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Short-Term Glycemic Response to Tirzepatide According to Prior Incretin Therapy in Patients with Type 2 Diabetes Mellitus

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Abstract

Aims

The aim of this study is to evaluate the short-term real-world glycemic response to tirzepatide according to prior incretin therapy in patients with type 2 diabetes mellitus (T2DM).

Methods

We retrospectively analyzed 114 patients with T2DM who initiated tirzepatide and had HbA1c measurements at baseline and three months. Patients were classified as incretin-naïve (G1, n=24), switched from dipeptidyl peptidase-4 (DPP-4) inhibitors (G2, n=24), or switched from glucagon-like peptide-1 receptor agonist (GLP-1RA)-based therapy (G3, n=66). Changes in HbA1c (ΔHbA1c) were compared among groups, and factors associated with ΔHbA1c were evaluated using multivariable linear regression.

Results

The overall median ΔHbA1c was -0.8% [interquartile range: -1.4 to -0.4] (P<0.001), with significant reductions in all three groups. ΔHbA1c differed significantly among groups (P=0.023), with a significant difference between G1 and G3 (P=0.034). After multivariable adjustment, G3 had a smaller HbA1c reduction than G1 (B=0.763, 95% CI: 0.367 to 1.158; P<0.001).

Conclusions

Tirzepatide initiation was associated with improved glycemic control across all prior incretin therapy groups. However, the magnitude of HbA1c reduction varied according to prior incretin therapy, with a smaller adjusted reduction in patients switched from GLP-1RA-based therapy than in incretin-naïve patients. These findings reflect the early treatment phase, during which some patients had not yet reached a maintenance dose, and may not represent longer-term glycemic responses.

Categories: Endocrinology/Diabetes/Metabolism
Keywords: hba1c, incretin-based therapy, real-world evidence, tirzepatide, type 2 diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disorder characterized by a gradual deterioration of glycemic control, frequently requiring treatment intensification or modification over the course of the disease. Despite the availability of multiple glucose-lowering agents, achieving and maintaining individualized glycemic targets while minimizing weight gain and hypoglycemia remains an important challenge in routine clinical practice [1]. Contemporary treatment strategies therefore emphasize a person-centered approach that considers not only glycemic efficacy but also effects on body weight, cardiovascular and kidney comorbidities, hypoglycemia risk, treatment burden, and individual patient characteristics [2]. Tirzepatide is a once-weekly dual agonist of the glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) receptors and has demonstrated substantial glucose-lowering and weight-reducing effects in patients with T2DM. The SURPASS clinical trial program demonstrated significant reductions in HbA1c and body weight with tirzepatide compared with placebo, basal insulin, and the GLP-1 receptor agonist (GLP-1RA) semaglutide [3-6]. These effects may be mediated through complementary GIP and GLP-1 receptor signaling, with previous studies demonstrating improvements in both β-cell function and insulin sensitivity [7,8]. Tirzepatide therefore represents an important therapeutic option for patients requiring further improvement in glycemic control and body weight. However, the glycemic response to tirzepatide in routine clinical practice may be associated with previous glucose-lowering therapy. In particular, patients initiating tirzepatide may have already received incretin-based therapies, including dipeptidyl peptidase-4 (DPP-4) inhibitors or GLP-1RAs. Several studies have demonstrated additional reductions in HbA1c and body weight after switching from GLP-1RAs, including dulaglutide and

semaglutide, to tirzepatide [9,10]. These findings support tirzepatide as a potential treatment-intensification option after previous incretin-based therapy. However, most switching studies have focused on patients previously treated with GLP-1RAs, and direct comparisons with incretin-naïve patients or those switching from DPP-4 inhibitors remain limited. Furthermore, outcomes observed in randomized controlled trials may not fully reflect those in routine clinical practice, where patients are more heterogeneous with respect to diabetes duration, baseline glycemic control, comorbidities, and concomitant medications. Real-world evidence can therefore provide complementary information regarding the effectiveness of tirzepatide in broader clinical populations [11]. Although recent real-world studies have supported the effectiveness of tirzepatide in routine care [12,13], evidence directly comparing glycemic responses according to prior incretin exposure remains limited. Clarifying whether prior incretin therapy is associated with the magnitude of glycemic response to tirzepatide may help characterize which clinical factors should be considered when anticipating treatment response in routine practice. Therefore, the present study aimed to evaluate the short-term real-world glycemic response to tirzepatide in patients with T2DM and to compare the magnitude of HbA1c reduction among incretin-naïve patients, patients switched from DPP-4 inhibitors, and those switched from GLP-1RA-based therapy. We additionally sought to identify baseline clinical factors associated with the magnitude of HbA1c reduction following tirzepatide initiation.

Materials And Methods

Study design

This single-center, retrospective, observational study used data from a prospectively maintained clinical database at Minoh City Hospital, Japan. The use of antidiabetic medications, including tirzepatide, was reviewed daily, and patients who newly initiated tirzepatide were consecutively identified and prospectively registered in the database at treatment initiation. The database included demographic characteristics, medical history, comorbidities, medication use, physical measurements, and laboratory data obtained during routine clinical care. The present study retrospectively analyzed data from this database. The study adhered to the ethical principles of the Declaration of Helsinki, and the protocol was approved by the Minoh City Hospital Ethics Committee (No. R0711B61). Informed consent was obtained using an opt-out procedure.

Subjects

Among consecutive patients with T2DM who initiated tirzepatide between August 2023 and August 2025, 155 patients were identified, of whom 114 met the eligibility criteria and were included in the final analysis. Eighteen patients were excluded because they did not undergo follow-up laboratory testing at approximately three months after tirzepatide initiation, and 23 were excluded because of the initiation of additional antidiabetic, antihypertensive, or lipid-lowering medications during the three-month follow-up period. We excluded patients younger than 20 years; patients who were initiated on additional antidiabetic, antihypertensive, or lipid-lowering medications within three months following tirzepatide initiation; patients who discontinued tirzepatide within three months; and patients with no follow-up laboratory data at approximately three months. Dose reductions and discontinuation of existing medications were permitted and did not constitute exclusion criteria. Insulin dose adjustments were permitted and were not considered changes in antidiabetic medications. Discontinuation of DPP-4 inhibitors when switching to tirzepatide and replacement of insulin degludec/liraglutide with insulin degludec plus tirzepatide were also permitted and did not constitute exclusion criteria. Figure *1* shows the flowchart of the study population.

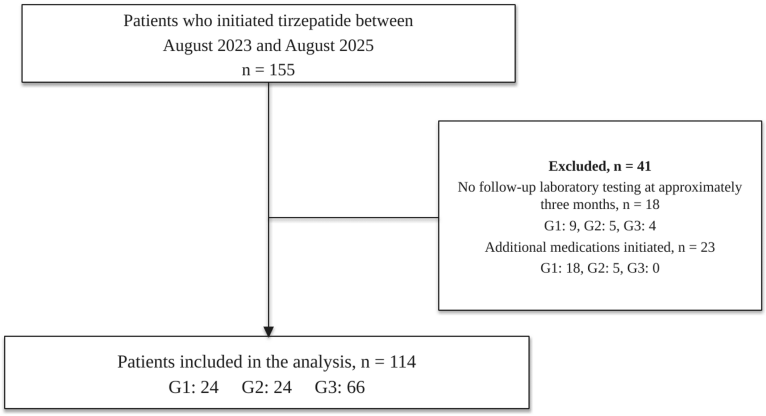


FIGURE 1: Flowchart of the Study Population

G1, incretin-naïve patients; G2, patients switched from DPP-4 inhibitors; G3, patients switched from GLP-1RA-based therapy.

DPP-4: Dipeptidyl peptidase-4; GLP-1RA: glucagon-like peptide-1 receptor agonist.

Tirzepatide dosage

Tirzepatide was initiated at a dose of 2.5 mg once weekly and generally titrated to 5 mg once weekly after four weeks. Further dose escalation was performed in a stepwise manner at the discretion of the treating physician based on glycemic response and tolerability.

Data collection

Demographic, clinical, and laboratory data were obtained from the prospectively maintained clinical database, including age, sex, body weight, body mass index, systolic blood pressure, heart rate, medical history, comorbidities, and medications. For patients previously treated with insulin degludec and liraglutide (IDegLira), total daily insulin doses at baseline and three months after tirzepatide initiation were calculated by summing the daily doses of all insulin preparations. At baseline, the degludec component of IDegLira was included in the total daily insulin dose. Baseline laboratory data were evaluated at the initiation of tirzepatide. Patients were followed at intervals determined by the treating physician, and blood tests were performed during routine clinical visits. HbA1c levels and other clinical and laboratory parameters at baseline and three months after tirzepatide initiation were analyzed. The three-month assessment was defined as the follow-up laboratory testing date closest to three months after tirzepatide initiation, without a predefined allowable time window. The actual interval between tirzepatide initiation and the follow-up HbA1c measurement was calculated in days for each patient.

Classification of subjects

A total of 114 patients with T2DM were classified into three subgroups: incretin-naïve (G1, n=24), those switched from DPP-4 inhibitors (G2, n=24), and those switched from GLP-1RA-based therapy (G3, n=66). Incretin-naïve patients were defined as those with no prior exposure to either DPP-4 inhibitors or GLP-1RAs. Patients in G3 were switched directly from GLP-1RA-based therapy to tirzepatide without a treatment-free interval. In patients previously treated with a fixed-ratio combination of insulin degludec and liraglutide (IDegLira), insulin degludec therapy was continued after switching to tirzepatide. The GLP-1RA-based therapies used before switching to tirzepatide in G3 are shown in Table *1*.

Prior GLP-1RA-based therapy	n (%)	Dose at switching
Oral semaglutide (mg/day)	23 (35)	14 (7, 14)
Insulin degludec/liraglutide (IDegLira) (dose/day)	22 (33)	23 (16, 31)
Semaglutide (mg/week)	7 (11)	0.5 (0.5, 0.9)
Liraglutide (mg/day)	7 (11)	1.8 (1.1, 1.8)
Dulaglutide (mg/week)	7 (11)	0.75 (0.75, 0.75)

TABLE 1: GLP-1RA-Based Therapies Before Switching to Tirzepatide

Data are presented as n (%) or median (interquartile range). Patients were switched directly to tirzepatide without a treatment-free interval.

GLP-1RA: Glucagon-like peptide-1 receptor agonist.

Study outcomes

The primary outcome was the change in HbA1c (ΔHbA1c) from baseline to three months after tirzepatide initiation. We evaluated ΔHbA1c in each subgroup and compared it among the three subgroups. Changes in BMI and other clinical and laboratory parameters were evaluated as secondary exploratory outcomes.

Statistical analysis

Continuous variables are presented as medians (interquartile ranges), whereas categorical variables are presented as numbers and percentages. Serial changes in clinical variables were assessed using the Wilcoxon signed-rank test for paired continuous data. Group differences were assessed using the Kruskal-Wallis test for continuous variables and the Fisher-Freeman-Halton exact test for categorical variables. When an overall group difference was significant, pairwise comparisons of continuous variables were performed using the Steel-Dwass test. Pairwise between-group differences in ΔHbA1c were additionally quantified using Hodges-Lehmann estimates, defined as the median of all pairwise differences between observations in the two groups. Unadjusted 95% confidence intervals were estimated using the percentile bootstrap method with 10,000 resamples within each group. As an exploratory subgroup analysis, ΔHbA1c was compared between patients previously treated with IDegLira and those previously treated with other GLP-1RA-based therapies within G3 using the Mann-Whitney U test. A sensitivity analysis excluding patients previously treated with IDegLira was also performed, comparing ΔHbA1c between G1 and the remaining G3 patients using the Mann-Whitney U test. Analyses of changes in secondary laboratory parameters were considered exploratory, and no adjustment for multiple testing was performed for these secondary outcomes. The correlation between ΔHbA1c and ΔBMI was assessed using Spearman's rank correlation coefficient. Univariable and multivariable linear regression analyses were performed with ΔHbA1c (defined as HbA1c at three months minus baseline HbA1c) as the dependent variable. The multivariable model included age, baseline BMI, duration of diabetes, baseline estimated glomerular filtration rate (eGFR), baseline HbA1c, and prior incretin therapy group (G1, G2, and G3), with G1 as the reference group. Multicollinearity was assessed using variance inflation factors (VIFs), and correlations among continuous covariates were examined using Spearman's rank correlation coefficients. To explore the discrepancy between the univariable and multivariable coefficients for diabetes duration, an additional linear regression model including diabetes duration and baseline HbA1c was fitted. As an exploratory sensitivity analysis, baseline insulin use and sulfonylurea/glinide use were additionally included as binary covariates in the multivariable linear regression model to evaluate potential confounding by concomitant glucose-lowering therapies. In a separate sensitivity analysis, the tirzepatide dose at three months was additionally included as a continuous covariate in the multivariable linear regression model (Model 1) to assess whether the association between prior incretin therapy and ΔHbA1c persisted after adjustment for the dose at follow-up (Model 2). An additional sensitivity analysis was performed using multivariable linear regression after excluding patients previously treated with IDegLira, with adjustment for the same covariates as Model 1 (Model 3). This analysis included 92 patients (G1, n=24; G2, n=24; G3, n=44), with G3 restricted to patients switched from other GLP-1RA-based therapies. To evaluate the influence of extreme observations on the regression results, residual-versus-fitted plots, normal Q-Q plots, and Cook's distances were examined for the univariable and multivariable linear regression models. Exploratory sensitivity analyses were performed after excluding the observation with the largest Cook's distance in the univariable model and the two observations with the largest Cook's distances in the multivariable model. In addition, robust linear regression using Huber M-estimation was performed without excluding observations to assess the stability of the regression coefficients. Eligibility for the primary analysis required HbA1c measurements at baseline and follow-up. Missing values for secondary clinical and laboratory variables did not constitute exclusion criteria. Descriptive analyses were based on available data for each variable at each time point, whereas paired comparisons were restricted to patients with measurements at both time points. Multivariable regression

analyses were performed using complete cases for all variables included in the model. No imputation of missing data was performed. P<0.05 was considered statistically significant. All statistical analyses were performed using EZR (version 1.70; Jichi Medical University, Tochigi, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). EZR is an enhanced version of R Commander that incorporates statistical functions commonly used in biostatistical analyses.

Results

Patient characteristics at the initiation of tirzepatide

Table 2 presents the patient characteristics across the three subgroups. Of the 114 patients, 66 (58%) switched from GLP-1RA-based therapy to tirzepatide, and 24 (21%) switched from DPP-4 inhibitors to tirzepatide. The median age was 59 (50, 68) years, and 62% of the patients were men. The median body weight and BMI were 77 (67, 85) kg and 27.8 (25.3, 30.9) kg/m^2, respectively. At three months after initiation, 30 (26%), 77 (68%), and seven (6%) patients were receiving 2.5 mg, 5 mg, and 7.5 mg of tirzepatide weekly, respectively. The median dose of tirzepatide at three months was 5.0 (2.5, 5.0) mg/week. Significant differences among the three subgroups were observed in age (P=0.041), duration of diabetes (P=0.030), use of sulfonylureas/glinides (P=0.015), and use of angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (angiotensin-converting enzyme inhibitor (ACE-I)/angiotensin II receptor blocker (ARBs)) (P=0.010). The median interval between tirzepatide initiation and follow-up HbA1c assessment was 101 days (interquartile range (IQR), 91-116.75 days), with no statistically significant difference among the three groups (Kruskal-Wallis test, H=3.648, P=0.161; Table 2). The intervals ranged from 55 to 175 days.

Clinical data	Overall (n=114)	G1 Incretin-naïve (n=24)	G2 Switched from DPP-4 inhibitors (n=24)	G3 Switched from GLP-1RA-based therapy (n=66)	H or Cramér's V	P value
Tirzepatide dosage at three months (mg/week)	5.0 (2.5, 5.0)	5.0 (2.5, 5.0)	5.0 (2.5, 5.0)	5.0 (5.0, 5.0)	3.994	0.136
Interval to HbA1c assessment (days)	101 (91, 117)	98 (84, 114)	98 (89, 106)	108 (91, 119)	3.648	0.161
Age (years)	59 (50, 68)	61 (50, 66)	68 (56, 72)	56 (48, 64)	6.383	0.041
Male	71 (62%)	12 (50%)	17 (71%)	42 (64%)	0.143	0.325
Body weight (kg)	77 (67, 85)	75 (67, 86)	77 (63, 85)	79 (68, 88)	2.046	0.360
Body mass index (kg/m^2)	27.8 (25.3, 30.9)	27.7 (25.7, 31.9)	25.9 (24.5, 29.6)	28.0 (25.3, 30.6)	1.862	0.394
Systolic blood pressure (mmHg)	125 (119, 135)	124 (120, 129)	134 (119, 140)	125 (116, 133)	1.500	0.472
Heart rate (bpm)	84 (78, 95)	80 (68, 88)	85 (77, 92)	85 (80, 98)	4.696	0.096
Duration of diabetes (years)	11 (5, 17)	6 (2, 13)	11 (8, 16)	12 (6, 19)	7.019	0.030
Hypertension	91 (80%)	19 (79%)	18 (75%)	54 (82%)	0.014	1.000
Dyslipidemia	103 (90%)	22 (92%)	19 (79%)	62 (94%)	0.123	0.457
Chronic kidney disease (eGFR < 60)	26 (23%)	4 (17%)	4 (17%)	18 (27%)	0.125	0.503
Laboratory data						
Hemoglobin (g/dL)	15.2 (13.8, 16.1)	15.1 (13.5, 16.2)	14.1 (13.6, 15.6)	15.5 (14.4, 16.2)	5.173	0.075
eGFR (mL/min/1.73 m^2)	74 (60, 84)	74 (66, 83)	73 (61, 82)	73 (58, 85)	0.288	0.866

Serum albumin (g/dL)	4.4 (4.2, 4.7)	4.4 (4.2, 4.7)	4.5 (4.2, 4.5)	4.4 (4.2, 4.7)	0.020	0.990
Uric acid (mg/dL)	5.3 (4.7, 6.2)	5.5 (4.7, 6.1)	5.4 (4.6, 6.4)	5.3 (4.6, 5.9)	0.431	0.806
HbA1c (%)	7.8 (6.9, 8.7)	7.4 (6.6, 8.8)	8.0 (7.2, 9.0)	7.8 (7.1, 8.5)	1.030	0.598
LDL cholesterol (mg/dL)	90 (73, 115)	103 (84, 124)	87 (68, 103)	88 (73, 114)	3.854	0.146
Non-HDL cholesterol (mg/dL)	119 (98, 144)	139 (109, 154)	118 (95, 129)	114 (95, 143)	5.885	0.053
HDL cholesterol (mg/dL)	51 (45, 60)	53 (46, 59)	50 (44, 59)	51 (45, 61)	0.379	0.827
Triglycerides (mg/dL)	134 (103, 186)	133 (81, 205)	125 (104, 170)	136 (112, 188)	1.441	0.486
C-reactive protein (mg/dL)	0.11 (0.07, 0.22)	0.13 (0.07, 0.27)	0.10 (0.07, 0.18)	0.10 (0.06, 0.22)	0.714	0.700
Medication						
SGLT2i	91 (80%)	18 (75%)	20 (83%)	53 (80%)	0.069	0.812
Biguanide	70 (61%)	14 (58%)	18 (75%)	38 (58%)	0.144	0.314
Insulin	46 (40%)	9 (38%)	6 (25%)	31 (47%)	0.178	0.160
Sulfonylurea/Glinide	10 (9%)	2 (8%)	6 (25%)	2 (3%)	0.273	0.015
α-Glucosidase inhibitor	4 (4%)	1 (4%)	1 (4%)	2 (3%)	0.030	1.000
Imeglimin	17 (15%)	2 (8%)	6 (25%)	9 (14%)	0.158	0.300
Statin	87 (76%)	18 (75%)	17 (71%)	52 (79%)	0.075	0.756
ACE-I/ARB	76 (67%)	18 (75%)	9 (38%)	49 (74%)	0.320	0.010

TABLE 2: Tirzepatide Dosage at Three Months and Baseline Characteristics of Patients at the Initiation of Tirzepatide, Stratified by Prior Incretin Therapy

Continuous variables are presented as median (interquartile range). Categorical data are presented as n (%). P values were calculated using the Kruskal–Wallis test for continuous variables and the Fisher–Freeman–Halton exact test for categorical variables. H represents the Kruskal–Wallis test statistic, and Cramér's V represents the effect size for categorical variables.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SGLT2i, sodium-glucose cotransporter 2 inhibitor.

Outcomes

Changes in Variables Three Months After Tirzepatide Initiation in the Three Subgroups

Table *3* presents the changes in clinical and laboratory variables three months after tirzepatide initiation. HbA1c significantly decreased from 7.8% (6.9, 8.7) at baseline to 6.7% (6.3, 7.4) at three months (P<0.001). HbA1c decreased from 7.4% (6.6, 8.8) to 6.3% (5.8, 6.6) in G1, from 8.0% (7.2, 9.0) to 6.8% (6.4, 7.1) in G2, and from 7.8% (7.1, 8.5) to 7.1% (6.4, 7.7) in G3 (all P<0.001) (Figure *2A*). Similarly, in the overall cohort, BMI significantly decreased from 27.8 kg/m² (25.3, 30.9) at baseline to 26.9 kg/m² (23.9, 29.7) at three months (P<0.001). BMI decreased from 27.7 kg/m² (25.7, 31.9) to 26.9 kg/m² (23.9, 30.3) in G1, from 25.9 kg/m² (24.5, 29.6) to 25.4 kg/m² (23.6, 29.4) in G2, and from 28.0 kg/m² (25.3, 30.6) to 27.2 kg/m² (24.7, 29.8) in G3 (all P<0.001) (Figure *2B*).

Clinical data	Overall (n=114)				G1 Incretin-naïve (n=24)				G2 Switched from DPP-4 inhibitors (n=24)				G3 Switched from GLP-1RA-based therapy (n=66)			
	0 months	3 months	z-value	P value	0 months	3 months	z-value	P value	0 months	3 months	z-value	P value	0 months	3 months	z-value	P value
Body weight (kg)	77 (67, 85)	75 (67, 85)	6.704	< 0.001	75 (67, 86)	70 (63, 81)	3.738	< 0.001	77 (63, 85)	74 (71, 83)	3.537	< 0.001	79 (68, 88)	78 (68, 86)	4.378	< 0.001
Body mass index (kg/m^2)	27.8 (25.3, 30.9)	26.9 (23.9, 29.7)	6.767	< 0.001	27.7 (25.7, 31.9)	26.9 (23.9, 30.3)	3.704	< 0.001	25.9 (24.5, 29.6)	25.4 (23.6, 29.4)	3.519	< 0.001	28.0 (25.3, 30.6)	27.2 (24.7, 29.8)	4.517	< 0.001
Systolic blood pressure (mmHg)	125 (119, 135)	125 (113, 134)	1.129	0.261	124 (120, 129)	117 (111, 131)	1.204	0.243	134 (119, 140)	125 (117, 131)	1.311	0.201	125 (116, 133)	125 (113, 134)	0.079	0.942
Heart rate (bpm)	84 (78, 95)	83 (77, 94)	0.537	0.596	80 (68, 88)	81 (73, 85)	0.296	0.813	85 (77, 92)	90 (77, 92)	0.404	0.721	85 (80, 98)	86 (77, 95)	0.332	0.751
Laboratory data																
Hemoglobin (g/dL)	15.2 (13.8, 16.1)	15.2 (14.0, 16.2)	0.981	0.328	15.1 (13.5, 16.2)	15.4 (14.0, 15.9)	0.748	0.465	14.1 (13.6, 15.6)	14.5 (13.8, 15.5)	0.822	0.423	15.5 (14.4, 16.2)	15.5 (14.4, 16.3)	0.571	0.571
eGFR (mL/min/1.73 m^2)	74 (60, 84)	71 (58, 84)	3.349	< 0.001	74 (66, 83)	73 (59, 89)	1.354	0.181	73 (61, 82)	75 (63, 84)	1.006	0.324	73 (58, 85)	69 (54, 82)	2.945	0.003
Serum albumin (g/dL)	4.4 (4.2, 4.7)	4.4 (4.1, 4.6)	1.788	0.075	4.4 (4.2, 4.7)	4.4 (4.1, 4.8)	0.981	0.339	4.5 (4.2, 4.5)	4.4 (4.2, 4.6)	0.632	0.544	4.4 (4.2, 4.7)	4.4 (4.2, 4.7)	2.194	0.029
Uric acid (mg/dL)	5.3 (4.7, 6.2)	5.3 (4.4, 6.0)	2.810	0.005	5.5 (4.7, 6.1)	4.9 (4.5, 6.0)	1.769	0.081	5.4 (4.6, 6.4)	5.4 (4.9, 5.8)	2.699	0.008	5.3 (4.6, 5.9)	5.1 (4.3, 6.0)	1.066	0.289
HbA1c (%)	7.8 (6.9, 8.7)	6.7 (6.3, 7.4)	8.208	< 0.001	7.4 (6.6, 8.8)	6.3 (5.8, 6.6)	4.289	< 0.001	8.0 (7.2, 9.0)	6.8 (6.4, 7.1)	4.202	< 0.001	7.8 (7.1, 8.5)	7.1 (6.4, 7.7)	5.596	< 0.001
LDL cholesterol (mg/dL)	90 (73, 115)	78 (65, 101)	4.877	< 0.001	103 (84, 124)	90 (71, 113)	1.981	0.049	87 (68, 103)	72 (58, 90)	2.502	0.013	88 (73, 114)	78 (64, 102)	3.716	< 0.001
Non–HDL cholesterol (mg/dL)	119 (98, 144)	105 (83, 130)	5.346	< 0.001	139 (109, 154)	111 (93, 141)	2.503	0.013	118 (95, 129)	90 (79, 118)	2.614	0.009	114 (95, 143)	108 (83, 130)	3.940	< 0.001
HDL cholesterol (mg/dL)	51 (45, 60)	51 (44, 59)	1.356	0.176	53 (46, 59)	51 (44, 58)	1.102	0.280	50 (44, 59)	49 (44, 59)	1.867	0.067	51 (45, 61)	52 (44, 60)	0.183	0.858
Triglycerides (mg/dL)	134 (103, 186)	117 (93, 172)	2.886	0.004	133 (81, 205)	115 (98, 187)	1.034	0.308	125 (104, 170)	116 (77, 140)	1.825	0.070	136 (112, 188)	122 (95, 172)	2.177	0.030
C-reactive protein (mg/dL)	0.11 (0.07, 0.22)	0.08 (0.04, 0.17)	1.745	0.082	0.13 (0.07, 0.27)	0.08 (0.06, 0.30)	0.569	0.587	0.10 (0.07, 0.18)	0.05 (0.03, 0.08)	2.588	0.011	0.10 (0.06, 0.22)	0.09 (0.04, 0.17)	0.468	0.645

TABLE 3: Changes in Clinical and Laboratory Parameters Three Months after the Initiation of Tirzepatide

Variables are presented as median (interquartile range). Descriptive statistics were calculated using available data at each time point. Tests for significance were conducted using the Wilcoxon signed-rank test in patients with paired measurements. Missing values were not imputed. z represents the standardized test statistic for the Wilcoxon signed-rank test.

DPP-4, Dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

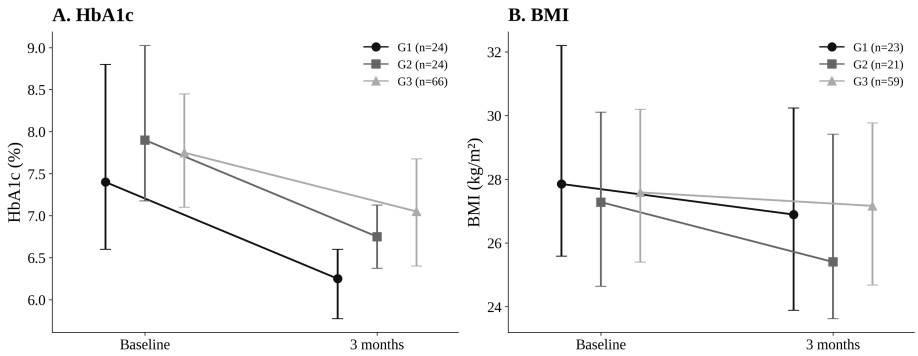


FIGURE 2: Changes in HbA1c and BMI From Baseline to Three Months After Tirzepatide Initiation According to Prior Incretin Therapy

(A) HbA1c and (B) body mass index (BMI) at baseline and three months after tirzepatide initiation, stratified by prior incretin therapy. G1, incretin-naïve patients; G2, patients switched from dipeptidyl peptidase-4 (DPP-4) inhibitors; G3, patients switched from glucagon-like peptide-1 receptor agonist (GLP-1RA)-based therapy. Data are presented as medians with interquartile ranges. Only patients with paired measurements were included for each outcome (HbA1c: n=114 (G1, 24; G2, 24; G3, 66); BMI: n=103 (G1, 23; G2, 21; G3, 59)).

Comparison of ΔHbA1c and ΔBMI Among the Three Subgroups

Table *4* presents a comparative analysis of ΔHbA1c among G1, G2, and G3. The overall median ΔHbA1c was -0.8% (-1.4, -0.4). The median ΔHbA1c was -1.0% (-2.2, -0.6) in G1, -0.9% (-1.9, -0.6) in G2, and -0.7% (-1.3, -0.2) in G3. The corresponding mean ± standard deviation values were -2.10±2.56% in G1, -1.61±1.78% in G2, and -0.81±1.18% in G3. As shown in Figure *3*, ΔHbA1c differed significantly among the three subgroups (P=0.023), with a significant difference between G1 and G3 in the Steel-Dwass test (P=0.034). The Hodges-Lehmann estimates of the between-group differences in ΔHbA1c were -0.10% (95% CI, -0.80 to 0.30) for G1 versus G2, -0.50% (95% CI, -1.20 to -0.10) for G1 versus G3, and -0.30% (95% CI, -0.90 to 0.00) for G2 versus G3 (Table *4*). Within G3, 22 patients (33.3%) had previously received insulin degludec/liraglutide (IDegLira), while 44 (66.7%) had received other GLP-1RA-based therapies. The median ΔHbA1c was -0.9% (IQR, -1.4 to -0.45%) in the IDegLira subgroup and -0.6% (IQR, -1.1 to -0.2%) in the other GLP-1RA subgroup, with no statistically significant difference between them (Mann-Whitney U test, P=0.065). In a sensitivity analysis excluding patients previously treated with IDegLira, the difference in ΔHbA1c between G1 and the remaining G3 patients persisted (median, -1.0% vs. -0.6%; Mann-Whitney U test, P=0.005). Among the 22 patients previously treated with IDegLira, the median daily insulin degludec dose was 23 units/day (IQR, 16-31) at baseline, corresponding to the degludec component of IDegLira, and 20 units/day (IQR, 8-26) at three months after tirzepatide initiation. The median change in daily degludec dose was -3 units/day (IQR, -7 to -1). Degludec dose was reduced in 16 patients (72.7%), increased in one (4.5%), and remained unchanged in five (22.7%). The median total daily insulin dose was 25 units/day (IQR, 20-35.5) at baseline and 22 units/day (IQR, 3-31.5) at three months. Total daily insulin dose decreased in 18 patients (81.8%), remained unchanged in three (13.6%), and increased in one (4.5%). Changes in BMI (ΔBMI) also differed significantly among the three subgroups (P=0.043, Figure *4*, Table *5*). The Steel-Dwass test showed a significant difference between G1 and G3 (P=0.049). As shown in Figure *5*, a weak but statistically significant positive correlation was observed between ΔBMI and ΔHbA1c (Spearman's ρ=0.269, P=0.006).

	Overall (n=114)	G1 Incretin-naïve (n=24)	G2 Switched from DPP-4 inhibitors (n=24)	G3 Switched from GLP-1RA-based therapy (n=66)	H	P value
ΔHbA1c (%)	-0.8 (-1.4, −0.4)	-1.0 (−2.2, -0.6)	-0.9 (-1.9, -0.6)	-0.7 (-1.3, -0.2)	7.561	0.023
Pairwise comparisons: Hodges-Lehmann estimates						
Comparison	HL estimate (%)	95% CI (%)	Steel-Dwass P value			
G1 − G2	-0.1	-0.80 to 0.30	0.848			
G1 − G3	-0.5	-1.20 to −0.10	0.034			
G2 − G3	-0.3	-0.90 to 0.00	0.174			

TABLE 4: Comparison of Changes in HbA1c across the Three Subgroups

ΔHbA1c values are presented as medians (interquartile ranges). The Kruskal-Wallis test was used for comparisons among the three groups. H represents the Kruskal-Wallis test statistic.

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c.

Pairwise comparisons were performed using the Steel-Dwass test; a significant difference was observed between G1 and G3 (P=0.034). Hodges-Lehmann estimates represent the median of all pairwise differences in ΔHbA1c between the two groups, calculated as the first group minus the second group. The 95% confidence intervals were obtained using percentile bootstrap resampling with 10,000 iterations and were not adjusted for multiple comparisons.

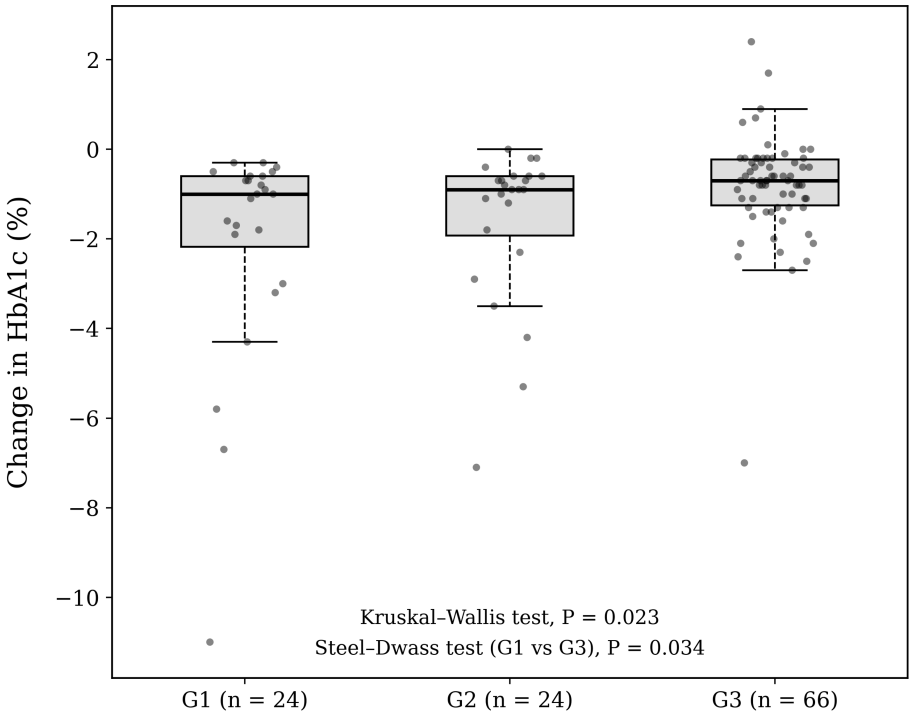


FIGURE 3: Comparison of Changes in HbA1c According to Prior Incretin Therapy

G1, incretin-naïve (n=24); G2, switched from DPP-4 inhibitors (n=24); G3, switched from GLP-1RA-based therapy (n=66). Box plots are overlaid with individual patient data points. Boxes represent the interquartile range, and the horizontal lines within the boxes indicate the median. Whiskers extend to the most extreme values within 1.5 times the interquartile range. Only the statistically significant pairwise comparison is shown.

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist.

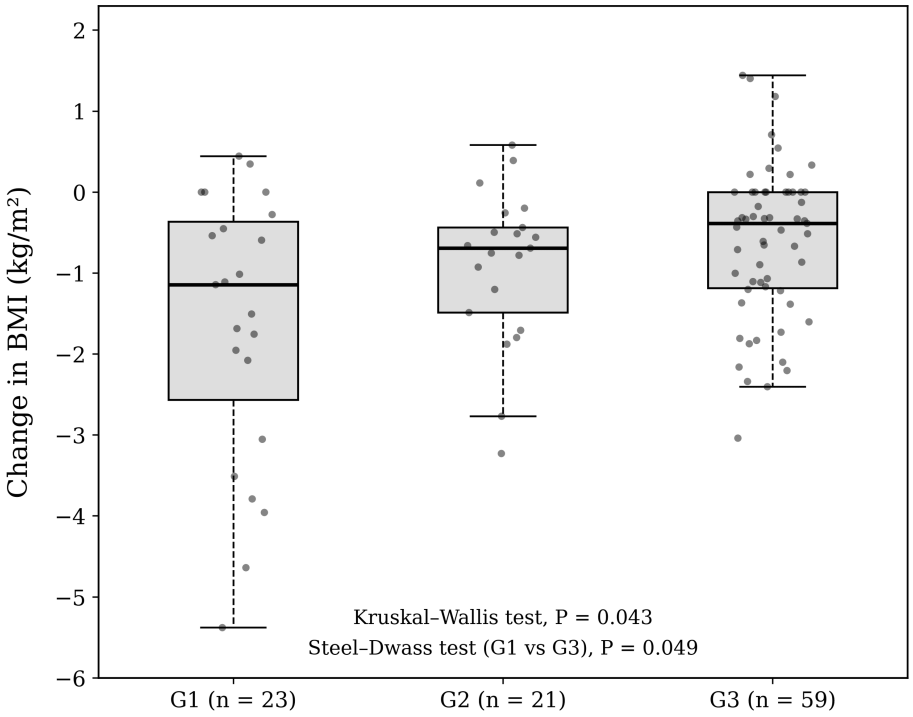


FIGURE 4: Comparison of Changes in BMI According to Prior Incretin Therapy

G1, incretin-naïve (n=23); G2, switched from DPP-4 inhibitors (n=21); G3, switched from GLP-1RA-based therapy (n=59). Box plots are overlaid with individual patient data points. Boxes represent the interquartile range, and the horizontal lines within the boxes indicate the median. Whiskers extend to the most extreme values within 1.5 times the interquartile range. Only patients with paired BMI measurements were included in the analysis. Only the statistically significant pairwise comparison is shown.

DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist.

	Overall (n = 103)	G1 Incretin-naïve (n = 23)	G2 Switched from DPP-4 inhibitors (n = 21)	G3 Switched from GLP-1RA-based therapy (n = 59)	H	P value
ΔBMI (kg/m²)	-0.6 (−2.1, 0.0)	-1.1 (-2.6, -0.4)	-0.7 (-1.5, -0.4)	-0.4 (-1.2, 0.0)	6.275	0.043

TABLE 5: Comparison of Changes in BMI across the Three Subgroups

Variables are presented as median (interquartile range). The Kruskal-Wallis test was used for comparisons among the three groups. H represents the Kruskal-Wallis test statistic.

BMI, body mass index; DPP-4, dipeptidyl peptidase-4; GLP-1RAs, glucagon-like peptide-1 receptor agonists.

Pairwise comparisons were performed using the Steel-Dwass test; a significant difference was observed between G1 and G3 (P=0.049).

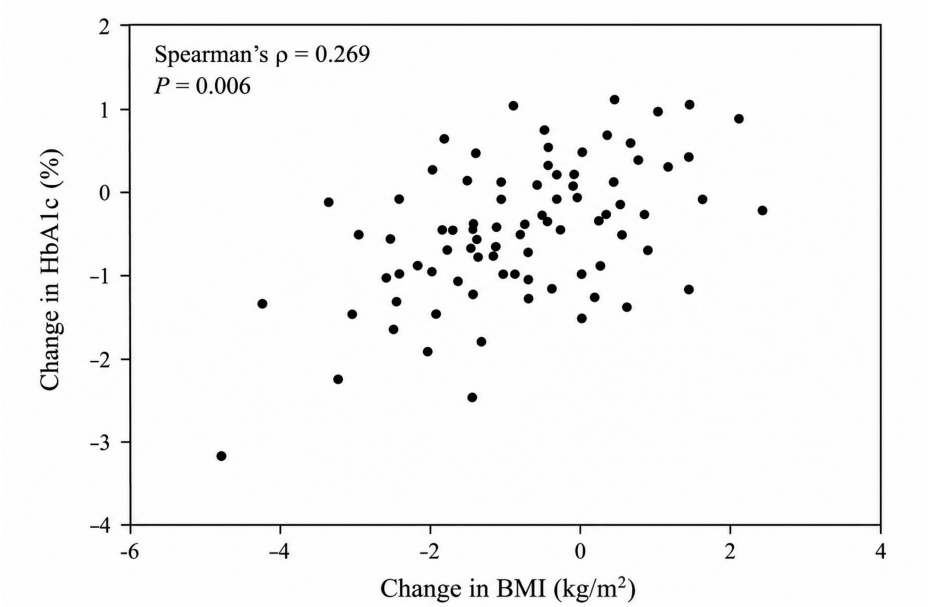


FIGURE 5: Correlation Between Changes in HbA1c and BMI 3 Months After Tirzepatide Initiation (n=103)

Factors associated with ΔHbA1c

The multivariable linear regression analysis included 113 patients, excluding one patient with missing baseline BMI data. As shown in Table *6*, multivariable linear regression analysis (Model 1) demonstrated that baseline HbA1c (B=-0.850, 95% CI: -0.936 to -0.763; P<0.001) and duration of diabetes (B=0.046, 95% CI: 0.025 to 0.067; P<0.001) were significantly associated with ΔHbA1c. Compared with G1, G3 had a significantly smaller HbA1c reduction (B=0.763, 95% CI: 0.367 to 1.158; P<0.001), whereas the difference between G2 and G1 was not statistically significant (B=0.419, 95% CI: -0.054 to 0.891; P=0.082). In Model 1, age, baseline BMI, and baseline eGFR were not significantly associated with ΔHbA1c. Variance inflation factor analysis showed no substantial multicollinearity among the covariates (VIFs for continuous covariates, 1.08-2.00; adjusted GVIF for prior incretin therapy group, 1.05). Spearman's rank correlation analysis showed positive correlations between diabetes duration and age (ρ=0.394) and between diabetes duration and baseline HbA1c (ρ=0.380). Although diabetes duration was not associated with ΔHbA1c in the univariable analysis (B=0.002, P=0.910), its coefficient increased to 0.045 (95% CI: 0.025 to 0.065; P<0.001) in a model additionally including baseline HbA1c, suggesting that adjustment for baseline HbA1c largely accounted for the difference between the univariable and multivariable coefficients. In a sensitivity analysis additionally adjusting for baseline insulin and sulfonylurea/glinide use, the associations of diabetes duration (B=0.045, 95% CI: 0.023 to 0.067; P<0.001) and prior GLP-1RA-based therapy (G3 vs. G1: B=0.773, 95% CI: 0.374 to 1.171; P<0.001) with ΔHbA1c remained significant. Neither insulin use (P=0.907) nor sulfonylurea/glinide use (P = 0.392) was significantly associated with ΔHbA1c in this model. In an exploratory sensitivity analysis additionally adjusting for the tirzepatide dose at three months (Model 2 in Table *6*), the association between prior GLP-1RA-based therapy and a smaller HbA1c reduction remained significant (G3 vs. G1: B=0.808, 95% CI: 0.413 to 1.204; P<0.001). The tirzepatide dose at three months was not significantly associated with ΔHbA1c (B=-0.098 per mg/week, 95% CI: -0.212 to 0.017; P=0.093). In an additional sensitivity analysis excluding patients previously treated with IDegLira (Model 3 in Table *6*), the association between switching from other GLP-1RA-based therapies and a smaller HbA1c reduction remained significant compared with G1 (B=0.726, 95% CI: 0.372 to 1.080; P<0.001). In this model, G2 also showed a significantly smaller HbA1c reduction than G1 (B=0.434, 95% CI: 0.034 to 0.834; P=0.034). Residual diagnostics revealed influential observations and deviations from normality in the tails of the residual distributions. In the univariable linear regression model, the coefficient for G3 versus G1 decreased from 1.286 to 0.899 (95% CI: 0.204 to 1.595; P=0.012) after excluding the observation with the largest Cook's distance. In the multivariable model (Model 1), the corresponding coefficient decreased from 0.763 to 0.625 (95% CI: 0.297 to 0.953; P<0.001) after excluding the two observations with the largest Cook's distances. Robust linear regression using Huber M-estimation yielded coefficients of 0.519 and 0.673 for G3 versus G1 in the univariable and multivariable models, respectively.

Variables	Univariable B (95% CI)	P value	Model 1		Model 2		Model 3	
			Multivariable B (95% CI)	P value	Multivariable B (95% CI)	P value	Multivariable B (95% CI)	P value
Age, per 1 year	-0.005 (-0.031 to 0.022)	0.716	-0.0002 (-0.017 to 0.017)	0.978	0.001 (-0.016 to 0.018)	0.876	-0.003 (-0.020 to 0.013)	0.666
BMI, per 1 kg/m²	0.015 (−0.065 to 0.096)	0.707	0.028 (-0.010 to 0.066)	0.148	0.038 (-0.002 to 0.077)	0.061	0.015 (-0.022 to 0.052)	0.431
Duration of diabetes, per 1 year	0.002 (−0.037 to 0.041)	0.91	0.046 (0.025 to 0.067)	<0.001	0.045 (0.024 to 0.066)	<0.001	0.045 (0.024 to 0.066)	<0.001
eGFR, per 1 mL/min/1.73 m²	−0.006 (−0.020 to 0.007)	0.353	0.008 (−0.00001 to 0.016)	0.05	0.009 (0.001 to 0.017)	0.031	0.004 (-0.003 to 0.012)	0.268
Baseline HbA1c, per 1%	-0.801 (-0.896 to -0.707)	<0.001	-0.850 (-0.936 to -0.763)	<0.001	-0.855 (-0.941 to -0.769)	<0.001	-0.888 (-0.964 to -0.813)	<0.001
Tirzepatide dose at 3 months, per 1 mg/week	0.036 (−0.197 to 0.270)	0.757	-	-	−0.098 (−0.212 to 0.017)	0.093	-	-
Prior incretin therapy								
G1: incretin-naïve	Reference	-	Reference	-	Reference	-	Reference	-
G2: switched from DPP-4 inhibitors	0.492 (-0.470 to 1.453)	0.313	0.419 (−0.054 to 0.891)	0.082	0.395 (−0.074 to 0.864)	0.098	0.434 (0.034 to 0.834)	0.034
G3: switched from GLP-1RA-based therapy	1.286 (0.493 to 2.080)	0.002	0.763 (0.367 to 1.158)	<0.001	0.808 (0.413 to 1.204)	<0.001	-	-
G3: switched from other GLP-1RA-based therapies (excluding IDegLira)	-	-	-	-	-	-	0.726 (0.372 to 1.080)	<0.001

TABLE 6: Linear Regression Analysis of Factors Associated With ΔHbA1c After Tirzepatide Initiation

B, Unstandardized regression coefficient; CI, confidence interval; BMI, body mass index; eGFR, estimated glomerular filtration rate; DPP-4, dipeptidyl peptidase-4; GLP-1RA, glucagon-like peptide-1 receptor agonist; IDegLira, insulin degludec/liraglutide.

Model 1 was adjusted for age, BMI, duration of diabetes, eGFR, baseline HbA1c, and prior incretin therapy. Model 2 was additionally adjusted for the tirzepatide dose at three months. Model 3 was a sensitivity analysis excluding patients previously treated with IDegLira and was adjusted for the same covariates as Model 1. In Model 3, G3 comprised 44 patients switched from other GLP-1RA-based therapies. G1 (incretin-naïve) was the reference group in all models. Models 1 and 2 included 113 patients, whereas Model 3 included 92 patients (G1, n=24; G2, n=24; G3, n=44).

Discussion

Main findings

In this real-world cohort of patients with type 2 diabetes mellitus, tirzepatide initiation was associated with significant reductions in HbA1c and body weight within three months. HbA1c decreased across all treatment-history subgroups, including incretin-naïve patients and those switched from DPP-4 inhibitors or GLP-1RA-based therapy. Notably, the HbA1c reduction was smaller in patients switched from GLP-1RA-based therapy than in incretin-naïve patients, and this difference remained significant after multivariable adjustment. This association persisted in exploratory sensitivity analyses additionally adjusting for the tirzepatide dose at three months and excluding patients previously treated with IDegLira.

Comparison with previous studies

The glycemic efficacy of tirzepatide has been well established through the SURPASS clinical trial program. In SURPASS-1, tirzepatide monotherapy significantly reduced HbA1c compared with placebo [5]. In SURPASS-2, tirzepatide demonstrated superior HbA1c and weight reductions compared with once-weekly semaglutide

[3]. Furthermore, SURPASS-3 [6] and SURPASS-4 [4] showed greater glycemic improvement compared with insulin degludec and insulin glargine, respectively. The glycemic effects of tirzepatide may involve improvements in both β-cell function and insulin sensitivity. Prior studies have demonstrated that tirzepatide improves markers of insulin sensitivity and β-cell function, with greater improvements observed than with GLP-1RAs such as dulaglutide and semaglutide [7,8]. Several studies have evaluated outcomes after switching from GLP-1RAs to tirzepatide and have reported significant improvements in glycemic control and body weight following switching, including from dulaglutide and semaglutide [9,10]. In addition, a network meta-analysis of randomized controlled trials in Japanese patients with T2DM showed greater reductions in HbA1c and body weight with tirzepatide than with several GLP-1RAs [14]. Importantly, few studies have directly compared incretin-naïve patients with those switched from DPP-4 inhibitors or GLP-1RA-based therapy within the same cohort, particularly in short-term real-world settings.

Influence of prior incretin therapy

Although HbA1c decreased significantly in all three groups, the magnitude of reduction differed among the subgroups. In the unadjusted comparison, the HbA1c reduction was significantly greater in incretin-naïve patients than in patients switched from GLP-1RA-based therapy. Importantly, this difference persisted after adjustment for age, baseline BMI, duration of diabetes, baseline eGFR, and baseline HbA1c, with patients switched from GLP-1RA-based therapy showing a significantly smaller HbA1c reduction than incretin-naïve patients. In contrast, the adjusted difference between patients switched from DPP-4 inhibitors and incretin-naïve patients was not statistically significant. These findings suggest that prior GLP-1RA-based therapy may be associated with a smaller short-term glycemic response to tirzepatide. G3 included patients previously treated with IDegLira, which provides a relatively low dose of liraglutide compared with conventional GLP-1RA regimens, as well as patients treated with other GLP-1RAs. In the exploratory subgroup analysis, the HbA1c reduction was numerically greater in patients previously treated with IDegLira than in those previously treated with other GLP-1RAs, although the difference was not statistically significant. Importantly, the difference in ΔHbA1c between G1 and the remaining G3 patients persisted after excluding those previously treated with IDegLira, both in the unadjusted comparison and after multivariable adjustment. These findings suggest that the observed difference between G1 and G3 was not solely driven by patients previously treated with IDegLira. Nevertheless, differences in prior GLP-1RA regimens and concomitant insulin treatment may have influenced the observed glycemic responses. Consistent with our findings, previous studies have also demonstrated significant improvements in HbA1c within a relatively short period after switching from GLP-1RAs to tirzepatide [9,10]. Similarly, Minakata et al. reported a greater HbA1c reduction in incretin-naïve patients than in patients previously treated with GLP-1RAs in a Japanese real-world cohort [13]. This finding is consistent with the smaller glycemic response observed in our GLP-1RA-based therapy group. The greater HbA1c reduction observed in incretin-naïve patients may reflect differences in prior exposure to incretin-based therapy as well as residual differences in patient characteristics not fully accounted for in the adjusted analysis. Notably, all patients in G3 were switched directly to tirzepatide without a treatment-free interval. Furthermore, in patients previously treated with IDegLira, insulin degludec therapy was continued after switching to tirzepatide. These treatment patterns may have reduced the potential influence of treatment interruption or discontinuation of basal insulin on the observed glycemic changes after switching to tirzepatide. In patients previously treated with GLP-1RA-based therapy, the HbA1c reduction observed following the switch may reflect the pharmacological profile of tirzepatide, including dual GIP/GLP-1 receptor agonism; however, the present observational study cannot determine the mechanism underlying the observed glycemic improvement. Importantly, the significant HbA1c reduction observed in patients switched from GLP-1RA-based therapy indicates that glycemic improvement can occur after switching to tirzepatide, even among patients previously exposed to incretin-based therapy. The discrepancy between the relatively small median difference in ΔHbA1c between G1 and G3 and the larger univariable regression coefficient reflects the difference between median-based and mean-based estimates. Extreme HbA1c reductions in G1 contributed to the larger difference in group means. Residual diagnostics and sensitivity analyses indicated that influential observations affected the magnitude of the regression coefficients, particularly in the univariable model. Although the estimated coefficients were attenuated after excluding influential observations and in robust regression analyses, the direction of the association remained consistent. Therefore, while prior GLP-1RA-based therapy was associated with a smaller short-term HbA1c reduction, the magnitude of this association should be interpreted cautiously.

Factors associated with glycemic response to tirzepatide

Higher baseline HbA1c was independently associated with a greater HbA1c reduction. Higher baseline HbA1c has also been associated with greater absolute HbA1c reductions following glucose-lowering therapy in previous studies [15,16]. In contrast, longer duration of diabetes was independently associated with a smaller HbA1c reduction. Longer duration of diabetes has previously been associated with smaller HbA1c reductions [17], potentially reflecting progressive β-cell dysfunction. Notably, baseline BMI was not independently associated with ΔHbA1c in the multivariable analysis.

Clinical implications

Tirzepatide initiation was associated with significant short-term improvements in glycemic control and body weight, including in patients switched from GLP-1RA-based therapy. These findings suggest that tirzepatide may be a treatment intensification option for patients with insufficient glycemic control despite

prior incretin-based therapy. In addition, glycemic response was associated with baseline HbA1c and duration of diabetes, with greater HbA1c reductions observed in patients with higher baseline HbA1c and shorter disease duration. Therefore, baseline HbA1c, disease duration, and treatment history may be relevant when anticipating the short-term glycemic response to tirzepatide.

Limitations

Several limitations should be acknowledged. First, this was a single-center, retrospective study with a relatively short (three-month) observation period. At three months, 26% of patients remained on the 2.5-mg starting dose, and the dose at a single time point may not adequately reflect cumulative exposure or the duration of treatment at doses of 5 mg or higher. Moreover, dose escalation may have been influenced by early glycemic response and tolerability. Therefore, the findings primarily reflect the early treatment phase rather than the full effects of maintenance therapy. Second, the sample sizes of G1 and G2 were relatively small, and no untreated control group was included. Third, the exclusion of patients who initiated additional antidiabetic, antihypertensive, or lipid-lowering medications or lacked follow-up laboratory data may have introduced selection bias. In particular, medication-related exclusions were more frequent in G1, potentially affecting between-group comparisons. Fourth, reductions or discontinuations of existing antidiabetic medications and insulin dose adjustments were permitted during follow-up and may have influenced HbA1c changes. Among patients previously treated with IDegLira, although degludec dose changes between baseline and three months were quantified, the dose prescribed immediately after switching and the timing of subsequent adjustments were unavailable. Fifth, G3 included heterogeneous prior GLP-1RA-based regimens, and differences in treatment history, baseline characteristics, and other unmeasured confounders may have influenced the observed associations despite multivariable adjustment. The exploratory comparison between patients previously treated with IDegLira and those treated with other GLP-1RA-based therapies was unadjusted. Although the sensitivity analysis excluding patients previously treated with IDegLira included multivariable adjustment, residual confounding cannot be excluded. Finally, follow-up HbA1c measurements were obtained 55-175 days after initiation. Although the intervals did not differ significantly among groups (P=0.161), earlier assessments may have underestimated the glycemic response, and variability in follow-up timing may have affected between-group comparisons. Larger, multicenter, prospective controlled studies with longer follow-up are warranted.

Conclusions

In this real-world cohort of patients with T2DM, tirzepatide initiation was associated with significant short-term improvements in glycemic control and body weight across different prior incretin treatment backgrounds. HbA1c decreased significantly in incretin-naïve patients, patients switched from DPP-4 inhibitors, and those switched from GLP-1RA-based therapy. However, the magnitude of HbA1c reduction differed according to prior treatment history. Patients switched from GLP-1RA-based therapy showed a smaller HbA1c reduction than incretin-naïve patients, and this difference remained significant after adjustment for age, baseline BMI, duration of diabetes, baseline eGFR, and baseline HbA1c. Higher baseline HbA1c was independently associated with a greater HbA1c reduction, whereas longer diabetes duration was associated with a smaller reduction. These findings indicate that short-term glycemic improvement can occur after tirzepatide initiation even in patients previously treated with incretin-based therapies, although the magnitude of HbA1c reduction may vary according to prior incretin exposure and baseline clinical characteristics. Prior treatment history, baseline HbA1c, and duration of diabetes may therefore be relevant clinical factors associated with the short-term glycemic response to tirzepatide in routine clinical practice. Because approximately one-quarter of patients remained on the starting dose at three months, these findings primarily reflect the early phase of tirzepatide treatment and should not be extrapolated to longer-term outcomes after maintenance-dose titration. Given the retrospective, single-center design and three-month follow-up of the present study, larger prospective multicenter studies with longer follow-up are warranted to confirm these findings and determine their implications for longer-term glycemic and metabolic outcomes.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

Human subjects: Informed consent for treatment and open access publication was obtained or waived by all participants in this study. Director of Minoh City Hospital issued approval R0711B61. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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