Triple Versus Dual Oral Therapy: Evaluating Impact of Empagliflozin Add-On to Metformin and Linagliptin on Glycemic Control and Safety Profiles in Type 2 Diabetes

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ABSTRACT
Background: Managing Type 2 Diabetes Mellitus (T2DM) in India is challenging due to a unique phenotype characterized by early-onset beta-cell dysfunction and poor target glycemic control on conventional dual therapies. This study evaluated the clinical efficacy and safety of adding the Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitor empagliflozin to a metformin and linagliptin dual backbone in an Eastern Indian tertiary care setting.
Materials and Methods: his was a 36-week, prospective, parallel-group, clinical observational study conducted on 60 patients with uncontrolled T2DM (HbA1c 8%-10.5%). Participants were divided into two arms (n = 30 per group): Group A (Intervention) received triple therapy (empagliflozin 10 mg + metformin 500 mg + linagliptin 5 mg), and Group B (Control) continued dual therapy (metformin 500 mg + linagliptin 5 mg). Glycemic parameters-Fasting Blood Sugar (FBS) and HbA1c were evaluated at baseline and at 12, 24, and 36 weeks.
Results: Group A was younger (48.5 ± 8.6 vs. 52.6 ± 5.4 years; p = 0.03) and presented with a higher baseline glycemic burden than Group B. Over 36 weeks, Group A demonstrated a significantly greater reduction in HbA1c (0.57%) compared to Group B (0.31%), achieving a superior endpoint HbA1c (7.58% ± 0.27% vs. 7.7% ± 0.29%; p = 0.045). For FBS, Group A started with a substantial baseline disadvantage (221.85 ± 19.85 mg/dl vs. 208.95 ± 10.59 mg/dl; p = 0.002) but experienced a progressive 9.92% drop (22.00 mg/dl). This led to a complete convergence and superior reversal by week 36, with Group A reaching a lower mean FBS than Group B (199.85 ± 17.85 mg/dl vs. 200.45 ± 10.51 mg/dl; p = 0.046). Adverse drug reactions (ADRs) were higher in Group A (65% vs. 35%), driven by mild, manageable lower urinary tract infections unique to the empagliflozin arm, with no dropouts.
Conclusion: Adding empagliflozin to a metformin-linagliptin dual regimen provides statistically superior and durable reductions in both HbA1c and FBS over 36 weeks. The triple oral regimen successfully overcomes severe baseline hyperglycemia with an acceptable and manageable safety profile, making it a highly viable treatment intensification strategy.
Key-words: Type 2 Diabetes Mellitus, Empagliflozin, Triple Oral Therapy, Glycated Hemoglobin (HbA1c), Fasting Blood Sugar
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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) has emerged as one of the most critical global public health challenges of the 21st century, imposing a massive clinical and economic burden on healthcare systems worldwide(1). The global prevalence of diabetes continues to escalate exponentially, driven by rapid urbanization, sedentary lifestyles, and shifting dietary patterns(2). India, frequently referred to as the "diabetes capital" of the world, faces a unique, aggressive trajectory of this epidemic. According to the landmark 2023 Indian Council of Medical

Research-India Diabetes (ICMR-INDIAB) national study, the country boasts an alarming burden of over

101 million individuals living with diabetes, alongside an additional 136 million individuals in the pre-diabetic phase(3). Crucially, Indian populations exhibit a distinct phenotype characterized by early-onset beta-cell dysfunction, profound insulin resistance at a lower Body Mass Index (BMI), and a high propensity for premature microvascular and macrovascular complications(3). Despite the expansion of national screening initiatives, target glycemic control (HbA1C < 7%) is achieved in fewer than 7% of self-reported Indian patients, underscoring a critical gap in optimal therapeutic management(3).

Because T2DM is a progressive metabolic disorder characterized by multiple, overlapping pathophysiological defects, single-agent or even conventional dual-agent therapies often fail to sustain long-term glycemic control(4). Metformin combined with the Dipeptidyl Peptidase-4 (DPP-4) inhibitor linagliptin is a widely adopted, guidelines-compliant dual regimen that targets insulin resistance and enhances glucose-dependent incretin action(4,5). However, as pancreatic beta-cell function continuously declines, a significant portion of patients on this dual therapy experience secondary treatment failure. In such scenarios, clinical guidelines increasingly support early treatment intensification via triple oral therapy by introducing complementary mechanisms of action rather than waiting for severe hyperglycemia to manifest(4).

Empagliflozin, a highly selective Sodium-Glucose Cotransporter-2 (SGLT-2) inhibitor, represents an ideal candidate for add-on therapy. Unlike metformin and linagliptin, empagliflozin exerts its therapeutic effect through an insulin-independent mechanism by blocking glucose reabsorption in the proximal convoluted tubules of the kidney, thereby promoting osmotic diuresis and significant urinary glucose excretion [5,6]. While the dual backbone of metformin and linagliptin works internally on glucose production and incretin pathways, the addition of empagliflozin introduces an external disposal pathway for glucose. Beyond glycemic lowering, this triple combination offers systemic advantages, including weight loss and blood pressure reduction, alongside established cardioprotective and renoprotective benefits(5,6).

While the theoretical synergy of combining a biguanide, a DPP-4 inhibitor, and an SGLT-2 inhibitor is recognized, prospective real-world data comparing triple oral therapy against continued dual therapy are lacking within the Indian demographic. Most existing literature focuses on Western cohorts or evaluates these drugs against placebo or older conventional therapies like glimepiride. The rationality of this study lies in addressing this evidence gap by providing a direct, comparative clinical evaluation of a representative SGLT-2 inhibitor versus a DPP-4 inhibitor, in a tertiary care set-up in Eastern India.

Materials and methods

This prospective, parallel-group, clinical observational study was conducted in the Department of Pharmacology in collaboration with Department of Medicine of SCB Medical College and Hospital, Cuttack from February 2020 to August 2021. The study protocol was reviewed and approved by the Institutional Ethics Committee (IEC Registration No: ECR/84/Inst/OR/2013/RR-20/162 dated 18.03.2020) and was conducted in strict accordance with the Declaration of Helsinki, the Indian Council of Medical Research (ICMR) National Ethical Guidelines for Biomedical and Health Research, and Good Clinical Practice (GCP) guidelines. Prior to enrolment, written informed consent was obtained from all participating patients in their vernacular language after a detailed explanation of the study objectives, procedures, and potential risks.

Patients presenting to the outpatient department diagnosed with uncontrolled T2DM who were on stable dual therapy of metformin and linagliptin for atleast three consecutive months were screened for eligibility. Patients aged between 18 to 65 years of age with confirmed diagnosis of T2DM with baseline glycated haemoglobin (HbA1c) between 8% to 10.5%, body mass index <40kg/m^2 and willing to participate and comply with the study procedure were included in the study. Patients with type-1 diabetes, secondary diabetes or history of diabetic ketoacidosis, severe renal or hepatic impairment, history of recurrent urinary tract infections, concomitant use of other anti-diabetic drugs other than the study drugs within three months prior to screening, any major adverse cardiovascular events, pregnant or lactating, were excluded from the study.

The sample size was estimated based on the expected difference in HbA1c reduction between the two groups from pilot data or similar literature, using the formula $N=2*(Z_{\alpha/2}+Z_{\beta})^2* SD^2/\delta^2$, where $Z_{\alpha/2}$ is 1.96, $\alpha = 0.05$ and $\beta = 0.2$ for a confidence interval of 95%. Expecting a loss to follow-up of 10%, the total sample size calculated was 60 (30 per group). Eligible patients were classified into one of the two groups- group A (triple therapy or the intervention group) received empagliflozin 10mg + metformin 500mg + linagliptin 5mg and group B (dual therapy or control group) received metformin 500mg + linagliptin 5mg, without the addition of the SGLT-2 inhibitor. Clinical parameters were recorded at baseline and at the end of 12, 24 and 36 weeks. Medical nutrition therapy (MNT) and advice regarding consistent physical activity were standardized and reinforced for patients in both arms at every visit. Compliance with medication was

monitored via pill counts at each follow-up. The primary end-point was change in the glycemic parameters (FBS and HbA1c) at the end of 12, 24 and 36 weeks from baseline.

Statistical analysis

Statistical analysis was performed using SPSS software version 22.0. Continuous variables were represented mean ± standard deviation (mean ± SD) if normally distributed or median (interquartile range) if skewed. Categorical data were expressed as frequencies and percentages. Intra-group comparison was evaluated using the Paired t-test and inter-group comparison with Independent Student t-test. P-value was significant at <0.05.

Observation

The study consisted of 35 males (58%) and 25 females (41%). Group A comprised 18 males (60%) and 12 females (40%) while group B consisted of 17 males (57%) and 13 females (43%). There is no statistically significant difference in the gender distribution between Group A and Group B (Chi-square test, p = 1.0). The average age of the study participants was 54.0±5.5 years. The average age of Group A and Group B participants were 48.5±8.6 and 52.6±5.4 years, respectively. Maximum participants belonged to the fourth and fifth decade of life (table 1). The difference in average age between group A and B is statistically significant (Student's t-test, p = 0.03). Group A was predominantly composed of individuals under 50 years old, whereas the majority in Group B were over 50.

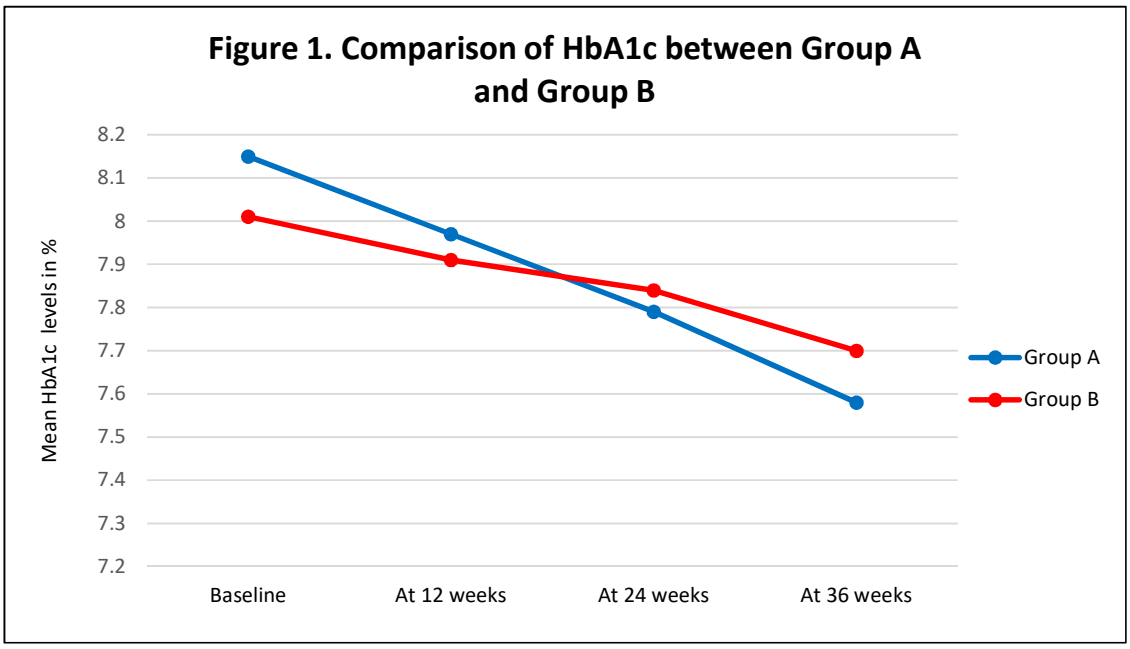
Age distribution (in years)	**Group A n(%)**	**Group B n(%)**	**Total**
31-40	6 (20)	-	6
41-50	14 (46.7)	10 (33.3)	24
51-60	8 (26.7)	16 (53.3)	24
> 60	2 (6.7)	4 (13.3)	6
Average age	48.5±8.6	52.6±5.4	54.0±5.5

Table 1. Age distribution and average age of the study participants across the two groups (N = 60)

The glycated haemoglobin levels (HbA1c) were measured at baseline, 12 weeks, 24 weeks and 36 weeks (figure 1 a & b). Both groups demonstrated a steady and continuous reduction in glycated hemoglobin (HbA1c) levels over the 36-week period. HbA1C dropped from a baseline of 8.15% to 7.58% (a total reduction of 0.57%) in group A, while it dropped from 8.01% to 7.70% (a total reduction of 0.31%) in group B (table 2). At the 12-week and 24-week marks, the differences between the two groups remained statistically significant (p = 0.012 and 0.039, respectively). Group A experienced a sharper decline in HbA1c, actually crossing below Group B's levels by week 24. By the end of the study at 36 weeks, Group A continued to show a lower mean HbA1c compared to Group B, which was statistically signicant (7.58% versus 7.70%, p = 0.045).

Timeline	**Group A (E+M+L) n = 30**	**Group B (M + L) n = 30**	**p-value***
Baseline	8.15 ± 0.23	8.01 ± 0.28	**0.013**
At 12 weeks	7.97 ± 0.24	7.91 ± 0.29	**0.012**
At 24 weeks	7.79 ± 0.25	7.84 ± 0.27	**0.039**
At 36 weeks	7.58 ± 0.27	7.7 ± 0.29	**0.045**

Table 2. Inter-group comparison of glycated haemoglobin (HbA1C) levels (%)
Data are presented as mean ± SD (%). p value is calculated by independent T-test, and significant at < 0.05.

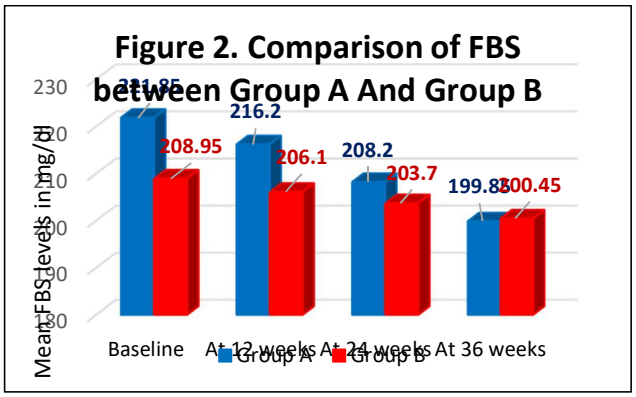


The inter-group analysis of fasting blood sugar (FBS) represented in table 3 revealed distinct patterns of glycemic reduction between the two treatment arms over the 36-week study period. At baseline, a statistically significant difference was observed between the groups ($p = 0.002$), with Group A exhibiting a higher mean FBS compared to Group B. Both groups demonstrated a progressive, time-dependent reduction in FBS levels. However, Group A experienced a more pronounced drop, decreasing by an absolute mean of 22.00 mg/dl (~9.92%) by week 36, compared to a modest reduction of 8.50 mg/dl (~4.07%) in Group B.

Statistically significant differences between the groups persisted through the early treatment phases. At 12 weeks, the mean FBS in Group A fell to 216.2 ± 19.03 mg/dl but remained significantly higher than Group B's mean of 206.1 ± 10.89 mg/dl ($p = 0.012$). By week 24, the glycemic gap narrowed, reaching the threshold of statistical significance (208.2 ± 18.97 mg/dl vs. 203.7 ± 10.97 mg/dl; $p = 0.050$). By week 36, Group A's aggressive downward trajectory resulted in a complete convergence and reversal of the glycemic profile. At this final time point, Group A achieved a lower absolute mean FBS (199.85 ± 17.85 mg/dl) than Group B (200.45 ± 10.51 mg/dl). This final difference was statistically significant ($p = 0.046$), demonstrating that the triple therapy protocol achieved a statistically superior endpoint reduction in FBS compared to the dual therapy control group, despite starting at a significantly higher baseline.

Timeline	**Group A (E+M+L) n = 30**	**Group B (M + L) n = 30**	**p-value***
Baseline	221.85 ± 19.85	208.95 ± 10.59	**0.002**
At 12 weeks	216.2 ± 19.03	206.1 ± 10.89	**0.012**
At 24 weeks	208.2 ± 18.97	203.7 ± 10.97	**0.050**
At 36 weeks	199.85 ± 17.85	200.45 ± 10.51	**0.046**

Table 3. Inter-group comparison of fasting blood sugar (FBS) levels (mg/dl)
Data are presented as mean ± SD (mg/dl). p value is calculated by independent T-test, and significant at < 0.05.



A total of 20 adverse drug reactions (ADRs) were reported among the study participants, 13 (65%) in group A and 7 (35%) in group B. The most frequently encountered ADR were nausea and vomiting and lower urinary tract infections (UTI). Cases of UTI were encountered only with those on add-on empagliflozin therapy. All the ADRs were mild in nature and easily managed.

Discussion

The present 36-week prospective study evaluated the clinical efficacy and safety of a triple oral therapy regimen, combining the sodium-glucose cotransporter-2 (SGLT2) inhibitor empagliflozin with metformin and the dipeptidyl peptidase-4

(DPP-4) inhibitor linagliptin (Group A) compared to a standard dual oral therapy of metformin and linagliptin (Group B). Our findings demonstrate that the addition of empagliflozin provides superior, durable glycemic control with a highly acceptable tolerability profile, despite higher baseline glycemic parameters in the triple therapy group.

The baseline analysis of our study cohort revealed a significant difference in age distribution between the two groups, with Group A having a lower average age (48.5 ± 8.6 years) compared to Group B (52.6 ± 5.4 years; p = 0.03). Interestingly, Group A was also characterized by a higher baseline glycemic burden, as evidenced by significantly higher starting HbA1c (8.15% ± 0.23% vs. 8.01% ± 0.28%; p = 0.013) and FBS levels (221.85 ± 19.85 mg/dl vs. 208.95 ± 10.59 mg/dl; p = 0.002) compared to Group B. This baseline asymmetry reflects real-world clinical practice in South Asian tertiary care settings, where younger patients presenting with more aggressive glycemic deterioration are frequently prioritized for early, intensive triple combination regimens rather than stepwise dual therapy.

Both therapeutic regimens led to a steady decline in HbA1c over the 36-week trial. However, Group A achieved a significantly greater overall reduction (0.57%) compared to Group B (0.31%), culminating in a statistically superior endpoint HbA1c at week 36 (7.58% ± 0.27% vs. 7.7% ± 0.29%; p = 0.045). The clinical superiority of Group A highlights the therapeutic synergy of the triple combination. Metformin addresses hepatic glucose overproduction, linagliptin enhances meal-dependent insulin secretion, and the SGLT2 inhibitor empagliflozin facilitates glucose excretion via the kidneys completely independent of insulin.

Our findings closely align with recent global literature. Park et al. (2024) evaluated a similar initial triple oral therapy (metformin, sitagliptin, and empagliflozin) over 24 months, demonstrating sustained and robust HbA1c target achievements (≤ 7.0%) and noting that targeting multiple pathophysiological pathways early prevents beta-cell exhaustion(7). A real-world prospective study by Islam et al. (2025) on the effectiveness of fixed-dose empagliflozin/linagliptin combination therapy in Bangladesh observed notable reductions in HbA1c (~1.0% to 2.0%) when combined with other baseline therapies, supporting our observations of SGLT2-add-on efficacy in South Asian populations(8). Furthermore, the Chinese Expert Consensus (2025) strongly endorsed triple oral therapy (metformin + DPP-4i + SGLT2i) as a high-potency, low-hypoglycemia regimen that provides durable glycemic control compared to dual combinations(4).

The temporal dynamics of Fasting Blood Sugar (FBS) in this study represent a compelling finding. Group A began with a massive glycemic disadvantage, with a baseline FBS 12.9 mg/dl higher than Group B (p = 0.002). Despite this, Group A exhibited a sharp, time-dependent reduction of 22.00 mg/dl (~9.92%) by week 36, compared to a nominal reduction of only 8.50 mg/dl (~4.07%) in Group B. This rapid decline resulted in a statistical "catch-up" by week 24 (p = 0.050), followed by a complete convergence and superior reversal at week 36 (199.85 ± 17.85 mg/dl in Group A vs. 200.45 ± 10.51 mg/dl in Group B; p = 0.046). This dramatic reduction is highly characteristic of the pharmacodynamics of SGLT2 inhibitors like empagliflozin. Because empagliflozin lowers the renal threshold for glucose, glucose excretion occurs continuously, markedly lowering fasting plasma levels even when fasting insulin levels are low.

This pattern is corroborated by a systematic review, which highlighted that adding an SGLT2 inhibitor to a DPP-4 inhibitor plus metformin backdrop

consistently yields a sharper, early-phase drop in fasting plasma glucose than dual therapy alone(9,10). The dramatic catch-up effect in patients with higher baseline fasting values was also highlighted in real-world clinical evidence from Hasan et al. (2024), who noted that the absolute reduction of blood glucose parameters is proportional to the severity of the baseline hyperglycemia when SGLT2 inhibitors are introduced(11).

While efficacy is paramount, the safety profile dictates clinical feasibility. In our study, a higher total number of ADRs was observed in the triple therapy group (13 cases, 65%) compared to the dual therapy group (7 cases, 35%). The primary driver of this difference was the occurrence of lower urinary tract infections (UTIs), which were documented exclusively in Group A (the empagliflozin add-on arm). This is a well-established class effect of SGLT2 inhibitors. By promoting therapeutic glucosuria, SGLT2 inhibitors create a glucose-rich microenvironment in the urinary tract, facilitating local microbial proliferation. This finding is thoroughly validated by clinical safety trials, such as those summarized in the UK NICE NG28 Guidelines (2026 update), which caution clinicians regarding SGLT2 inhibitor-induced genitourinary infections but reinforce that these events are generally mild, non-recurring, and easily managed with standard oral antimicrobials and counseling on perineal hygiene. Importantly, all ADRs in our study including mild nausea and vomiting were classified as mild and did not result in treatment discontinuation, demonstrating that the triple regimen remains highly tolerated in routine clinical practice.

Conclusion

In conclusion, adding empagliflozin to a metformin and linagliptin dual regimen (Group A) provides statistically superior and clinically meaningful improvements in both HbA1c and fasting blood sugar over 36 weeks compared to dual therapy (Group B). The triple therapy regimen successfully overcomes a higher baseline glycemic deficit, resulting in a superior fasting glycemic profile at endpoint. Although SGLT2 inhibitor-mediated glucosuria slightly increases the incidence of mild, manageable lower UTIs, the overall safety profile, paired with robust glycemic efficacy, strongly supports the early adoption of this triple oral therapy in patients inadequately controlled on dual oral regimens.

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