Does Combination Antidiabetic Therapy Improve Outcomes After Total Joint Arthroplasty?

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Introduction

Type 2 diabetes mellitus (T2DM) is common among patients undergoing total joint arthroplasty and increases the risk of infection, wound complications, and readmission. Metformin, the standard first-line therapy, has been linked to lower postoperative complication rates, likely through its anti-inflammatory and metabolic effects. Newer agents, including glucagon-like peptide-1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2i), offer additional metabolic benefits and may further reduce perioperative risk, though each carries specific management considerations. Despite their growing use, outcomes comparing metformin monotherapy with combination therapy including GLP-1 RA or SGLT2i after arthroplasty remain undefined. This study uses a large national database to compare postoperative complications following primary total hip and knee arthroplasty in patients treated with metformin alone versus combination therapy, aiming to clarify whether adjunctive agents confer additional benefit beyond metformin.

Methods

Data were retrospectively analyzed from the TriNetX Research Network. Patients with type 2 diabetes mellitus who underwent total hip or knee arthroplasty were identified using ICD-10 and CPT codes. Medication exposure was determined using ATC codes, comparing metformin monotherapy to metformin combined with GLP-1 receptor agonists or SGLT2 inhibitors. Propensity score matching (1:1) was performed for age, sex, BMI, tobacco use, and major comorbidities. Medical complications (including venous thromboembolism VTE, renal/urinary complications, stroke, myocardial infarction, sepsis, pneumonia) were evaluated at 3- and 6-month follow-up, while implant-related outcomes were assessed through 24 months. Odds ratios (OR) with 95% confidence intervals (CI) were calculated, and a subgroup analysis was performed to compare the cohorts based on glycemic control, with each cohort stratified by HbA1c level <7.5 or ≥7.5.

Results

An initial query identified 18,311 receiving metformin monotherapy and 4,125 receiving combination therapy. After 1:1 propensity score matching, each cohort included 4,124 patients.

At 3 months, monotherapy was associated with higher rates of postoperative blood transfusion (7.6 vs. 6.3%; OR: 1.22; p=0.02), hospital readmissions (27.4 vs. 21.4%; OR: 1.38; p<0.001), and medical complications (20 vs. 17.5%; OR: 1.18, p=0.004) compared to the combination therapy group. At 6 months, medical complications remained significantly higher in the monotherapy group (OR: 1.21; p=0.03), with 1.3 higher odds of VTE compared to the combination therapy group (p=0.03). They also had significantly higher postoperative blood transfusion and hospital readmission (all p <0.05) (Table 1). Importantly, no increases in surgical or infectious complications were observed with combination therapy, supporting its perioperative safety.

At 1-, and 2-year follow-up, no significant differences in implant-related outcomes were observed between cohorts (p > 0.05).

In the subgroup analysis stratified by glycemic control, patients with HbA1c < 7.5 showed no significant differences in postoperative outcomes between cohorts. However, among those with HbA1c ≥ 7.5, the metformin monotherapy group (N=978) demonstrated 1.3 times higher odds of medical complications compared with the combination therapy (N=978) (p=0.03).

Discussion

This study represents, to our knowledge, the first large-scale comparative analysis of metformin monotherapy versus combination therapy with GLP-1 receptor agonists or SGLT2 inhibitors in diabetic patients undergoing total joint arthroplasty. Combination therapy was associated with fewer early postoperative medical complications, transfusions, and readmissions, without increased risk of infection or surgical complications. These findings suggest that the metabolic and anti-inflammatory effects of GLP-1 RA and SGLT2i may enhance early postoperative recovery and physiologic stability. Notably, subgroup analysis demonstrated that the benefit of combination therapy was most pronounced in patients with poor glycemic control (HbA1c ≥ 7.5), while no significant differences were observed among well-controlled patients, underscoring the potential importance of optimizing medical therapy in this higher-risk group. By one and two years, outcomes were comparable, indicating that benefits are concentrated in the acute postoperative phase. Further prospective research is needed to confirm these results and define optimal perioperative management strategies for patients receiving these agents.

Clinical Significance

Combination therapy with metformin and GLP-1 RA or SGLT2i reduces early postoperative complications after total joint arthroplasty, particularly in patients with poor glycemic control, supporting its safety and potential to enhance perioperative outcomes.

Table 1- Monotherapy vs. Combination therapy adverse outcomes at 3-, and 6-month follow-up period (n, Number of patients)

Outcomes	3 Months				6 Months			
	Monotherapy (N=4,124)	Combination therapy (N=4,124)	OR (95% CI)	P-value	Monotherapy (N=4,124)	Combination therapy (N=4,124)	OR (95% CI)	P-value
Medical complications, n(%)	823 (20.0)	721 (17.5)	1.18 (1.05, 1.32)	**0.004**	646 (20.6)	554 (17.7)	1.21 1.07, 1.37)	**0.003**
Myocardial infarction, n(%)	24 (0.6)	28 (0.7)	0.86 (0.5, 1.48)	0.58	73 (1.8)	85 (2.1)	0.86 (0.62, 1.17)	0.34
Renal/urinary complications, n(%)	273 (6.6)	236 (5.7)	1.17 (0.98, 1.40)	0.09	499 (12.4)	502 (12.4)	0.99 (0.87, 1.13)	0.92
Postop blood transfusion, n(%)	312 (7.6)	260 (6.3)	1.22 (1.03, 1.44)	**0.02**	388 (9.6)	333 (8.2)	1.18 (1.02, 1.38)	**0.03**
VTE, n(%)	135 (3.3)	108 (2.6)	1.26 (0.97, 1.63)	0.08	202 (5.0)	162 (4.0)	1.26 (1.02, 1.56)	**0.03**
Pneumonia, n(%)	59 (1.4)	67 (1.6)	0.88 (0.62, 1.25)	0.47	43 (1.4)	55 (1.8)	0.78 (0.52, 1.16)	0.22
Sepsis, n(%)	52 (1.3)	53 (1.3)	0.98 (0.67, 1.44)	0.92	39 (1.2)	36 (1.1)	1.08 (0.69, 1.71)	0.73
Prosthetic complications, n(%)	31 (0.8)	30 (0.7)	1.03 (0.62, 1.71)	0.90	56 (1.4)	60 (1.5)	0.93 (0.65, 1.35)	0.71
Revision surgery, n(%)	44 (1.1)	30 (0.7)	1.47 (0.92, 2.35)	0.1	67 (1.7)	57 (1.4)	1.18 (0.83, 1.68)	0.37
PJI, n(%)	56 (1.4)	44 (1.1)	1.28 (0.86, 1.90)	0.23	78 (1.9)	62 (1.5)	1.26 (0.90, 1.77)	0.17
Surgical site complications, n(%)	62 (1.5)	79 (1.9)	0.78 (0.56, 1.09)	0.15	87 (2.2)	104 (2.6)	0.83 (0.62, 1.11)	0.21
ER visits, n(%)	593 (14.4)	575 (13.9)	1.04 (0.92, 1.17)	0.57	474 (15.1)	478 (15.3)	0.99 (0.86, 1.14)	0.89
Hospital readmissions, n(%)	1,128 (27.4)	883 (21.4)	1.38 (1.25, 1.53)	**<0.001**	929 (29.7)	716 (22.9)	1.42 (1.27, 1.59)	**<0.001**