

# Comparison of Postoperative Outcomes Between Semaglutide and Tirzepatide in Patients Undergoing Total Knee Arthroplasty: A Propensity Score-Matched Cohort Study

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**INTRODUCTION:** Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), specifically Semaglutide and Tirzepatide, are increasingly used in patients with type 2 diabetes mellitus (T2DM) for glycemic control and weight management. Tirzepatide, a dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RA, has demonstrated greater weight loss and improved glycemic control compared to Semaglutide in recent clinical trials. These pharmacologic differences may influence perioperative outcomes, particularly in orthopedic procedures where obesity and metabolic status impact recovery. Prior research suggests that GLP-1 RA use may reduce postoperative complications in patients undergoing total joint arthroplasty; however, no studies have directly compared the safety profiles of Semaglutide versus Tirzepatide in the context of total knee arthroplasty (TKA). The purpose of this study was to evaluate whether there are differences in short-term postoperative outcomes between TKA patients treated with Semaglutide versus Tirzepatide in the perioperative period. Given the pharmacologic distinctions and emerging evidence favoring Tirzepatide for metabolic control, we hypothesized that Tirzepatide users would have similar or potentially improved short-term complication profiles compared to Semaglutide users in the setting of TKA.

**METHODS:** We performed a retrospective cohort study using the TriNetX research network, a federated electronic health record database. IRB exemption was obtained by our institution prior to study initiation. Adult patients with T2DM who underwent primary TKA between June 1, 2022, and December 31, 2024, and had an active prescription for either Semaglutide or Tirzepatide within 90 days prior to surgery were included. 1:1 propensity score matching was conducted based on age, sex, race, BMI, HbA1c, comorbidity burden, and concurrent diabetes medication use, yielding 415 matched pairs. Outcomes were assessed at 90 and 180 days postoperatively. These included medical complications, surgical complications, and healthcare utilization. Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated using logistic regression.

**RESULTS SECTION:** After matching, 415 patients (Semaglutide: 124 male, 274 female; Tirzepatide: 130 male, 267 female) in each cohort were analyzed. No significant differences were found in 90-day medical complications (OR 1.122, 95% CI 0.736-1.710, P = 0.591) or 180-day surgical complications (OR 1.632, 95% CI 0.845-3.152, P = 0.141) between the Semaglutide and Tirzepatide groups. Individual complications, including myocardial infarction, stroke, pneumonia, sepsis, pulmonary embolism, deep vein thrombosis, acute kidney injury (OR 0.867, 95% CI 0.417-1.801, P = 0.701), urinary tract infection (OR 1.562, 95% CI 0.863-2.827, P = 0.138), mortality, surgical site infection (OR 1.726, 95% CI 0.782-3.810, P = 0.172), periprosthetic infection, wound dehiscence, and revision surgery, were statistically similar (all P > 0.05). Healthcare utilization metrics showed no significant difference in emergency department visits or readmission at 90 days (OR 0.775, 95% CI 0.570-1.052, P = 0.102) or 180 days (OR 0.887, 95% CI 0.672-1.170, P = 0.397). Several individual outcomes had low event counts in both groups, limiting the precision of effect estimates and resulting in ORs of 1.000 with wide CIs.

**DISCUSSION:** This large, propensity-matched cohort study found no significant differences in short-term postoperative complication rates between Semaglutide and Tirzepatide users undergoing primary TKA. These findings suggest that both agents can be safely continued in the perioperative period. Our study exhibited several limitations, including: inherent retrospective limitations, reliance on administrative coding (ICD-10-CM and CPT codes), inability to access detailed intraoperative variables, and limited sample size in both exposure groups prevented assessment of rare events. Future studies with extended follow-up and functional outcomes are warranted to evaluate long-term clinical and metabolic differences.

**SIGNIFICANCE/CLINICAL RELEVANCE:** Semaglutide and Tirzepatide demonstrated similar safety profiles following TKA. These findings support continued use of either agent in T2DM patients undergoing TKA.

**Table 1.** Demographic and clinical characteristics of patients undergoing total knee arthroplasty who were prescribed semaglutide or tirzepatide.

	Before PSM, Mean ± SD or No. (%)			After PSM, Mean ± SD or No. (%)		
	Semaglutide (N=1,345)	Tirzepatide (N=417)	P Value	Semaglutide (N=415)	Tirzepatide (N=415)	P Value
Age	64.9 ± 7.8	63.4 ± 8.0	0.001	63.9 ± 8.0	63.5 ± 8.0	0.476
Race						
White	934 (69.4)	296 (71.0)	0.549	302 (72.8)	294 (70.8)	0.537
Black or African American	213 (15.8)	65 (15.6)	0.903	61 (14.7)	65 (15.7)	0.699
Asian	48 (3.6)	13 (3.1)	0.660	12 (2.9)	13 (3.1)	0.839
Native Hawaiian or Other Pacific Islander	10 (0.7)	10 (2.4)	0.005	10 (2.4)	10 (2.4)	>0.999
American Indian or Alaska Native	10 (0.7)	10 (2.4)	0.005	10 (2.4)	10 (2.4)	>0.999
Other Race	37 (2.8)	10 (2.4)	0.696	10 (2.4)	10 (2.4)	>0.999
Unknown Race	98 (7.3)	33 (7.9)	0.670	30 (7.2)	33 (8.0)	0.694
Sex						
Male	440 (32.7)	130 (31.2)	0.557	124 (29.9)	130 (31.3)	0.651
Female	859 (63.9)	269 (64.5)	0.811	274 (66.0)	267 (64.3)	0.610
Unknown	46 (3.4)	18 (4.3)	0.393	17 (4.1)	18 (4.3)	0.863
Medical Comorbidities						
Hypertension	1,049 (78.0)	324 (77.7)	0.899	317 (76.4)	323 (77.8)	0.620
Chronic Ischemic Heart Disease	245 (18.2)	68 (16.3)	0.373	70 (16.9)	68 (16.4)	0.852
Heart Failure	121 (9.0)	29 (7.0)	0.192	29 (7.0)	29 (7.0)	>0.999
CKD	212 (15.8)	51 (12.2)	0.077	55 (13.3)	51 (12.3)	0.677
Acute Kidney Failure	54 (4.0)	19 (4.6)	0.628	17 (4.1)	18 (4.3)	0.863
Cerebral Infarction	30 (2.2)	10 (2.4)	0.841	11 (2.7)	10 (2.4)	0.825
Atherosclerosis	48 (3.6)	14 (3.4)	0.838	13 (3.1)	14 (3.4)	0.845
COPD	105 (7.8)	33 (7.9)	0.943	29 (7.0)	33 (8.0)	0.597
Asthma	179 (13.3)	73 (17.5)	0.032	66 (15.9)	71 (17.1)	0.640
Nicotine Dependence	191 (14.2)	58 (13.9)	0.881	64 (15.4)	58 (14.0)	0.556
Mood (Affective) Disorders	342 (25.4)	109 (26.1)	0.771	100 (24.1)	108 (26.0)	0.552
Metformin Use	592 (44.0)	162 (38.8)	0.062	152 (36.6)	161 (38.8)	0.519
Insulin Use	320 (23.8)	99 (23.7)	0.983	108 (26.0)	99 (23.9)	0.470
Laboratory Investigations						
Average BMI (kg/m <sup>2</sup> )	36.2 ± 6.0	36.6 ± 5.7	0.338	36.0 ± 5.7	36.6 ± 5.7	0.258
Average HbA1c (%)	6.4 ± 0.9	6.4 ± 0.9	0.112	6.4 ± 1.0	6.4 ± 0.9	0.566

BMI = Body Mass Index; CKD = Chronic Kidney Disease; COPD = Chronic Obstructive Pulmonary Disease; GLP-1 = Glucagon-Like Peptide 1; HbA<sub>1c</sub> = Glycated Hemoglobin; PSM = Propensity Score Matching; SD = Standard Deviation

