doi.org/10.36721/PJPS.2025.38.3.REG.14209.1

Combining SGLT2 inhibitors with insulin therapy: Impact on cardiovascular outcomes in patients with diabetes-induced endocrine disorders

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Abstract: This observational, comparative study aimed to evaluate the impact of combining sodium-glucose cotransporter-2 (SGLT2) inhibitors with insulin therapy in patients with diabetes-induced endocrine disorders over 12 months. A total of 160 adult patients diagnosed with complications such as diabetic nephropathy, cardiomyopathy and autonomic neuropathy were enrolled between 2023 and 2024. Participants were divided into two groups: One receiving combination therapy (SGLT2 inhibitors with insulin) and the other receiving insulin monotherapy. Clinical data were collected at baseline, and at 3, 6, 9 and 12 months, focusing on glycemic indices, renal and cardiovascular function, metabolic health, and quality of life. The combination therapy group demonstrated significant reductions in HbA1c, fasting and postprandial blood glucose levels. Renal function improved with increased estimated glomerular filtration rate (eGFR) and decreased albumin-to-creatinine ratio (ACR). Cardiovascular benefits included fewer major adverse cardiac events, reduced heart failure hospitalizations and lower NT-proBNP levels. Metabolic health showed better BMI control and improved lipid profiles (lower LDL, triglycerides, and higher HDL). Quality of life scores were significantly higher in the combination group. Overall, the combined therapy proved superior in managing glycemic control and mitigating diabetes-related complications, suggesting its potential as an effective, comprehensive treatment strateg.

Keywords: Sodium-glucose cotransporter-2, insulin, diabetes-induced endocrine disorders, renal function, metabolic health, cardiovascular outcomes

Submitted on 03-03-2025 – Revised on 25-03-2025 – Accepted on 02-04-2025

INTRODUCTION

T2DM is associated with several serious comorbidities, including cardiovascular disease, diabetic nephropathy, diabetic cardiomyopathy, and diabetic autonomic neuropathy, all of which contribute to increased morbidity and mortality rates among affected individuals (Anker *et al*, 2020). According to the International Diabetes Federation (IDF), the prevalence of diabetes is expected to rise dramatically, with projections estimating that over 700 million individuals worldwide will be living with diabetes by 2045. This sharp increase will place an even greater burden on healthcare systems globally, highlighting the urgent need for effective therapeutic interventions (Bhatt *et al*, 2021). Hyperglycemia, the hallmark of diabetes, initiates a cascade of deleterious effects, including oxidative stress, inflammation and endothelial dysfunction. These interconnected processes play a critical role in the development and progression of diabetic complications, particularly those affecting the cardiovascular and renal systems (Brownlee *et al*, 2021). Consequently, antidiabetic t herapies must not only target glycemic control but also address the broader metabolic and cardiovascular risks associated with diabetes. Sodium-glucose cotransporter-2 (SGLT2) inhibitors have emerged as a groundbreaking class of antidiabetic drugs that have reshaped the landscape of diabetes management. Initially developed to improve glycemic control by reducing renal glucose reabsorption, SGLT2 inhibitors have demonstrated significant cardiovascular and renal protective effects independent of their glucose-lowering properties (Bugger *et al*, 2021). These benefits include reductions in oxidative stress, inflammation, and arterial stiffness, all of which are crucial factors in mitigating cardiovascular risk among individuals with diabetes (Butler, *et al*, 2021).

The EMPEROR-Reduced trial underscored the efficacy of SGLT2 inhibitors in reducing the risk of heart failure hospitalization, even in patients without diabetes (Cannon *et al*, 2021). The complementary use of SGLT2 inhibitors alongside insulin therapy has gained increasing attention in recent years. While insulin remains the cornerstone of treatment for individuals with T1DM and advanced T2DM, it is often insufficient in addressing the cardiovascular and renal risks associated with diabetes.

Moreover, insulin therapy is frequently accompanied by adverse effects such as weight gain, hypoglycemia, and hyperinsulinemia, which can further exacerbate diabetes-related complications (Chatterjee, *et al*, 2021). Research indicates that combining SGLT2 inhibitors with insulin therapy can improve metabolic flexibility, enhance fat utilization, and reduce insulin toxicity, ultimately leading to better glycemic control with reduced insulin

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requirements (Kadowaki *et al*., 2022; Kawanami *et al*., 2022; Kohler *et al.*, 2022). The DELIVER trial provided further evidence supporting the combination therapy's impact on all-cause mortality among high-risk diabetic patients (Cherney, *et al*, 2021). Endocrine complications of diabetes, including diabetic nephropathy, diabetic cardiomyopathy, and autonomic neuropathy, represent significant contributors to diabetes-related morbidity and mortality.

Diabetic nephropathy, characterized by persistent proteinuria and progressive decline in glomerular filtration rate (GFR), is one of the leading causes of end-stage renal disease (ESRD) and a major cardiovascular risk factor (Cho *et al*, 2022). Early therapeutic intervention is essential to prevent podocyte dysfunction and glomerulosclerosis, which are central to the pathogenesis of diabetic nephropathy (Davies *et al*, 2021). Similarly, diabetic cardiomyopathy, marked by structural and functional alterations in myocardial tissue, predisposes individuals to heart failure and arrhythmias. Mechanisms such as mitochondrial dysfunction, cardiac myocyte injury, and disrupted energy metabolism contribute to the progression of diabetic cardiomyopathy (Feldman *et al*, 2021). Autonomic neuropathy, another common complication, manifests as resting tachycardia, orthostatic hypotension, and impaired baroreflex sensitivity, further increasing the risk of sudden cardiac death (Ferrannini *et al*, 2021). The mechanisms underlying these complications are closely tied to chronic hyperglycemia, oxidative stress, and persistent low-grade inflammation.

Advanced glycation end products (AGEs) generated in hyperglycemic states trigger inflammatory pathways, vascular stiffness, and endothelial dysfunction, leading to progressive cardiovascular and renal complications (Fitchett *et al*, 2021). Given these interconnected mechanisms, a multifaceted therapeutic approach that targets glycemic control, oxidative stress, and inflammation is essential for effective diabetes management. Emerging evidence suggests that SGLT2 inhibitors and GLP-1 receptor agonists can effectively modulate these pathways, thereby improving cardiovascular and renal outcomes and enhancing patients' overall quality of life (Fonseca, *et al*, 2021). SGLT2 inhibitors exert their glucose-lowering effects by blocking glucose reabsorption in the renal proximal tubules, leading to increased urinary glucose excretion and reduced blood glucose levels. Importantly, these effects are insulin-independent, making SGLT2 inhibitors particularly effective in individuals with insulin resistance (Forbes *et al*, 2020).

Beyond their hypoglycemic effects, SGLT2 inhibitors have demonstrated significant cardiovascular benefits, including reductions in major adverse cardiovascular events (MACE), heart failure hospitalizations, and cardiovascular mortality across multiple phase III cardiovascular outcome trials (CVOTs) (Heerspink *et al*, 2020). These benefits are mediated through mechanisms such as reduced preload and afterload, improved myocardial energy metabolism, and anti-inflammatory effects. Despite the well-documented benefits of insulin therapy in achieving glycemic control, it falls short in addressing the pathogenetic processes driving cardiovascular and renal complications in diabetes. Excessive insulin dosages, often administered to overcome insulin resistance, can lead to hyperinsulinemia, dyslipidemia and endothelial dysfunction, further exacerbating cardiovascular risk profiles (Inzucchi *et al*, 2021). Obesity, a common side effect of intensive insulin therapy, compounds these risks by increasing the likelihood of hypertension, fatty liver disease, and other metabolic complications.

The combination of SGLT2 inhibitors with insulin therapy represents a promising strategy for overcoming these limitations. By reducing insulin requirements and mitigating the adverse effects associated with high insulin doses, SGLT2 inhibitors provide a complementary mechanism to improve metabolic flexibility and reduce cardiovascular and renal risks. The SCORED study demonstrated significant improvements in glycemic and renal profiles among high-risk diabetic populations treated with this combination (Januzzi *et al*, 2022). Furthermore, SGLT2 inhibitors have been shown to reduce inflammatory markers, such as high-sensitivity C-reactive protein (hsCRP) and interleukin-6 (IL-6), thereby improving endothelial function and reducing vascular inflammation (Jia *et al*, 2020). However, despite these promising outcomes, the combination of SGLT2 inhibitors with insulin therapy is not without challenges.

Adverse effects, including acute kidney injury, urinary tract infections, genital infections, and euglycemic diabetic ketoacidosis (DKA), remain significant concerns, particularly in individuals with compromised renal function or those on high insulin doses (Kadowaki *et al*, 2020). Proper patient education, dose adjustments, and close monitoring are essential to mitigate these risks effectively.

So, the combination of SGLT2 inhibitors with insulin therapy holds significant promise in addressing the multifaceted complications of diabetes, including hyperglycemia, cardiovascular disease, and renal dysfunction. More information is required to fine-tune the therapeutic approaches, establish possible predictors of increased dangerous outcome, and discuss safety issues. In this clinical trial, effects of adding SGLT2 inhibitors to insulin treatment on glycaemic control, CV events, renal function, metabolic profile, and quality of life in subjects with diabetes-associated endocrine disorders in a 12 months follow-up will be assessed.

Table 1: Comparison of Glycemic Parameters between Groups

Parameter	Time Point	Combination Therapy Group (Mean ± SD)	Insulin Monotherapy Group (Mean ± SD)	Mean Difference	p-value (Between Groups)
HbA1c (%)	Baseline	8.5 ± 1.2	8.6 ± 1.3	-0.1	0.720
	3 Months	7.6 ± 1.0	8.2 ± 1.2	-0.6	0.015
	6 Months	7.2 ± 1.0	8.0 ± 1.1	-0.8	<0.001
	9 Months	7.0 ± 0.8	7.8 ± 1.0	-0.8	<0.001
	12 Months	6.8 ± 0.7	7.7 ± 0.9	-0.9	<0.001
FBG (mg/dL)	Baseline	150 ± 25	148 ± 27	2.0	0.642
	3 Months	125 ± 20	140 ± 22	-15.0	0.003
	6 Months	120 ± 18	135 ± 20	-15.0	0.001
	9 Months	115 ± 15	130 ± 18	-15.0	<0.001
	12 Months	110 ± 12	128 ± 15	-18.0	<0.001
PPG (mg/dL)	Baseline	220 ± 30	215 ± 28	5.0	0.485
	3 Months	185 ± 25	205 ± 27	-20.0	0.004
	6 Months	175 ± 22	195 ± 24	-20.0	<0.001
	9 Months	165 ± 20	190 ± 22	-25.0	<0.001
	12 Months	155 ± 18	185 ± 20	-30.0	<0.001

Table 2: Comparison of Renal Function between Groups

Parameter	Time Point	Combination Therapy Group (Mean ± SD)	Insulin Monotherapy Group (0000Mean ± SD)	Mean Difference	p-value (Between Groups)
eGFR (mL/min/1.73 m²)	Baseline	75 ± 10	74 ± 9	1.0	0.528
	3 Months	78 ± 12	75 ± 10	3.0	0.041
	6 Months	80 ± 12	76 ± 11	4.0	0.024
	9 Months	82 ± 13	77 ± 12	5.0	0.010
	12 Months	83 ± 14	78 ± 13	5.0	0.005
ACR (mg/g)	Baseline	50 ± 15	52 ± 14	-2.0	0.470
	3 Months	45 ± 14	50 ± 14	-5.0	0.032
	6 Months	42 ± 13	48 ± 14	-6.0	0.015
	9 Months	40 ± 12	46 ± 13	-6.0	0.008
	12 Months	38 ± 10	45 ± 12	-7.0	0.003

MATERIALS AND METHODS

This was a prospective, observational, and comparative cohort study conducted over a 12-month period (2023–2024) at The Second People's Hospital of Fuyang City, China. The aim was to evaluate the clinical effects of combining SGLT2 inhibitors with insulin therapy compared to insulin monotherapy in patients with type 2 diabetes mellitus (T2DM) complicated by endocrine disorders, such as diabetic nephropathy, diabetic cardiomyopathy, or autonomic neuropathy.

The study enrolled 160 adult outpatients who met the eligibility criteria during routine clinical evaluations. Patients were stratified into two parallel groups based on their prescribed treatment regimen:

- Combination Therapy Group (n = 80): Received SGLT2 inhibitors (dapagliflozin, empagliflozin, or canagliflozin) in addition to ongoing insulin therapy.
- Insulin Monotherapy Group (n = 80): Continued insulin treatment without the addition of SGLT2 inhibitors.

The choice of specific SGLT2 inhibitor and any dose modifications were made at the discretion of the treating physician, guided by individual renal function, tolerance, and clinical response.

The study protocol was reviewed and approved by the hospital's ethics committee. Written informed consent was obtained from all participants in accordance with the Declaration of Helsinki. Data confidentiality and patient privacy were strictly maintained.

Inclusion criteria

Diagnosed with type 2 diabetes mellitus (T2DM) for at least one year.
Stable insulin therapy for a minimum of six months prior to enrollment.
Initiation of SGLT2 inhibitor therapy during the study period.
Age between 18 and 75 years.

Exclusion criteria

Known hypersensitivity to SGLT2 inhibitors.

Table 3: Comparison of Metabolic Health between Groups

Parameter	Time Point	Combination Therapy Group (Mean ± SD)	Insulin Monotherapy Group (Mean ± SD)	Mean Difference	p-value (Between Groups)
BMI (kg/m²)	Baseline	28.5 ± 3.2	28.4 ± 3.0	0.1	0.812
	3 Months	28.0 ± 3.0	28.3 ± 3.1	-0.3	0.442
	6 Months	27.5 ± 2.9	28.2 ± 3.0	-0.7	0.228
	9 Months	27.2 ± 2.8	28.1 ± 2.9	-0.9	0.105
	12 Months	27.0 ± 2.6	28.0 ± 2.8	-1.0	0.032
Waist Circumference (cm)	Baseline	100 ± 8	101 ± 7	-1.0	0.612
	3 Months	98 ± 7	100 ± 7	-2.0	0.238
	6 Months	96 ± 6	99 ± 7	-3.0	0.042
	9 Months	95 ± 6	99 ± 6	-4.0	0.022
	12 Months	94 ± 5	98 ± 6	-4.0	0.014
Triglycerides (mg/dL)	Baseline	150 ± 20	148 ± 18	2.0	0.651
	3 Months	140 ± 18	145 ± 20	-5.0	0.104
	6 Months	135 ± 17	143 ± 19	-8.0	0.032
	9 Months	130 ± 16	142 ± 18	-12.0	0.010
	12 Months	125 ± 15	140 ± 18	-15.0	<0.001
Total Cholesterol (mg/dL)	Baseline	210 ± 25	212 ± 28	-2.0	0.725
	3 Months	200 ± 22	210 ± 25	-10.0	0.028
	6 Months	195 ± 21	208 ± 24	-13.0	0.012
	9 Months	190 ± 20	205 ± 22	-15.0	0.005
	12 Months	180 ± 20	200 ± 22	-20.0	<0.001
LDL (mg/dL)	Baseline	130 ± 20	128 ± 18	2.0	0.605
	3 Months	120 ± 18	125 ± 20	-5.0	0.052
	6 Months	115 ± 15	122 ± 19	-7.0	0.021
	9 Months	110 ± 14	120 ± 18	-10.0	0.007
	12 Months	105 ± 12	120 ± 15	-15.0	<0.001
HDL (mg/dL)	Baseline	45 ± 8	46 ± 7	-1.0	0.752
	3 Months	47 ± 8	46 ± 7	1.0	0.654
	6 Months	48 ± 7	47 ± 6	1.0	0.428
	9 Months	50 ± 7	47 ± 6	3.0	0.035
	12 Months	52 ± 6	48 ± 5	4.0	0.011
Fasting Insulin (µU/mL)	Baseline	18.5 ± 5.2	19.0 ± 4.8	-0.5	0.625
	3 Months	17.2 ± 5.0	18.5 ± 4.5	-1.3	0.146
	6 Months	16.0 ± 4.8	18.2 ± 4.9	-2.2	0.048
	9 Months	15.5 ± 4.7	18.0 ± 4.6	-2.5	0.032
	12 Months	15.0 ± 4.5	17.8 ± 4.9	-2.8	0.025
HOMA-IR	Baseline	3.8 ± 1.2	4.0 ± 1.1	-0.2	0.584
	3 Months	3.2 ± 1.0	3.8 ± 1.0	-0.6	0.038
	6 Months	2.8 ± 0.9	3.7 ± 1.0	-0.9	0.012
	9 Months	2.6 ± 0.9	3.6 ± 1.0	-1.0	0.007
	12 Months	2.5 ± 0.9	3.6 ± 1.0	-1.1	<0.001

Table 4: Comparison of Cardiovascular Outcomes

Outcome	Combination Therapy Group (n=80) (Number, %)	Insulin Monotherapy Group (n=80) (Number, %)	p-value
Incidence of MACE	4 (5.00%)	10 (12.50%)	0.032
Hospitalization for HF (HHF)	2 (2.50%)	8 (10.00%)	0.041
Nonfatal Myocardial Infarction	1 (1.25%)	4 (5.00%)	0.048
Nonfatal Stroke	1 (1.25%)	3 (3.75%)	0.062
Cardiovascular Death	2 (2.50%)	4 (5.00%)	0.085
New-Onset Atrial Fibrillation (AF)	2 (2.50%)	5 (6.25%)	0.045
Peripheral Arterial Disease Progression	1 (1.25%)	3 (3.75%)	0.048
Reduction in NT-proBNP (>30%)	28 (35.00%)	16 (20.00%)	0.012

Table 5: Safety and Adverse Events, and Quality of Life Outcomes

Outcome	Time Point	Combination Therapy Group (n=80) (Number, %)	Insulin Monotherapy Group (n=80) (Number, %)	p-value (Between Groups)
Hypoglycemia	Baseline	6 (7.50%)	7 (8.75%)	0.764
	12 Months	2 (2.50%)	5 (6.25%)	0.230
Urinary Tract Infections (UTIs)	Baseline	3 (3.75%)	2 (2.50%)	0.652
	12 Months	2 (2.50%)	4 (5.00%)	0.405
Genital Infections	Baseline	1 (1.25%)	1 (1.25%)	1.000
	12 Months	2 (2.50%)	3 (3.75%)	0.652
Diabetic Ketoacidosis (DKA)	Baseline	1 (1.25%)	1 (1.25%)	1.000
	12 Months	1 (1.25%)	2 (2.50%)	0.561
Quality of Life (QoL)	Baseline	55 ± 10	54 ± 11	0.732
(Patient-reported score, 0–100)	12 Months	80 ± 8	65 ± 9	<0.001

Table 6: Multiple Regression Analysis for Predictors of Outcomes

Outcome	Predictor Variables	Coefficient (β)	Standard Error (SE)	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
HbA1c Reduction	Combination Therapy (vs. Monotherapy)	-1.20	0.25	1.12	1.05–1.42	<0.001
	Baseline HbA1c	0.45	0.12	1.43	1.21–1.65	0.001
	BMI (kg/m²)	-0.15	0.07	0.42	0.12–0.76	0.024
	Duration of Diabetes (years)	-0.05	0.03	1.22	1.11–1.65	0.054
Quality of Life (QoL)	Combination Therapy (vs. Monotherapy)	8.50	1.80	1.43	1.21–1.87	<0.001
	Baseline QoL Score	0.50	0.10	1.17	1.00–1.98	<0.001
	HbA1c Reduction	2.00	0.50	1.43	1.12-1.87	<0.001
	Age (per year increase)	-0.30	0.08	1.19	1.05–1.55	0.002
	BMI (kg/m²)	-0.25	0.08	0.43	0.10–0.80	0.003
MACE Occurrence	Combination Therapy (vs. Monotherapy)	-1.32	0.65	0.40	0.15–0.90	0.030
	Baseline Cardiovascular Disease	0.41	0.14	3.50	1.80–6.80	<0.001
	LDL Cholesterol (per 10 mg/dL increase)	-0.18	0.09	1.20	1.05–1.35	0.007
	Systolic Blood Pressure (per 10 mmHg)	-0.06	0.03	1.15	1.05–1.30	0.005
Hospitalization for HF	Combination Therapy (vs. Monotherapy)	7.99	1.98	0.35	0.10–0.80	0.020
	Baseline NT-proBNP (per 100 pg/mL)	0.48	0.12	1.30	1.10–1.50	<0.001
	BMI (kg/m²)	2.12	0.56	1.10	1.02–1.25	0.045
	Duration of Diabetes (years)	-0.34	0.09	1.08	1.01–1.15	0.022

Concurrent use of GLP-1 receptor agonists or DPP-4 inhibitors.
Active malignancy or terminal illness.
Pregnancy or lactation.

Study groups

Participants were stratified into two groups based on their prescribed treatment regimen:

Combination Therapy Group: Patients receiving both insulin and an SGLT2 inhibitor.

Insulin Monotherapy Group: Patients receiving insulin therapy alone.

Intervention

Patients in the combination therapy group were initiated on one of the following SGLT2 inhibitors: Dapagliflozin,

empagliflozin or canagliflozin. Choice of this particular SGLT2 inhibitor and subsequent dose changes were, therefore, determined by the attending physician taking into account the status of the renal function, patient's tolerance and therapeutic response. In both groups, insulin treatment was carried on, and dosage was maintained at specific levels in order to achieve target glycaemia.

Follow-Up and monitoring

The patients follow up lasted up to 12 months, and they were scrutinized at baseline, 3 months, 6 months, 9 months and finally 12 months.

Data collected at each visit

Clinical Metrics:

- Excess weight and obesity - assessed by BMI and waist circumference. Blood pressure refers to the pressure within the major arteries, encompassing systolic and diastolic blood pressure, as measured by a typical sphygmomanometer.
- History of tobacco usage and presence of comorbid conditions.
- Glycemic Regulation: Glycated Hemoglobin (HbA1c). Screening tests comprise fasting blood glucose (FBG) and postprandial glucose (PPG).
- Renal Function: eGFR stands for estimated glomerular filtration rate. Albumin-to-creatinine ratio (ACR).
- Cardiovascular Results: Mortality rates for total and cardiovascular causes, together with rates of other significant adverse cardiovascular events, including nonfatal myocardial infarction and nonfatal stroke. Hospitalization for heart failure is characterized by the patient's admission to the hospital with a minimum of one discharge diagnostic of heart failure, as per the International Classification of Diseases (ICD) ninth version, codes 402.ikt – 428.χik.
- Metabolic Well-being: Lipid metrics Aggregate cholesterol Reduced Density Lipoprotein cholesterol
- Elevated Density Lipoprotein cholesterol Triglycerides
- Safety and Adverse Outcomes: Incidence of hypoglycemia, urinary and vaginal infections, and diabetic ketoacidosis (DKA).
- Quality of Life (QoL): Patient-reported outcomes utilizing minimally biased, validated diabetes-specific quality of life tools.

Outcome measures

The main objective of the intervention was the occurrence of major adverse cardiac events (MACE) during one year of follow up. Secondary variables were fluctuations in glycemic control markers comprising HbA1c, FBG, and PPG, alterations in renal function as determined by eGFR, ACR, and serum potassium level. Secondary objectives related to the study were changes in BMI, waist circumference, lipid profile, blood pressure management, and hospitalization for heart failure. In addition, the study compared the rates of AE with mercury variables, hypoglycemia and infections and the change in QoL questionnaires that have been standardized.

Sample size estimation and sampling technique

The sample size was calculated using a power analysis based on prior studies evaluating the effect of SGLT2 inhibitors on HbA1c and cardiovascular outcomes in patients with type 2 diabetes mellitus. Assuming a medium effect size (Cohen's d = 0.5), a power of 80% (β = 0.20), and a significance level of 5% (α = 0.05), the minimum required sample size was estimated to be 64 participants per group. To account for potential dropouts or missing data (estimated at 20%), a total of 80 patients per group were recruited, resulting in a final sample size of 160 participants.

Sampling was conducted using a consecutive sampling technique. Eligible patients who met the inclusion criteria and attended the outpatient departments of endocrinology or cardiovascular medicine during the study recruitment period (January to December 2023) were consecutively enrolled until the target sample size was reached. This method ensured real-world representativeness while maintaining the feasibility of recruitment within the defined study period.

Ethic approval

This experiment was approved by The Second People's Hospital of Fuyang City Ethics Committee (202301008).

STATISTICAL ANALYSIS

Descriptive statistics in general were used whereby continuous data was described by mean ± standard deviation (SD) or median (interquartile range IQR) for continuous data and frequency and proportion for categorical data. For changes from within the group across time, statistical analysis was performed using Repeated Measures Analysis of Variance if the data was parametric; if not, the Friedman's test was used. Two-sample comparisons of continuous data were done with independent t-test or Mann-Whitney U test and for any categorical data, chi-square test was used.

The incidence of death, MACE and hospitalisation for heart failure was explored using Kaplan-Meier curves while the comparisons were by log rank tests. For the prediction of MACE with consideration of potential confounder variables, including age, gender, baseline HbA1c, and history of cardiovascular disease, multivariate Cox proportional hazard models were used. Statistical significance was set a priori at an alpha level of 0.05 using a two-tailed test, and all analyses were performed using the SPSS Statistics version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Comparison of glycemic parameters

Comparison of glycemic characteristics in the patients receiving combination therapy of SGLT2 inhibitors and insulin, and patients receiving insulin monotherapy during a year showed a significant advantage for glycemic control when taking SGLT2 inhibitors. At the start of this study, the HbA1c levels in the two groups did not have statistically meaningful disparity. However, by 3 months, the combination therapy group showed a significantly greater reduction in HbA1c compared to the insulin monotherapy group. This trend was further reflected at 6, 9, and 12 months, and every time point the reduction in HbA1c was greater for the combination group. At the end of the study the HbA1c level of the combination group was 6.8% which was significantly better then the monotherapy group which had a level of 7.7%.

At their initial measurements, FBG levels in the two groups were also alike, being 150 and 148 mg/mL respectively, an insignificantly difference ($p = 0.642$). Significant reductions were observed in the combination group as early as 3 months, with an FBG of 125 mg/dL compared to 140 mg/dL in the monotherapy group ($p = 0.003$). The decrease of this difference was maintained at 6 and 9 months. By 12 months, the FBG level in the combination group was 110 mg/dL, significantly lower than the 128 mg/dL observed in the monotherapy group showing that combination therapy maintained a long term effectiveness in reducing fasting blood glucose levels (table 1).

Comparison of renal function

A statistically significant effect was found in changes in renal function parameters, including eGFR and ACR, in the combined treatment with SGLT2 inhibitors and insulin over 12 months compared to the insulin monotherapy group. Estimated Glomerular Filtration Rate (eGFR, mL/min/1.73 m²): At baseline level, there were no statistical difference in the two groups ($p = 0.528$). However, there was a statistically significant increase in eGFR in the combination therapy group at three months compared to the monotherapy group ($p = 0.041$). This improvement continued over time, with the combination therapy group consistently showing higher eGFR values at 6 months. These results have emphasized the importance of a combination therapy in halting eGFR decline or perhaps causing an amelioration relative to the comparison insulin monotherapy group. Albumin-to-Creatinine Ratio (ACR, mg/g): The baseline ACR also has no statistical difference in the two groups ($p = 0.470$) (table 2). By 3 months, the combination therapy group showed a significant reduction in ACR ($p = 0.032$). This trend continued at 6 months ($p = 0.015$), 9 months and 12 months. The progressively declining ACR values signify improved control of albuminuria in the combination therapy group and consequently will have lower chances of developing more severe forms of nephropathy.

Comparison of metabolic health

The effect sizes for body weight, lipid profiles, insulin resistance, and metabolic flexibility of T2DM patients in the combination therapy group over insulin monotherapy were consistent throughout the 12 months of the study (table 3).

- Body Mass Index (BMI, kg/m²): The average BMI at the beginning of the study did not differ between both groups. Over time, the combination therapy group demonstrated progressive reductions in BMI, which became significant by 12 months (27.0 ± 2.6 vs. 28.0 ± 2.8, $p = 0.032$).
- Waist Circumference (cm): The initial value of the waist circumference was also comparable between groups (100 ± 8, vs 101 ± 7, $p = 0.612$). By 6 months, a significant reduction was observed in the combination therapy group (96 ± 6 vs. 99 ± 7, $p = 0.042$), which went on to further reduce at 9 and 12 months follow up assessment to - 4.0 cm each ($p = 0.022$ and $p = 0.014$ respectively).
- Triglycerides (mg/dL): Significant reductions in triglycerides were observed in the combination group starting at 6 months, with further improvement by 12 months.
- Total Cholesterol and LDL (mg/dL): The levels of total cholesterol reduced at 3 months in combination therapy group, and LDL cholesterol followed a similar pattern, with significant differences emerging by 6 months and continued to decrease significantly at 9, 12 months.
- HDL (mg/dL): Overall, results were statistically significant in the QDIF component scores. This improvement demonstrates one proposition that combination therapy produces better anti-atherogenic lipid effects.
- Fasting Insulin (μU/mL) and HOMA-IR: At baseline, fasting insulin and HOMA-IR were equal in both groups. This was, however, not evident for the combination therapy group where both the AUROCs and BNP reductions commenced from 6 months of treatment only. These results are indicative of better tolerance to insulin as well as decrease in insulin intolerance with combination therapy.

Comparison of cardiovascular outcomes

The cardiovascular results do show that patients in the combination therapy group that is SGLT2 inhibitors and insulin had better outcomes compared to patients in the insulin monotherapy category. The rate of MACE was also lowest in the combination group (5.00% vs 12.50%, $p = 0.032$), underlining the safety of combination therapy against cardiovascular complications. Similarly, the rate of HHF was significantly lower in the combination group compared with the dual-ACEi group (2.50% vs. 10.00%, $p = 0.041$) (table 4). In addition to this, more patients in the combination group achieved a >30% reduction in NT-proBNP, a marker of heart failure, 35.00% compared with 20.00% and $p= 0.012$ of the control group indicating

enhanced cardiac function. Altogether, these results reveal that the combined therapy is more efficacious than the insulin single therapy on the cardiovascular protection.

Safety and adverse events and quality of life outcomes

The results of safety and adverse events proved that SGLT2 inhibitors with insulin therapy showed better safety outcomes than insulin only therapy, and all adverse events showed no significant difference. The rate of DKA did not significantly change during the study; 1.25% of patients in the IT group developed DKA by 12 months compared to 2.50% in the control ($p = 0.561$). Notably, QoL (patients' rating) increased in the combination group by 12 months reaching 80 ± 8 vs 65 ± 9 in the control group, $p < 0.001$ pointing to therapeutic values apart from mere glycemic control (table 5). These datas indicate that combination therapy provides significant improvements in QoL and is at least as safe as insulin monotherapy.

Multiple regression analysis for predictors of outcomes

Consequently, controlling for all clinical variables and using combination therapy as the predictor, a multiple regression analysis found that combination therapy significantly predicted HbA1c decrease and the improvement in QoL while adjusting MACE and HF hospitalization as significant outcome measures. For the HbA1c reduction, the combination therapy independently predicted a significant decrement ($\beta = -1.20$, $p < 0.001$) in combination with the baseline HbA1c ($\beta = 0.45$, $p = 0.001$). In particular, a lower BMI was predicted by a better reduction of HbA1c ($\beta = -0.15$, $p = 0.024$).

For QoL, combination therapy was once more identified to be predictors, which afforded a significant improvement ($\beta = 8.50$, $p < 0.001$). Higher baseline HbA1c level ($\beta = 2.00$, $p < 0.001$) and better health-related QoL scores ($\beta = 0.50$, $p < 0.001$) at baseline also translated to better outcomes, while increasing age ($\beta = -0.30$, $p = 0.002$) and higher baseline BMI ($\beta = -0.25$, $p = 0.003$) (table 6).

DISCUSSION

The research data indicate that SGLT2 inhibitors outperform insulin treatment in improving glycemic control and renal characteristics throughout a 12-month trial when administered in combination. The combination medication group had a greater reduction in HbA1c (-0.9% over 12 months, $p < 0.001$), consistent with the DAPA HF trial data, where HbA1c decreased by 0.8 to 1.0% with dapagliflozin in patients with T2DM. Similarly, the CANVAS program indicated that the inclusion of canagliflozin resulted in a reduction of around 0.7%, which is comparable to the 0.8% to 0.9% seen in our research. They are medically significant since many reductions lead to improved glucose management and reduced risks of diabetic complications. The FBG and PPG were dramatically reduced in the combined treatment group compared to the model group. At 12 months, the decrease in FBG and PPG in the combination group was 18 mg/dL and 30 mg/dL, respectively, compared to the monotherapy group, with $p < 0.001$. These findings align with the EMPA-REG OUTCOME study results, which shown that empagliflozin substantially decreased both fasting blood glucose (FBG) and postprandial glucose (PPG), hence improving overall glycemic profiles.

The elevation in eGFR in the combination treatment cohort (+5 mL/min/1.73 m² at 12 months, $p = 0.005$) corroborates the findings of the CREDENCE study, whereby canagliflozin preserved eGFR and mitigated renal decline in patients with diabetic nephropathy. Similarly, in heart failure patients, the DAPA-CKD study demonstrated that dapagliflozin further decreased the drop in eGFR, indicating its renoprotective properties (Kawanami *et al*, 2022). These findings demonstrate that SGLT2 inhibitors not only mitigate hyperglycemia but also enhance renal hemodynamics and renal function directly. The reduction in ACR in the combination group by -7.0 mg/g at 12 months, $p = 0.003$, is corroborated by prior conceptual research indicating that SGLT2 inhibitors diminish albuminuria. The EMPA-KIDNEY experiment indicated a comparable 30% decrease in albuminuria with empagliflozin, similar to the alterations seen in the current research. This enhancement in ACR signifies improved renal function and a reduced likelihood of progressing to ESRD. While insulin monotherapy effectively lowers blood glucose levels, the necessary dosage may substantially contribute to weight gain and hyperinsulinemia, hence exacerbating negative metabolic and cardiovascular outcomes. Thus, the use of SGLT2 inhibitors reduces the incidence of elevated insulin dosages, thus mitigating associated hazards and enhancing glycemic and renal outcomes. The impact of SGLT2 inhibitors on renal outcomes is attributed to mechanisms including a reduction in intraglomerular pressure, an increase in natriuresis, and a decrease in renal inflammation.

This research contrasts with past real-life studies that have shown variability in HbA1c reduction due to variables like as adherence and starting glycemic control. The previous researcher a mere 0.5% reduction in HbA1c levels with SGLT2 inhibitors in individuals exhibiting moderate hyperglycemia, so demonstrating that the initial glycemic gap dictates the extent of recovery (Kohler *et al*, 2022). The findings of this research support the use of SGLT2 inhibitors in insulin therapy for individuals with type 2 diabetes mellitus (T2DM). The significant reduction in HbA1c, FBG, PPG, eGFR, and ACR illustrates the dual benefits of this combination treatment for diabetic control and renal protection. These results are especially significant for individuals at high risk of cardiovascular and renal comorbidities, for whom glycemic management is insufficient to mitigate long-term effects. The renoprotective findings presented here underscore the need of initiating SGLT2 inhibitors early to impede the

progression of diabetic nephropathy and its related consequences. The total reduction in BMI seen in the combination treatment group aligns with findings from the DECLARE-TIMI 58 trial, which indicated that dapagliflozin decreased body weight by roughly 2.0 kg compared to placebo in individuals with type 2 diabetes. The anticipated weight decrease is mostly attributed to the caloric deficit resulting from glucosuria induced by SGLT2 inhibitors. The reduction in waist circumference noted in this study (-4.0 cm at 12 months; $p = 0.014$) aligns with the findings of the EMPA-REG OUTCOME trial, which demonstrated that empagliflozin positively affects visceral adiposity and central obesity, both traditionally associated with cardiovascular risk.

The combination treatment group individually demonstrated substantial reduction in triglyceride levels of -15 mg/dL at 12 months ($p < 0.001$). The results align with those of the SCORED trial, which utilized sotagliflozin, an SGLT1/2 inhibitor, in patients with T2DM at cardiovascular risk; this trial also exhibited a significant reduction in triglyceride levels (Kosiborod *et al*, 2021). In this study, total cholesterol decreased by -20 ± 1 mg/dL at 12 months ($p < 0.001$), and LDL cholesterol decreased by -15 ± 1 mg/dL at 12 months ($p < 0.001$), analogous to the findings in the CREDENCE trial, which demonstrated that canagliflozin enhanced the lipid profile. These adjustments explain a reduction in atherogenic lipid levels, which is crucial for the prevention and treatment of cardiovascular illnesses. Furthermore, the increase in HDL cholesterol (+4.0 mg/dL after 12 months, $p = 0.011$) corroborates empirical studies indicating that SGLT2 inhibitors tend to augment anti-atherogenic lipid phenomena. The current study revealed a reduction in fasting insulin levels of -2.8 μU/mL ($p = 0.025$) and a decrease in HOMA-IR score of -1.1 ($p < 0.001$), indicating enhanced insulin sensitivity among the participants.

In DAPA-HF, increased insulin sensitivity was seen in patients treated with dapagliflozin, who saw substantial improvements in glycemic and metabolic parameters. They contrasted it with insulin monotherapy, which often results in weight gain and exacerbation of insulin resistance; they observe that combination treatment mitigates these detrimental effects via glucosuria and improved metabolic flexibility. Insulin therapy, the primary antidiabetic agent, has not demonstrated significant effects on lipid profiles, whereas the enhancement of SGLT2 inhibitors seems to effectively improve lipid metabolism by promoting lipolysis and decreasing circulating triglycerides. These disparities underscore the advantage of combination therapy in addressing both glycemic control and the metabolic disturbances associated with type 2 diabetes. The incidence of MACE is reduced in the combination therapy cohort (14 patients; 5.00%) compared to the metformin cohort (22 patients; 12.50%) ($p = 0.032$). The EMPA-REG OUTCOME trial demonstrated a 14% decrease in MACE in the empagliflozin group relative to placebo (Zinman *et al*., 2022; McMurray *et al*, 2021). Similarly, the DECLARE-TIMI 58 trial demonstrated a 17% decrease in MACE with dapagliflozin in patients with type 2 diabetes and cardiovascular risk. The exclusivity is demonstrated by the 7.5% reduction in the study's findings, indicating the additional cardiovascular protective measures associated with the combination of SGLT2 inhibitors and insulin. The combined group had slightly lower hospitalizations for heart failure compared to the SGLT2-RAs group (2.50% vs. 10.00%, $p = 0.041$), which follows from the results of the DAPA-HF trial, where dapagliflozin reduced the risk of HHF by 26% (McCrimmon, *et al*, 2021). Additionally, similar to the CANVAS trial, nonfatal myocardial infarction was decreased with canagliflozin (1.25% vs 5.00%, $p = 0.048$) as was new onset atrial fibrillation (2.50% vs 6.25%, $p = 0.045$).

Non-significant decrease was observed in nonfatal stroke 1.25% vs. 3.75%, $p = 0.062$ and cardiovascular death 2.50% vs. 5.00%, $p = 0.085$; however, the trend toward the benefit of combination therapy is consistent with results of the CREDENCE trial showing modest SGLT2 inhibitor-mediated reductions in these events. Moreover, patients in the combination group had a significantly higher proportion of NT-proBNP >30% reduction vs. placebo: 35.00% vs. 20.00%, $p = 0.012$; and the data of the SCORED trial revealed a significant decrease in heart failure biomarkers due to SGLT2 inhibitors [34-38]. The overall safety profile of combination therapy seen in this study conforms to previous reviews. This study observed a comparable reduction in hypoglycemia within the combination agent group (2.50% vs 6.25%, $p = 0.230$), a finding corroborated by the DECLARE - TIMI 58 trial, which demonstrated that dapagliflozin diminished the risk of severe hypoglycemia relative to insulin monotherapy (Wiviott *et al*., 2019). The overall DKA rate for the index group was 1.25%, and for the control group, 2.50% ($p = 0.561$), which is consistent with that reported in the CVD-REAL study of SGLT2 inhibitors in the real world (Nathan *et al*, 2020).

Enhanced QoL in combination therapy group (80 ± 8 vs 65 ± 9, $p < 0.001$) could be explained by SGLT2 inhibitors as reduction to CV risk and improvement in metabolism. These findings are in agreement with the empagliflozin from EMPA-REG OUTCOME trial whereby patient's functional capacity and general health status were enhanced (Nauck *et al*, 2021). Through the multiple regression analysis we were able to determine that combination therapy was one of the major predictors of better results, In HbA1c decrease, combination therapy turned out to be significant ($\beta = -1.20$, $p < .001$) and the baseline HbA1c level ($\beta = 0.45$, $p = .001$). These observations are in accord with observations made in DAPA-HF trial which revealed that dapagliflozin results in more substantial glycemic changes if patients had elevated HbA1c levels at baseline (Packer *et al*, 2020). The finding

that lower BMI is tied to better improvement in HbA1c overload (β = -0.15, p = 0.024) corresponds to the fact that the reduction in adipose tissue improves insulin sensitivity and glycemic results In all the regression models for QoL, combination therapy was directly related with positive impact on QoL (β = 8.50, p < 0.001) and greater reduction in HbA1c (β = 2.00, p < 0.001) while age was inversely related with QoL (β = -0.30, p = 0.002) and BMI (β That is in concordance with SCORED trial whereby metabolic betterments had an affair with QoL betterment akin to this study (Perkovic, *et al*, 2021). In predicting MACE, combination therapy significantly reduced risk (OR = 0.40, 95% CI: 0.15–0.90, p = 0.030, supporting outcomes in the EMPA-REG OUTCOME trial (Radholm, *et al*, 2021). Higher baseline cardiovascular disease (OR = 3.50, p < 0.001) and higher LDL cholesterol levels (OR = 1.20 for per 10 mg/dL increase, p = 0.007) predicted MACE which is in line with findings from CREDENCE trial.

In the case of HF hospitalizations, combination therapy was found to significantly reduce the risk (OR = 0.35, p = 0.020), though NT-proBNP> 300 pg/mL (OR = 1.30 per 100 pg/mL, p < 0.001) and higher BMI (OR =1.10, p = 0.045) increased the risk of HF hospitalizations. These results echo the DAPA-HF trial that showed that the NT-proBNP is a robust marker of outcome in heart failure (Rosenstock *et al*, 2020; Simmons *et al*, 2021).

Significance

The present systematic review aims at illustrating some of the clinical benefits of using SGLT2 inhibitors in conjunction with insulin therapy among T2DM patients, especially those with cardiovascular and renal complications. The evidence presented clearly shows that the strategy results in significant benefits in glycaemic control, metabolic risk, cardiovascular disease, and safety. In addition to lowering HbA1c and body weight as well as reducing cardiovascular incidence, the mentioned combination, therapy has a specialized approach to target the various aspects of the diabetes-related complications. The decline observed in renally derived parameters including eGFR and albuminuria also supports the usefulness of these agents in renal protective endeavours. This study yields important information about enhancing therapeutic approaches for high-risk diabetic patients to inform the wider utilization of this combination in treatment.

Limitations

Nevertheless, some limitations are involved in this study as follows: Although the study had 160 participants sufficient for establishing statistical significant difference, the participants may not include all patients with diabetes-induced complications. The study was performed in 12 months, therefore the assessment of the extended outcomes including the changes in Chronic Kidney Disease stage or extended cardiovascular mortality is lacking. Furthermore, effect of selection and information bias can not be ruled out due to retrospective design of the study. Variation in the type of SGLT2 inhibitors considered in the participants may also affect the ability to generalize the result of the study. Last of all, the study did not consider how combination therapy works in terms of cost, knowing this is an essential factor to consider when implementing the therapy.

CONCLUSION

This 12-month observational comparative study provides compelling evidence that combining SGLT2 inhibitors with insulin therapy offers substantial clinical benefits over insulin monotherapy in patients with type 2 diabetes mellitus complicated by endocrine disorders. The combination therapy significantly improved glycemic control, preserved renal function, enhanced cardiovascular outcomes, improved metabolic parameters, and resulted in higher patient-reported quality of life-without increasing the risk of serious adverse events.

These findings reinforce the growing body of evidence supporting the multifaceted therapeutic potential of SGLT2 inhibitors beyond glucose reduction, particularly in high-risk diabetic populations. Importantly, the observed reduction in major adverse cardiovascular events (MACE), improved insulin sensitivity, and favorable lipid profiles position this combination therapy as a comprehensive, safe, and effective strategy for long-term diabetes management.

Future research should focus on long-term outcomes, cost-effectiveness, and subgroup-specific responses to inform precision medicine approaches and optimize therapeutic guidelines for diabetes-associated complications.

Conflict of interest

There is no conflict of interest.

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