregnancy, active malignancy, severe renal or hepatic disease, uncontrolled thyroid disease, or concurrent participation in another interventional clinical trial.

Treatment and Follow-Up

Tirzepatide was initiated according to standard clinical practice, starting at a dose of 2.5 mg once weekly and titrated in 2.5-mg increments every 4 weeks to the highest tolerated dose. In this cohort, the maximum maintenance dose was 12.5 mg weekly. Dose escalation and maintenance decisions were individualized based on clinical response, tolerability, and shared decision-making between the patient and physician. All participants received standard lifestyle counseling, including structured dietary recommendations, physical activity guidance,

and behavioral support for weight management throughout the treatment period.

Participants were stratified into two groups based on treatment duration: a short-term treatment group, defined as those receiving tirzepatide for ≤ 1 year, and a long-term treatment group, defined as those treated for > 1 year. Treatment persistence was defined as continuous therapy, allowing for a maximum 60-day gap between prescription refills, based on electronic medical record (EMR) data.

Data Collection and Outcomes

Demographic, clinical, anthropometric, and laboratory data were collected at baseline and at the most recent follow-up visit. Analyses excluded missing laboratory or anthropometric data. Available reasons for treatment discontinuation, such as gastrointestinal intolerance, cost or access barriers, and loss to follow-up, were retrieved from EMR records; however, they were not considered in subgroup stratification due to incomplete documentation. Parameters included body weight, BMI, waist circumference, fasting glucose, HbA1c, lipid profile (total cholesterol, low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C], triglycerides), liver enzymes (aspartate aminotransferase [AST, SGOT] and alanine aminotransferase [ALT, SGPT]), and renal function markers (serum creatinine, estimated glomerular filtration rate [eGFR], and blood urea nitrogen [BUN]).

The outcomes were the percentage change in body weight from baseline to follow-up, changes in BMI, waist circumference, glycemic markers, lipid profile, liver and renal function parameters, hypertension improvement and the proportion of patients achieving clinically significant weight reduction (≥ 5%, ≥ 10%, and ≥ 15%) of baseline weight.

Statistical Analysis

Continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), Ninety-five percent confidence intervals (95% CI) were provided where appropriate. Categorical variables were presented as absolute numbers and percentages. Comparisons of baseline characteristics between groups were performed using independent-sample *t* tests or Mann–Whitney *U* tests for continuous variables and chi-square or Fisher's exact tests for categorical variables. Within-group changes from baseline were assessed using paired *t* tests or Wilcoxon signed-rank tests. Between-group differences were evaluated using Mann–Whitney *U* test or analysis of covariance (ANCOVA) adjusted for baseline values where appropriate. Correlations between weight change and metabolic outcomes were examined using Spearman correlation coefficients. All statistical tests were two-sided, and a p value < 0.05 was considered statistically significant.

RESULTS

Study Population

The analysis included 100 adults (25 women, 75 men) with obesity (mean age 37.6 ± 10.0 years; baseline BMI 35.0 [33.0–39.0] kg/m^2) and without T2DM, treated with tirzepatide in a real-world clinical setting. The mean duration of obesity prior to treatment initiation was 3 years. Approximately 57% of participants had class II or III obesity (BMI ≥ 35 kg/m^2). The mean baseline weight was 109.3 ± 14.2 kg, waist circumference 116.2 ± 10.1 cm, total cholesterol 5.6 ± 1.1 mmol/l, and triglycerides 1.9 ± 0.8 mmol/l. Hypertension was present in 12% of participants and obstructive sleep apnea in 7%. None had past history of stroke or myocardial infarction.

Participants were stratified according to treatment duration into Group 1 (≤ 1 year; n = 50) and Group 2 (> 1 year; n = 50). The two groups differed in LDL-C (p < 0.001), HDL-C (p = 0.003), triglycerides (p < 0.001), and SGOT (p = 0.001). Other baseline anthropometric and metabolic parameters were similar between groups (all p > 0.05) and are presented in Table 1. Within the ≤ 1-year group, 12 women (24%) and 38 men (76%) were included, while the > 1-year

Table 1 Effects of tirzepatide therapy at baseline and at the end of treatment in patients with obesity and without T2DM ($n = 100$)

	Up to 1 year ($n = 50$)		More than 1 year ($n = 50$)		% Change (median) and p value (within groups, Wilcoxon signed-rank test/paired t test)		p Value (between groups, Mann–Whitney U test/ANCOVA)
	Baseline	Follow-up	Baseline	Follow-up	Up to 1 year	More than 1 year	
Weight (kg)	100.7 ± 21.1 [90.7–118.1]	93.0 ± 21.9 [79.1–106.13]	95.5 ± 16.9 [88.0–102.0]	72.9 ± 19.5 [68.3–82.0]	− 8.1 (< 0.001)	− 22.6 (< 0.001)	< 0.001
BMI (kg/m^2)	36.0 ± 5.8 [33.3–39.8]	33.0 ± 6.5 [29.0–36.0]	34.5 ± 4.8 [33.0–37.8]	27.0 ± 5.9 [25.0–30.0]	− 8.3 (< 0.001)	− 19.1 (< 0.001)	< 0.001
Waist circumference (cm)	99.0 ± 8.1 [95.0–105.0]	94.5 ± 8.2 [90.0–99.0]	98.0 ± 8.2 [96.0–102.0]	85.5 ± 11.9 [79.0–96.5]	− 4.0 (< 0.001)	− 9.2 (< 0.001)	< 0.001
HbA1c (%)	5.6 ± 1.0 [5.2–6.0]	5.4 ± 0.6 [5.2–5.6]	5.6 ± 0.6 [5.3–5.8]	5.2 ± 0.5 [4.9–5.4]	− 5.0 (< 0.001)	− 7.2 (< 0.001)	0.071
Total cholesterol (mg/dl)	198.9 ± 26.7 [191.3–206.5]	174.3 ± 28.3 [166.3–182.4]	204.9 ± 23.3 [198.3–211.6]	166.1 ± 31.8 [157.1–175.1]	− 10.1 (< 0.001)	− 18.7 (< 0.001)	0.005
LDL-cholesterol (mg/dl)	136.1 ± 26.7 [128.5–143.7]	119.9 ± 28.0 [111.9–127.9]	154.1 ± 29.3 [145.8–162.4]	110.8 ± 32.4 [101.6–120.0]	− 9.6 (< 0.001)	− 30.5 (< 0.001)	< 0.001
HDL-cholesterol (mg/dl)	44.8 ± 10.8 [39.1–54.9]	44.6 ± 10.4 [39.3–53.1]	39.3 ± 8.0 [36.2–43.4]	45.4 ± 7.9 [41.5–50.4]	2.4 (0.592)	13.9 (< 0.001)	< 0.001
Triglycerides (mg/dl)	99.8 ± 67.3 [87.1–124.5]	91.7 ± 36.4 [78.2–107.5]	193.4 ± 112.4 [101.5–279.9]	127.2 ± 49.8 [80.9–140.9]	− 11.2 (< 0.001)	− 32.5 (< 0.001)	< 0.001
SGOT (U/l)	19.2 ± 9.9 [16.3–28.3]	22.6 ± 7.5 [17.9–29.6]	30.7 ± 18.2 [18.4–48.3]	24.9 ± 11.9 [21.4–31.8]	5.2 (0.035)	− 11.3 (< 0.001)	< 0.001
SGPT (U/l)	29.4 ± 17.9 [18.3–41.6]	27.3 ± 18.1 [17.2–43.4]	34.5 ± 20.2 [23.5–46.4]	31.8 ± 13.1 [20.8–40.8]	1.3 (0.973)	− 13.2 (0.009)	0.043
Creatinine (mg/dl)	0.8 ± 0.1 [0.7–0.9]	0.7 ± 0.2 [0.6–0.8]	0.8 ± 0.2 [0.7–0.9]	0.6 ± 0.2 [0.5–0.8]	− 3.7 (0.073)	− 6.6 (< 0.001)	0.107

Table 1 continued

	Up to 1 year ($n = 50$)		More than 1 year ($n = 50$)		% Change (median) and p value (within groups, Wilcoxon signed-rank test/paired t test)		p Value (between groups, Mann–Whitney U test/ANCOVA)
	Baseline	Follow-up	Baseline	Follow-up	Up to 1 year	More than 1 year	
eGFR (ml/min/1.73 m^2)	108.2 ± 19.0 [102.8–113.6]	112.8 ± 22.7 [106.3–119.3]	109.2 ± 18.5 [103.9–114.4]	128.2 ± 38.5 [117.2–139.2]	2.2 (0.081)	3.2 (0.001)	0.013
BUN (mg/dl)	27.1 ± 7.9 [22.0–32.6]	25.2 ± 8.4 [20.9–31.7]	30.8 ± 7.8 [24.8–35.3]	27.0 ± 6.8 [22.4–33.6]	− 6.4 (0.474)	− 7.8 (0.006)	0.276
Microalbuminuria (μg/ml)	64.9 ± 21.7 [48.8–76.3]	56.0 ± 23.6 [36.9–81.2]	61.9 ± 26.4 [38.7–84.9]	59.7 ± 23.1 [39.2–79.7]	− 5.9 (0.560)	− 6.5 (0.768)	0.515

Group 1 includes 50 patients with obesity and without T2DM receiving up to 1 year of treatment with tirzepatide (mean: 0.74 years)

Group 2 includes 50 patients with obesity and without T2DM receiving more than 1 year of treatment with tirzepatide (mean: 1.5 years)

Data are presented as mean ± standard deviation and median [interquartile range]

BMI body mass index, *HbA1c* glycated hemoglobin, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *SGOT* aspartate aminotransferase, *SGPT* alanine aminotransferase, *eGFR* estimated glomerular filtration rate, *BUN* blood urea nitrogen

group comprised 13 women (26%) and 37 men (74%), confirming a comparable sex distribution between treatment duration groups ($p=0.817$).

Tirzepatide Doses

Patients received a broad range of tirzepatide dosages, reflecting individualized dose titration based on clinical response and tolerability. Overall, most participants in both groups remained on moderate maintenance doses, with 5 mg as the preferred dosage in the short-term group and 10 mg as the preferred dosage in the long-term group. In detail, in the short-term group, the maintenance doses were distributed as follows: 10% of patients were on 2.5 mg, 42% were on 5 mg, 26% were on 7.5 mg, 20% were on 10 mg, and 2% were on 12.5 mg. By contrast, in the long-term group, the maintenance doses were distributed as follows: 8% of patients were on 5 mg, 18% were on 7.5 mg, 62% were on 10 mg, 8% were on 12.5 mg, and 4% were on 15 mg.

Anthropometric Outcome

Tirzepatide treatment led to significant, duration-dependent reductions in body weight and adiposity. Participants who remained on tirzepatide for more than 1 year achieved substantially greater weight, BMI and waist circumference reductions than those treated for ≤ 1 year (Table 1). Specifically, 90.0% vs 68.0% of participants achieved at least 5% weight reduction ($p=0.007$), 74.0% vs 38.0% achieved at least 10% ($p<0.001$), 62.0% vs 20.0% achieved at least 15% ($p<0.001$), and 54.0% vs 10.0% achieved at least 20% weight reduction ($p<0.001$) from baseline to follow-up (Fig. 1).

Glycemic Outcomes

Although none of the participants had diabetes at baseline, significant improvements in glycemic markers were observed (Table 1). Throughout the observation period, no participant developed T2DM.

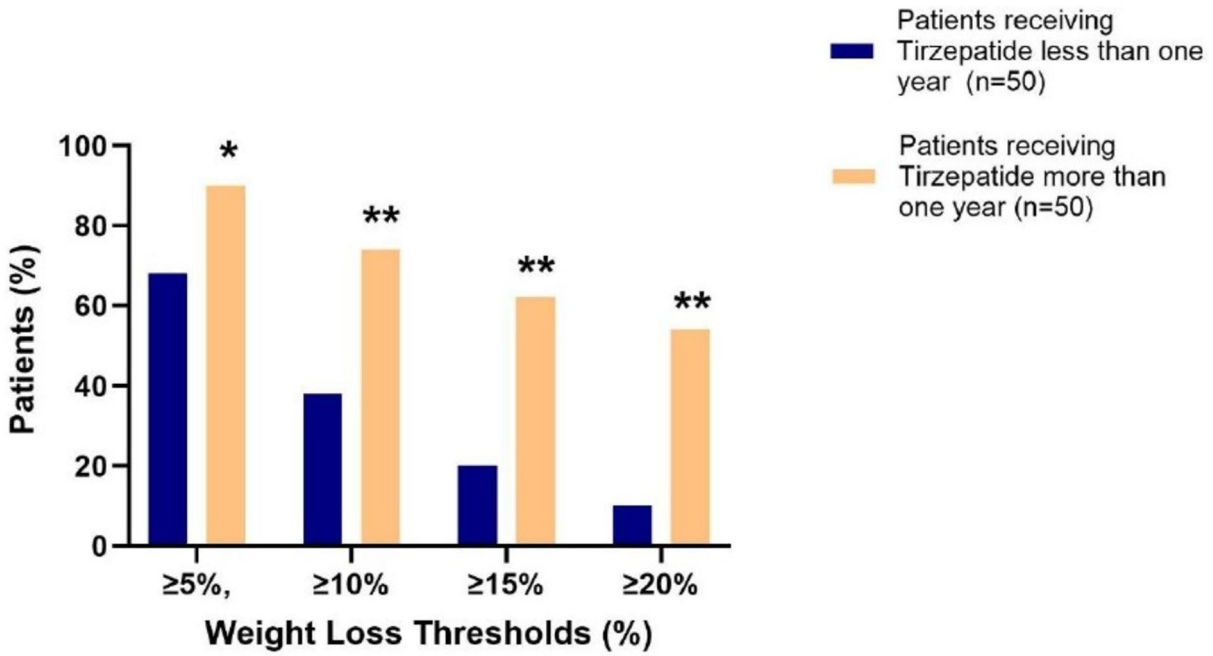

Fig. 1 Percentage of participants achieving weight loss thresholds (≥ 5%, ≥ 10%, ≥ 15%, and ≥ 20%) among those receiving tirzepatide for less than 1 year compared with those receiving tirzepatide for more than 1 year. *$p < 0.01$; **$p < 0.001$

Lipid Profile

Tirzepatide produced improvements in lipid parameters, with larger effects in the long-term group (Table 1).

Hepatic and Renal Outcome

Liver enzymes improved significantly with longer treatment. Serum creatinine and blood urea nitrogen decreased in the long-term group, with no significant between-group difference. Estimated glomerular filtration rate significantly increased in the long-term group, with a significant difference between groups ($p = 0.013$). Changes in microalbuminuria did not differ significantly between short- and long-term persistent participants (Table 1).

Hypertension

In Group 1, two out of five patients with baseline hypertension achieved normal blood pressure. In Group 2, four out of seven patients experienced remission of hypertension.

Correlation Analysis

Weight and BMI were strongly correlated ($\rho = 0.957$). Weight reduction was significantly associated with improvements in LDL-C, triglycerides, and SGOT. HDL-C changes inversely correlated with weight and triglyceride changes, suggesting that weight loss mediates a cascade of metabolic benefits. All correlation data are provided in Table 2.

Adverse Effects

Adverse events most frequently reported included nausea, which affected forty-one patients, with twenty-two cases occurring in the first group and nineteen in the second group. Diarrhea was observed in fourteen patients, ten in the first group and four in the second. Vomiting was documented in an equal number of patients across both groups, with seven cases each. Additionally, a single case of acute pancreatitis was reported in the first group. No cases of gallstones or other clinically significant adverse events were observed. Overall, the treatment was well tolerated in both groups, consistent with the established safety profile of similar therapeutic interventions.

DISCUSSION

This real world study demonstrates that tirzepatide caused substantial and sustained weight reduction accompanied by broad metabolic and organ-specific benefits in adults with obesity. The magnitude of these effects was significantly greater among individuals treated for more than 1 year than those treated less than 1 year. A central observation is the pronounced persistence-dependent cumulative gradient across all outcome domains, highlighting the necessity of continued therapy to achieve the full therapeutic potential of tirzepatide.

Participants who remained on therapy for more than 1 year achieved nearly twice the relative weight reduction of short-term users, with more than 60% attaining > 15% weight loss. These effects were accompanied by significant decreases in BMI and waist circumference, and were comparable between men and women. Beyond weight reduction, tirzepatide elicited marked improvements in lipid metabolism, with long-term treatment resulting in greater reductions in total cholesterol, LDL-C, and triglycerides, as well as an increase in HDL-C. Glycemic parameters improved despite normoglycemia at baseline, suggesting benefits extending to diabetes prevention. Liver transaminases declined significantly with prolonged treatment over 1 year, indicating potential hepatic benefit. Serum creatinine and blood urea nitrogen decreased in the long-term persistent group, with no significant between-group difference. Changes in microalbuminuria did not differ significantly between short- and long-term persistent participants. Correlation analyses confirmed that weight loss was strongly associated with improvements in lipid and hepatic indices, underscoring the interdependence between adiposity reduction and metabolic normalization.

Table 2 Correlation data (Spearman rho) for patients with obesity

	Weight	BMI	WC	HbA1c	TC	TG	HDL	LDL	SGOT	SGPT	Bilirubin	TP	Albumin	Creatinine	eGFR	BUN	UM
Weight	–	0.957**	0.459**	0.317**	0.457**	0.442**	− 0.482**	0.595**	0.229*	0.047	0.181	0.117	− 0.096	0.288**	− 0.373**	0.076	− 0.182
BMI	0.957**	–	0.461**	0.322**	0.448**	0.432**	− 0.504**	0.578**	0.248*	0.034	0.188	0.094	− 0.069	− 0.251*	− 0.299*	0.060	− 0.108
WC	0.459**	0.461**	–	0.284**	0.295**	0.475**	− 0.481**	0.380**	0.382**	0.079	0.062	0.083	− 0.035	0.317**	− 0.293*	0.092	− 0.065
HbA1c	0.317**	0.322**	0.284**	–	0.365**	0.255**	− 0.317**	0.379**	0.125	0.169	0.003	0.111	0.059	0.182	− 0.181	0.104	0.001
TC	0.457**	0.448**	0.295**	0.365**	–	0.288**	− 0.375**	0.857**	0.248*	0.152	0.136	0.015	− 0.123	0.319**	− 0.345*	0.219*	0.001
TG	0.442**	0.432**	0.475**	0.255*	0.288**	–	− 0.503**	0.383**	0.385**	0.082	0.049	0.071	0.002	0.283**	− 0.225	0.189	− 0.045
HDL	− 0.482**	0.504**	− 0.481**	− 0.317**	− 0.375**	− 0.503**	–	− 0.477**	− 404**	− 0.107	− 0.253*	− 0.034	0.083	− 0.422**	0.471**	− 0.030	0.065
LDL	0.595**	0.578**	380**	0.379**	0.857**	0.383**	− 0.477**	–	0.336**	0.122	0.106	0.069	− 0.140	0.395**	− 0.353*	0.234*	− 0.079
SGOT	0.229*	0.248*	0.382**	0.125	0.248*	0.385**	− 0.404**	0.336**	–	0.471**	0.060	− 0.009	− 0.007	0.235*	− 0.185	0.058	− 0.079
SGPT	0.047	0.034	0.079	0.169	0.152	0.082	− 0.107	0.122	− 471**	–	− 0.014	0.049	0.142	0.202*	− 0.067	0.092	− 0.046
Bilirubin	0.181	0.188	0.062	0.003	0.136	0.049	− 0.253*	0.106	0.060	− 0.014	–	− 0.075	− 0.190	0.124	0.059	− 0.055	0.078
TP	0.117	0.094	0.083	0.111	0.015	0.071	− 0.034	0.069	− 009	0.049	0.142	–	0.040	− 0.032	0.091	0.016	− 0.035
Albumin	− 0.096	− 0.069	− 0.035	0.558	− 0.123	0.002	0.083	− 0.140	− 007	0.142	0.202*	0.124	–	− 0.096	− 0.047	− 0.045	− 0.162
Creatinine	0.288**	− 0.251*	0.317**	0.182	0.319**	0.283**	− 0.422**	0.395**	0.235*	0.202*	0.092	− 0.055	0.016	–	− 0.991**	0.182	− 0.079
eGFR	− 0.373**	− 0.299*	− 0.293*	− 0.181	− 0.345*	− 0.225	0.471**	− 0.353*	− 0.185	− 0.067	0.059	0.091	− 0.047	− 0.991**	–	− 0.157	0.334*
BUN	0.076	0.060	0.092	0.104	0.219*	0.189	− 0.030	0.234*	0.058	0.092	− 0.046	− 0.035	− 0.162	− 0.079	− 0.157	–	− 0.031
UM	− 0.182	− 0.108	− 0.065	0.001	0.001	− 0.045	0.065	− 0.079	− 0.079	− 0.046	0.078	− 0.035	− 0.162	0.434	0.334*	0.763	–

BMI body mass index, *HbA1c* glycated hemoglobin, *WC* waist circumference, *TC* total cholesterol, *TG* triglycerides, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *SGOT* aspartate aminotransferase, *SGPT* alanine aminotransferase, *TP* total protein, *BUN* blood urea nitrogen, *UM* urinary microalbuminuria

The findings extend the evidence from the SURMOUNT clinical program by providing real-world confirmation of tirzepatide's long-term multisystemic effectiveness [4]. The degree of weight reduction observed in our population is comparable to the magnitude reported in the Optum analysis, despite differences in baseline characteristics, sample size, and treatment duration [6]. Both studies suggest that real-world tirzepatide effectiveness approximates outcomes observed in the SURMOUNT clinical trials, even though dose escalation is slower and the maximum doses are often not reached.

Our results reinforce the central role of treatment persistence in mediating multidimensional benefits across the CKM continuum in adults with obesity [8]. Participants receiving tirzepatide therapy for more than 1 year experienced significantly greater reductions in body weight, BMI, waist circumference, and glycaemic control compared with those who discontinued earlier, a pattern consistent with the persistence-dependent gradient reported in SURMOUNT-1 and SURMOUNT-4 trials [1, 9].

Improvements in lipid profile in the long-term group, including significant reductions in LDL-C and triglycerides with concurrent HDL-C elevation, aligns the cardioprotective role observed in real-world analyses of tirzepatide's phase 3 program [6]. Such atherogenic lipid attenuation translates into improved cardiovascular risk modulation, consistent with the objectives of the emerging CKM framework proposed by the American Heart Association Presidential Advisory [10].

Persistent therapy for more than 1 year led to progressive decline in hepatic transaminases (SGOT and SGPT), suggesting additional liver benefits, including potential mitigation of steatotic and inflammatory processes in metabolic dysfunction-associated steatotic liver disease (MASLD). Similar hepatoprotective effects have been reported in the SURPASS-3 trial and its Magnetic Resonance Imaging (MRI) substudy, as well as in other incretin-based intervention studies [11].

Renal function was preserved in both groups and showed a favorable persistence-dependent trend with longer treatment duration. These findings are consistent with clinical evidence showing that incretin-based therapies may exert neutral or protective renal effects through reductions in glomerular hyperfiltration, as observed in the SURPASS-4 post-hoc renal analysis [12].

Overall, in this real-world analysis, longer persistence with tirzepatide was associated with consistent and progressive improvements across anthropometric, metabolic, hepatic, and renal outcomes. These data reinforce the clinical relevance of sustained therapy to achieve the full cardiometabolic benefit of dual GIP/GLP-1 receptor agonist [13, 14] and support its role in the long-term management of obesity-related CKM dysregulation.

Study Strengths and Limitations

There are several limitations of this study. Its observational design may be subject to selection bias. The sample size was modest; however, the study was conducted within a single high-volume metabolic obesity center, where a uniform treatment protocol and standardized follow-up procedures ensured data consistency and minimized inter-site variability. Furthermore, adherence was not systematically monitored, which may influence the observed treatment effects.

A key strength of this study is that it provides the first real-world evidence from a single-center cohort with a comprehensive evaluation of persistence-dependent outcomes across the CKM spectrum. Compared to the two previously published real-world analyses (6, 7) our study provides important methodological and clinical advantages. First, by evaluating outcomes in individuals persisting on tirzepatide for more than 1 year, we directly captured a graded association with treatment duration that was not assessed in the Optum or Veradigm datasets (6,7). Second, our cohort included richer CKM phenotyping that allows more comprehensive insight into organ-level responses. Third, we demonstrated a clear hepatic signal in long term persistent group, with significant reductions in SGOT and SGPT, an outcome not characterized in the prior database analyses. Finally, by representing a Middle Eastern population, our study expands the geographic and demographic

generalizability of evidence on tirzepatide use in individuals with obesity without T2DM.

CONCLUSIONS

In conclusion, the effectiveness of treatment with tirzepatide is associated with sustained treatment duration, emphasizing the need for patient-centered strategies to support long term treatment continuation. We should include proactive management of side effects, improve reimbursement pathways, structure follow-up, and provide realistic patient education. Sustained tirzepatide therapy is essential, as cumulative benefits emerge after prolonged treatment, reflecting a gradual biological recalibration beyond initial phase of weight loss. Premature discontinuation of tirzepatide may prevent patients from gaining its most important benefits.

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Declarations

Conflict of Interest. Andrej Janez has served as a consultant and is on Speakers Bureaus for AstraZeneca, Boehringer Ingelheim, Eli Lilly, Abbott, Novo Nordisk, Medtronic, and Sanofi. Mojca Jensterle reports receiving lecture honoraria from Novo Nordisk, Eli Lilly, Pfizer, Amgen, AstraZeneca, Novartis and Sanofi and being an advisory board member of Novo Nordisk, Eli Lilly, Amgen and Pfizer. Manfredi Rizzo has given lectures, received honoraria and research support and participated in conferences, advisory boards and clinical trials sponsored by many pharmaceutical companies, including Amgen, AstraZeneca, Biodexa, Boehringer Ingelheim, Kowa, Eli Lilly, Meda, Mylan, Merck Sharp & Dohme, Novo Nordisk, Novartis, Roche, Sanofi and Servier. Manfredi Rizzo is an Editorial Board member of Diabetes Therapy. Manfredi Rizzo was not involved in the selection of peer reviewers for the manuscript nor any of the subsequent editorial decisions. Imran Rashid Rangraze, Mohamed El-Tanani, Viviana Maggio, Syed Arman Rabbani, Ana Munda, Elhadi Eltayeb Abbas, Humam Sami Ali, Mohammad Rashid Farooqi, and Mohamed Anas Faruk Patni have nothing to disclose.

Ethical Approval. The study adhered to the principles of the Declaration of Helsinki and was approved on September 5, 2024 by the institutional ethical committee of the RAK Hospital, Ras Al Khaimah (protocol n. RAKMHSU-HEC-86-2023/24-F-M). All participants provided written informed consent for participation and for the use of anonymized data for research purposes.

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