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Original Research Article

Comparative Effectiveness of Second-Line Oral Antidiabetic Drugs Added to Metformin Monotherapy in People with Type 2 Diabetes

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Conflict of interest: Nil

Abstract

Background: Despite metformin being the established first-line pharmacotherapy for type 2 diabetes mellitus, many patients require additional antidiabetic agents to achieve glycemic targets. The comparative effectiveness of second-line oral antidiabetic drug classes in real-world clinical settings requires further evaluation.

Methods: A prospective observational study was conducted involving 180 patients with inadequately controlled type 2 diabetes on metformin monotherapy, who were prescribed either sulfonylurea (n=60), DPP-4 inhibitor (n=60), or SGLT-2 inhibitor (n=60) as add-on therapy. Glycemic parameters, body weight, and adverse events were assessed at baseline and after 24 weeks of treatment.

Results: All three drug classes significantly reduced HbA1c from baseline. The SGLT-2 inhibitor group demonstrated the greatest HbA1c reduction (-1.18 ± 0.42%), followed by sulfonylurea (-1.08 ± 0.48%) and DPP-4 inhibitor (-0.86 ± 0.38%) groups (p=0.001). Significant weight reduction occurred with SGLT-2 inhibitors (-2.84 ± 1.42 kg; p<0.001), while weight gain was observed with sulfonylureas (+1.62 ± 1.18 kg; p<0.001). Hypoglycemia incidence was highest with sulfonylureas (18.3% vs. 3.3% DPP-4 inhibitors vs. 5.0% SGLT-2 inhibitors; p=0.006).

Conclusion: SGLT-2 inhibitors and sulfonylureas provide superior glycemic efficacy compared to DPP-4 inhibitors when added to metformin, with SGLT-2 inhibitors offering additional weight reduction benefits and lower hypoglycemia risk.

Keywords: Type 2 Diabetes Mellitus, Metformin, SGLT-2 Inhibitors, DPP-4 Inhibitors, Sulfonylureas, Glycemic Control, And Comparative Effectiveness.

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Introduction

Type 2 diabetes mellitus represents a growing global health challenge, affecting approximately 537 million adults worldwide with projections indicating substantial increases in prevalence over coming decades [1]. The progressive nature of pancreatic beta-cell dysfunction necessitates treatment intensification for most patients, with many requiring combination therapy to achieve and maintain glycemic targets [2]. Sustained hyperglycemia contributes to microvascular and macrovascular complications, emphasizing the importance of effective glycemic management.

Metformin remains the cornerstone of pharmacological therapy for type 2 diabetes, recommended as first-line treatment by major international guidelines due to its established efficacy, favorable safety profile, cardiovascular neutrality, and low cost [3]. However, despite adequate metformin titration, a significant proportion of patients fail to achieve target glycated hemoglobin (HbA1c) levels below 7.0%, necessitating addition of second-line agents [4]. The contemporary therapeutic landscape offers multiple oral antidiabetic drug classes for second-line therapy, each possessing distinct mechanisms of action and clinical profiles. Sulfonylureas, the oldest class of oral agents, enhance insulin secretion through pancreatic beta-cell stimulation and remain widely prescribed due to their proven efficacy and affordability [5]. However, concerns regarding weight gain, hypoglycemia risk, and potential cardiovascular effects have influenced prescribing patterns.

Dipeptidyl peptidase-4 inhibitors represent a newer drug class that enhances incretin hormone activity, providing glucose-dependent insulin secretion and glucagon suppression. These agents demonstrate favorable tolerability with weight neutrality and minimal hypoglycemia risk, though their glycemic efficacy is generally considered moderate [6]. Their excellent safety profile has contributed to widespread adoption, particularly in elderly populations.

Sodium-glucose cotransporter-2 inhibitors constitute the newest class of oral antidiabetic agents, functioning through insulin-independent mechanisms to promote urinary glucose excretion. Beyond glycemic benefits, SGLT-2 inhibitors provide weight reduction, blood pressure lowering, and demonstrated cardiovascular and renal protective effects in landmark clinical trials [7]. These pleiotropic benefits have positioned SGLT-2 inhibitors as preferred second-line agents in patients with established cardiovascular disease or chronic kidney disease.

While randomized controlled trials have established the efficacy of individual drug classes, head-to-head comparative effectiveness data in real-world clinical settings remain valuable for informing treatment decisions. Patient populations in routine clinical practice often differ from trial participants, and real-world studies provide complementary evidence regarding treatment outcomes [8].

Contemporary treatment guidelines emphasize individualized therapy selection based on patient characteristics, comorbidities, and treatment goals. However, for patients without compelling indications for specific drug classes, comparative effectiveness evidence can guide clinician and patient decision-making [9]. Furthermore, healthcare resource considerations in developing countries influence the accessibility and adoption of newer, more expensive agents.

Despite extensive literature on individual antidiabetic drug classes, comparative studies evaluating multiple second-line options in Indian patient populations remain limited. Ethnic variations in drug response, distinct phenotypic characteristics of diabetes in South Asian populations, and varying disease trajectories warrant population-specific investigations [10].

The aim of this study was to compare the effectiveness, safety, and tolerability of sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors as second-line oral antidiabetic therapy added to metformin monotherapy in patients with type 2 diabetes mellitus.

Materials and Methods

Study Design and Setting: This prospective observational cohort study was conducted at the Department of Endocrinology and Internal Medicine at a tertiary care hospital between January 2022 and December 2023.

Study Population: Patients with type 2 diabetes mellitus attending the outpatient diabetes clinic who were inadequately controlled on metformin monotherapy and requiring second-line oral antidiabetic therapy were screened for eligibility.

Inclusion Criteria

- Adults aged 30-70 years
- Diagnosed type 2 diabetes mellitus for at least 6 months
- Stable metformin therapy (≥1500 mg/day) for at least 3 months
- HbA1c between 7.5% and 10.0% at screening
- Estimated glomerular filtration rate (eGFR) ≥60 mL/min/1.73m²
- Willingness to comply with study procedures

Exclusion Criteria

- Type 1 diabetes or secondary diabetes
- Current insulin therapy or prior insulin use within 6 months
- Prior use of any second-line antidiabetic agent
- Pregnancy or breastfeeding
- Significant hepatic impairment (AST/ALT >3× upper normal limit)
- History of diabetic ketoacidosis or hyperosmolar hyperglycemic state
- Active malignancy or life-limiting illness
- Known hypersensitivity to study medications
- Recurrent genitourinary infections

Sample Size: Based on previous studies reporting mean HbA1c differences of 0.3% between drug classes with standard deviation of 0.5%, a minimum of 52 patients per group was required for 80% power at α=0.05. Accounting for 15% attrition, 60 patients were enrolled in each treatment arm, totaling 180 participants.

Treatment Groups: Patients were allocated to treatment groups based on prescribing physician judgment considering clinical characteristics, patient preferences, and formulary availability. The three treatment groups were:

Group A (Sulfonylurea): Glimepiride 1-4 mg once daily, titrated based on glycemic response

Group B (DPP-4 Inhibitor): Sitagliptin 100 mg once daily or equivalent

Group C (SGLT-2 Inhibitor): Dapagliflozin 10 mg or empagliflozin 10-25 mg once daily

All patients continued stable metformin therapy throughout the study period.

Data Collection and Assessments: Baseline assessments included demographic characteristics, diabetes duration, concomitant medications, anthropometric measurements, and laboratory parameters.

Follow-up assessments were conducted at 12 and 24 weeks.

Glycemic Parameters:

- HbA1c (measured by high-performance liquid chromatography)
- Fasting plasma glucose (FPG)
- Postprandial plasma glucose (PPG)

Anthropometric Measurements:

- Body weight
- Body mass index (BMI)
- Waist circumference

Safety Parameters:

- Hypoglycemia episodes (self-reported and documented)
- Adverse events assessment
- Renal function (serum creatinine, eGFR)
- Hepatic function (AST, ALT)

Definitions

Glycemic target achievement: HbA1c <7.0% at 24 weeks

Hypoglycemia: Blood glucose <70 mg/dL with or without symptoms

Severe hypoglycemia: Episode requiring third-party assistance

Statistical Analysis: Statistical analysis was performed using SPSS version 25.0 (IBM Corporation, Armonk, NY). Continuous variables were expressed as mean ± standard deviation, while categorical variables were presented as frequencies and percentages. Normality was assessed using Shapiro-Wilk test. One-way ANOVA with Tukey's post-hoc test compared continuous variables across groups. Chi-square test compared categorical variables. Paired t-test assessed within-group changes from baseline. Analysis of covariance (ANCOVA) adjusted for baseline differences. A two-tailed p-value <0.05 was considered statistically significant.

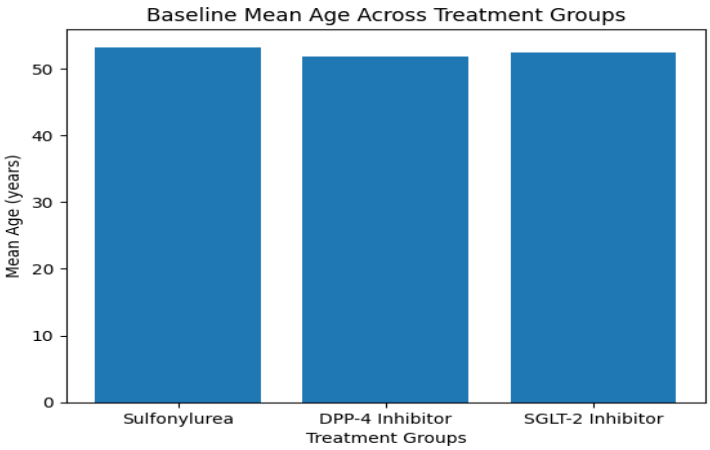
Results

Baseline Characteristics: A total of 180 patients were enrolled and completed the 24-week study period. The mean age was 52.4 ± 9.8 years, with slight male predominance (54.4%). Groups were comparable regarding demographic characteristics, diabetes duration, and baseline glycemic parameters. Baseline characteristics are presented in Table 1.

Table 1: Baseline Demographic and Clinical Characteristics

Variable	Sulfonylurea (n=60)	DPP-4 Inhibitor (n=60)	SGLT-2 Inhibitor (n=60)	p-value
Age (years), mean ± SD	53.2 ± 10.2	51.8 ± 9.4	52.4 ± 9.8	0.724
Male, n (%)	34 (56.7)	32 (53.3)	32 (53.3)	0.912
Diabetes duration (years), mean ± SD	6.4 ± 3.2	5.8 ± 3.0	6.2 ± 3.4	0.542
Metformin dose (mg/day), mean ± SD	1780 ± 280	1820 ± 260	1760 ± 290	0.468
BMI (kg/m²), mean ± SD	28.4 ± 4.2	27.8 ± 3.8	28.2 ± 4.0	0.682
Body weight (kg), mean ± SD	74.6 ± 12.8	72.4 ± 11.6	73.8 ± 12.2	0.584
Waist circumference (cm), mean ± SD	96.4 ± 10.2	94.8 ± 9.6	95.6 ± 10.0	0.686
HbA1c (%), mean ± SD	8.42 ± 0.68	8.36 ± 0.64	8.48 ± 0.72	0.612
FPG (mg/dL), mean ± SD	168.4 ± 32.6	164.2 ± 28.4	172.6 ± 34.2	0.318
PPG (mg/dL), mean ± SD	248.6 ± 48.2	242.4 ± 44.6	254.8 ± 52.4	0.354
eGFR (mL/min/1.73m²), mean ± SD	86.4 ± 14.2	88.2 ± 12.8	84.8 ± 15.6	0.412
Hypertension, n (%)	32 (53.3)	28 (46.7)	34 (56.7)	0.524
Dyslipidemia, n (%)	38 (63.3)	36 (60.0)	40 (66.7)	0.734

BMI: Body mass index; eGFR: Estimated glomerular filtration rate; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose; SD: Standard deviation



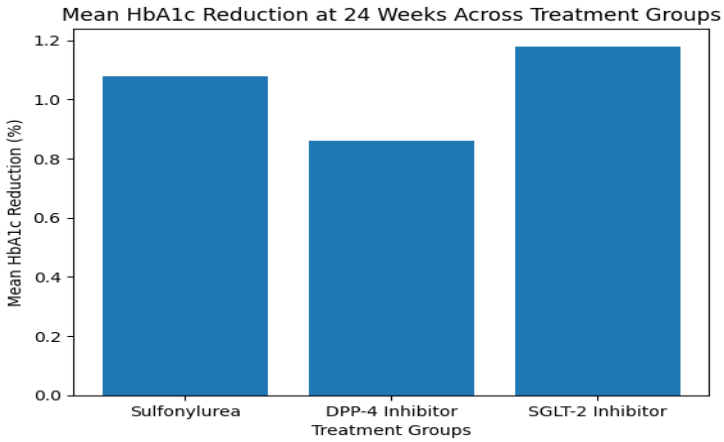
Graph 1. Comparison of Baseline mean age across treatment groups

Glycemic Efficacy Outcomes: All treatment groups demonstrated significant HbA1c reductions from baseline at 24 weeks. The SGLT-2 (n=60) inhibitor group showed the greatest mean HbA1c reduction (-1.18 ± 0.42%), followed by sulfonylurea (n=60) (-1.08 ± 0.48%) and DPP-4 inhibitor (n=60) (-0.86 ± 0.38%) groups. ANCOVA confirmed significant between-group differences (p=0.001). Glycemic outcomes are detailed in Table 2.

Table 2: Glycemic Parameters at Baseline and 24 Weeks

Parameter	Sulfonylurea (n=60)	DPP-4 Inhibitor (n=60)	SGLT-2 Inhibitor (n=60)	p-value (between groups)
HbA1c (%)				
Baseline	8.42 ± 0.68	8.36 ± 0.64	8.48 ± 0.72	0.612
24 weeks	7.34 ± 0.56	7.50 ± 0.52	7.30 ± 0.48	0.086
Change from baseline	-1.08 ± 0.48*	-0.86 ± 0.38*	-1.18 ± 0.42*	0.001**
FPG (mg/dL)				
Baseline	168.4 ± 32.6	164.2 ± 28.4	172.6 ± 34.2	0.318
24 weeks	128.6 ± 24.8	134.8 ± 22.6	124.2 ± 26.4	0.048**
Change from baseline	-39.8 ± 18.4*	-29.4 ± 16.2*	-48.4 ± 20.6*	<0.001**
PPG (mg/dL)				
Baseline	248.6 ± 48.2	242.4 ± 44.6	254.8 ± 52.4	0.354
24 weeks	186.4 ± 38.6	192.6 ± 36.4	184.2 ± 40.8	0.426
Change from baseline	-62.2 ± 28.4*	-49.8 ± 24.6*	-70.6 ± 32.2*	0.001**
Target Achievement				
HbA1c <7.0%, n (%)	22 (36.7)	16 (26.7)	26 (43.3)	0.142
HbA1c <7.5%, n (%)	38 (63.3)	32 (53.3)	42 (70.0)	0.148

***p<0.05 within-group change from baseline; *p<0.05 between-group comparison; FPG: Fasting plasma glucose; PPG: Postprandial plasma glucose**



Graph 2: Mean HbA1c reduction at 24 weeks across treatment group

Body Weight and Anthropometric Changes: Significant between-group differences were observed in body weight changes.

The SGLT-2 inhibitor group demonstrated significant weight reduction (-2.84 ± 1.42 kg; p<0.001), while the sulfonylurea group showed weight gain (+1.62 ± 1.18 kg; p<0.001). The DPP-4 inhibitor group remained weight-neutral (-0.28 ± 0.86 kg; p=0.412).

Safety and Tolerability: Hypoglycemia incidence was significantly higher in the sulfonylurea group compared to other groups.

Genitourinary infections occurred more frequently with SGLT-2 inhibitors. No severe hypoglycemia or serious adverse events requiring hospitalization were reported. Safety outcomes are presented in Table 3.

Table 3: Body Weight Changes and Adverse Events at 24 Weeks

Parameter	Sulfonylurea (n=60)	DPP-4 Inhibitor (n=60)	SGLT-2 Inhibitor (n=60)	p-value
Body Weight Changes				
Baseline weight (kg)	74.6 ± 12.8	72.4 ± 11.6	73.8 ± 12.2	0.584
Weight at 24 weeks (kg)	76.2 ± 13.2	72.1 ± 11.4	71.0 ± 11.8	0.042*
Weight change (kg)	+1.62 ± 1.18	-0.28 ± 0.86	-2.84 ± 1.42	<0.001*
BMI change (kg/m²)	+0.58 ± 0.42	-0.10 ± 0.32	-1.02 ± 0.52	<0.001*
Waist circumference change (cm)	+1.2 ± 0.8	-0.2 ± 0.6	-2.4 ± 1.2	<0.001*
Adverse Events, n (%)				
Any hypoglycemia	11 (18.3)	2 (3.3)	3 (5.0)	0.006*
Severe hypoglycemia	0 (0.0)	0 (0.0)	0 (0.0)	-
Genitourinary infections	1 (1.7)	2 (3.3)	8 (13.3)	0.018*
Gastrointestinal symptoms	4 (6.7)	6 (10.0)	4 (6.7)	0.724
Dizziness/Postural symptoms	2 (3.3)	1 (1.7)	4 (6.7)	0.346
Peripheral edema	2 (3.3)	1 (1.7)	0 (0.0)	0.358
Treatment discontinuation	2 (3.3)	1 (1.7)	3 (5.0)	0.582
Blood Pressure Changes				
SBP change (mmHg)	-0.8 ± 4.2	-1.2 ± 3.8	-4.6 ± 5.4	<0.001*
DBP change (mmHg)	-0.4 ± 2.8	-0.6 ± 2.4	-2.2 ± 3.2	0.002*

Statistically significant (p<0.05); BMI: Body mass index; DBP: Diastolic blood pressure; SBP: Systolic blood pressure

Subgroup Analyses: In patients with baseline BMI ≥30 kg/m² (n=62), SGLT-2 inhibitors demonstrated greater HbA1c reduction compared to sulfonylureas (-1.32 ± 0.48% vs. -0.96 ± 0.52%; p=0.024). Among patients aged ≥60 years (n=48), DPP-4 inhibitors showed comparable efficacy to sulfonylureas with significantly fewer hypoglycemia events.

Discussion

This prospective observational study demonstrates that sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors all provide clinically meaningful glycemic improvements when added to metformin monotherapy in patients with type 2 diabetes. However, important differences in glycemic efficacy, weight effects, and safety profiles were observed that have implications for individualized treatment selection.

The HbA1c reductions observed across treatment groups align with findings from large-scale randomized controlled trials evaluating these drug classes. The SGLT-2 inhibitor group demonstrated the greatest HbA1c reduction, consistent with meta-analyses reporting mean HbA1c reductions of 0.5-1.0% for this drug class [11]. The magnitude of glycemic improvement reflects the insulin-independent mechanism that remains effective regardless of beta-cell function status.

The glycemic efficacy of sulfonylureas in our study, with mean HbA1c reduction of 1.08%, confirms the established potency of this drug class. Historical data from the UKPDS demonstrated durable glycemic benefits with sulfonylurea therapy [12]. Despite concerns regarding progressive beta-cell decline with sulfonylurea use, short-term glycemic efficacy remains robust, though long-term durability may favor newer agents.

The modest HbA1c reduction with DPP-4 inhibitors (-0.86%) is consistent with their established efficacy profile. Pooled analyses of DPP-4 inhibitor trials have reported mean HbA1c reductions of 0.6-0.8% when added to metformin [13]. The glucose-dependent mechanism provides inherent safety advantages but may limit maximum glycemic efficacy compared to insulin secretagogues or agents with insulin-independent actions. The significant weight reduction observed with SGLT-2 inhibitors (-2.84 kg) represents a clinically important advantage in the predominantly

overweight and obese diabetic population. Glycosuria-induced caloric loss translates to sustainable weight reduction, addressing the obesogenic tendency of several antidiabetic medications [14]. Conversely, weight gain with sulfonylureas reflects enhanced insulin secretion promoting lipogenesis and may counteract cardiovascular benefits of improved glycemic control.

The higher hypoglycemia incidence with sulfonylureas (18.3%) compared to DPP-4 inhibitors (3.3%) and SGLT-2 inhibitors (5.0%) confirms established safety differences between drug classes. Sulfonylurea-induced hypoglycemia results from non-glucose-dependent insulin secretion, while incretin-based and SGLT-2 inhibitor mechanisms provide inherent protection against hypoglycemia [15]. This safety consideration particularly influences treatment selection in elderly patients and those with hypoglycemia unawareness.

The blood pressure reductions observed with SGLT-2 inhibitors align with their established hemodynamic effects. Modest natriuresis and osmotic diuresis contribute to blood pressure lowering, providing additional cardiovascular risk factor modification beyond glycemic control [16]. These pleiotropic effects underpin the cardiovascular outcome benefits demonstrated in landmark trials including EMPA-REG OUTCOME and CANVAS.

Genitourinary infections with SGLT-2 inhibitors represent a recognized class effect resulting from glucosuria-enhanced microbial growth. The 13.3% incidence observed in our study falls within reported ranges, with most infections being mild and manageable with standard antimicrobial therapy [17]. Appropriate patient counseling regarding genital hygiene can minimize infection risk. The treatment selection in our observational study reflected real-world prescribing patterns influenced by patient characteristics, physician preferences, and formulary considerations. While this introduces potential selection bias, the comparable baseline characteristics between groups and statistical adjustment for confounders strengthen comparative validity. Real-world evidence complements randomized trial data by demonstrating effectiveness in routine clinical populations [18].

The findings support current guideline recommendations advocating individualized second-line agent selection based on patient characteristics. For patients prioritizing weight management or with established cardiovascular disease, SGLT-2 inhibitors offer compelling advantages. For cost-sensitive patients without hypoglycemia risk factors, sulfonylureas remain effective options. DPP-4 inhibitors provide favorable tolerability profiles suitable for elderly or frail patients [19].

Several limitations merit acknowledgment. The observational design precludes definitive causal inferences. The 24-week duration may not capture long-term efficacy and durability differences. Single-center recruitment may limit generalizability. Additionally, cardiovascular and renal outcomes, increasingly important treatment endpoints, were not assessed.

Conclusion

This study demonstrates that sulfonylureas, DPP-4 inhibitors, and SGLT-2 inhibitors all provide effective glycemic control when added to metformin monotherapy in patients with type 2 diabetes mellitus. SGLT-2 inhibitors and sulfonylureas demonstrated superior HbA1c reduction compared to DPP-4 inhibitors, with SGLT-2 inhibitors offering additional benefits including significant weight reduction, blood pressure lowering, and low hypoglycemia risk.

Sulfonylureas remain effective and affordable options but are associated with weight gain and higher hypoglycemia rates. DPP-4 inhibitors provide favorable tolerability with weight neutrality, suitable for patients prioritizing safety over maximal glycemic efficacy. These findings support individualized second-line therapy selection based on patient characteristics, treatment goals, and adverse effect profiles.

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