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Comparative Effects of Dapagliflozin versus Linagliptin as Add-on to Metformin on Glycemic and Renal Outcomes: A 24-Week Non-Randomized Prospective Observational Cohort Study in Indian Patients with Type 2 Diabetes Mellitus and Stage 2-3a chronic kidney disease

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Abstract

Background: Diabetic nephropathy remains one of the leading causes of end-stage renal disease among individuals diagnosed with type 2 diabetes mellitus (T2DM). Achieving optimal glycaemic control plays a vital role in slowing the progression of diabetic kidney disease. However, real-world evidence directly comparing the impact of SGLT2 inhibitors versus DPP-4 inhibitors on kidney outcomes in Indian patients with diabetes is currently limited.

This study evaluated the efficacy and safety profile of dapagliflozin in comparison with linagliptin, each added to background metformin therapy, with respect to glycemic control and renal parameters in patients presenting with uncontrolled T2DM and coexisting diabetic kidney disease.

Methods: This 24-week, single-centre, non-randomized open-label prospective cohort study included 94 adult patients with uncontrolled T2DM (HbA1c 8.0–10%) and CKD stage 2-3a (eGFR 45–89 mL/min/1.73 m²). Based on treating physician's clinical judgement, patients received either linagliptin 5 mg daily (n=47) or dapagliflozin 10 mg daily (n=47) in addition to ongoing metformin therapy. The primary outcome was the change in HbA1c at 24 weeks. Secondary outcomes included mean changes in eGFR, urinary albumin-to-creatinine ratio (uACR), and the proportion of patients achieving HbA1c <7%.

Results: A total of 88 patients completed the study (6 lost to follow-up). Both treatment arms demonstrated significant reductions in HbA1c (linagliptin: −0.79%; dapagliflozin: −1.11%), fasting plasma glucose, and uACR at 24 weeks ($p<0.05$ within each group). The decline in eGFR was minimal and non-significant in both groups (−0.8 vs −1.0 mL/min/1.73 m², $p=0.67$). Adverse events were mild (26% vs 24%) and no serious adverse events occurred that required discontinuation of study medication.

Conclusion: Dapagliflozin produced significantly greater reductions than linagliptin in urinary albumin-to-creatinine ratio, body weight, and serum uric acid (all $p<0.05$), while between-group differences in glycemic control (HbA1c, fasting plasma glucose) and eGFR did not reach statistical significance. Larger studies are required to confirm whether these observed trends translate into clinically meaningful benefits favouring SGLT2 inhibitors in this population. This pilot study confirms the feasibility of conducting future larger trials. No funding was received for this study.

Key Points

This 24-week, single-centre, non-randomized prospective observational cohort study compared dapagliflozin 10 mg vs linagliptin 5 mg as add-on to metformin in 94 Indian patients with uncontrolled T2DM (HbA1c 8.0–10%) and stage 2-3a CKD (eGFR 45–89 mL/min/1.73 m²).

Both agents significantly improved glycemic control and reduced albuminuria. Dapagliflozin showed significantly greater reductions in uACR (−57.18 vs −43.16 mg/g), body weight (−4.07 kg vs −0.87 kg), and serum uric acid (all $p<0.05$), and a numerically greater, non-significant reduction in HbA1c (−1.11% vs −0.79%).

eGFR decline was minimal and comparable between groups (−0.8 vs −0.97 mL/min/1.73 m², p=0.67), with no serious adverse events in either arm.

Dapagliflozin demonstrated significantly greater reductions in uACR, body weight, and uric acid (all p<0.05), supporting its potential metabolic and renal advantages in this population.

The study provides real-world Indian evidence favouring SGLT2 inhibitors in early diabetic kidney disease, though larger randomized trials are needed to confirm long-term hard renal outcomes.

Introduction

Type 2 diabetes mellitus (T2DM) currently affects around 77 million individuals in India according to IDF 2021 estimates, and diabetic nephropathy accounts for nearly 50% of all cases of end-stage renal disease. The stage 2 CKD window (eGFR 45–89 mL/min/1.73 m²) represents a crucial period for therapeutic intervention before irreversible glomerular damage sets in. Uncontrolled T2DM leads to glomerular hyperfiltration, progressive albuminuria, and gradual decline in glomerular filtration rate, ultimately resulting in fatigue, edema, hypertension, and heightened cardiovascular risk. The RSSDI 2022 guidelines recommend prioritizing SGLT2 inhibitors over DPP4 inhibitors as add-on therapy after metformin in high-risk patients; however, supporting real-world evidence from the Indian context is still insufficient.

Major global trials such as EMPA-KIDNEY and DAPA-CKD have established the nephroprotective role of SGLT2 inhibitors, yet these studies largely excluded patients with early-stage CKD and individuals of South Asian ethnicity. Dapagliflozin reduces intraglomerular pressure and exerts anti-inflammatory effects, whereas linagliptin provides renal safety through predominant biliary elimination without the need for dose adjustment in CKD.

To date, no prospective studies from India have directly compared dapagliflozin versus linagliptin when added to metformin in patients with stage 2-3a CKD and T2DM. Available literature is constrained by small sample sizes, short follow-up periods, or populations that do not represent Indian patients.

Aims and Objectives

The objective of this non-randomized prospective cohort study was to compare the efficacy (HbA1c, eGFR, uACR) and safety of dapagliflozin 10 mg versus linagliptin 5 mg, each added to metformin (≥ 2000 mg/day), over 24 weeks in patients with T2DM and stage 2-3a CKD.

Hypothesis

Dapagliflozin would demonstrate non-inferior or numerically superior trends across glycemic and renal endpoints compared with linagliptin, thereby supporting the conduct of larger multicenter trials.

Primary outcome

Change in HbA1c from baseline to 24 weeks.

Secondary outcomes

Changes in eGFR, uACR, weight, blood pressure, and adverse events.

Materials and Methods

Study Design

This was a prospective, open-label, non-randomized 24-week, single-centre observational cohort study that compared dapagliflozin versus linagliptin as add-on therapy to metformin in adults with uncontrolled type 2 diabetes mellitus and stage 2-3a chronic kidney disease (eGFR 45–89 mL/min/1.73 m²). Treatment allocation was determined by the treating physician's clinical judgement with prospective stratification according to baseline urinary albumin-to-creatinine ratio (uACR < 300 vs > 300 mg/g) to ensure balance between groups. A total of 94 patients were enrolled: linagliptin 5 mg (n = 47) plus metformin and dapagliflozin 10 mg (n = 47) plus metformin.

The study was conducted between March 2021 and May 2022 at the Department of General Medicine in collaboration with the Department of Pharmacology, Hamdard Institute of Medical Sciences and Research, Jamia Hamdard, New Delhi, India.

Ethical approval

was obtained from the Institutional Ethics Committee (HIMSR/IEC/018/2021) in accordance with the Declaration of Helsinki and ICH-GCP guidelines. Written informed consent was obtained from all participants in the local language.

Sample Size Calculation

Sample size was calculated based on pilot data and existing literature for the primary endpoint of HbA1c change. Assuming a minimum clinically important difference of 0.5% in HbA1c reduction between groups, a standard deviation of 0.8%, 80% power, and alpha of 0.05, approximately 41 patients per group were required. The recruited sample of 94 patients (47 per group) provided adequate power for the primary endpoint while remaining exploratory for certain renal outcomes such as eGFR changes.

Outcomes

Primary outcome:

Mean change in HbA1c (%) from baseline to 24 weeks comparing dapagliflozin versus linagliptin, both added to metformin monotherapy in patients with uncontrolled T2DM and diabetic kidney disease.

Secondary outcomes:

1. Change in eGFR after addition of either drug to metformin.
2. Change in uACR after 24 weeks of therapy.
3. Proportion of patients achieving HbA1c target of < 7% at 24 weeks.

Inclusion Criteria

Eligible participants were adults aged 18–65 years with T2DM, HbA1c 8.0–10.0% on stable metformin monotherapy (≥ 2000 mg/day for ≥ 6 weeks), uACR 30-3000 mg/g confirmed from three consecutive first-void morning urine samples, and eGFR 45–89 mL/min/1.73 m² (CKD-EPI creatinine-cystatin C equation, CKD stage 2-3a). Patients were required to be on stable RAAS inhibitor monotherapy (ACEi or ARB, no dual blockade) and antihypertensives for ≥ 10 weeks before screening.

Metformin monotherapy was specified as an inclusion criterion by design, rather than reflecting inadequate background management. Restricting the study population to a single antidiabetic background drug allowed a head-to-head comparison of dapagliflozin and linagliptin specifically as add-on agents, isolating the effect of each drug class — linagliptin, a DPP-4 inhibitor with presumed class-level renoprotective potential, versus dapagliflozin, an SGLT2 inhibitor with an independently established renoprotective mechanism — without confounding from heterogeneous background combination therapy.

Exclusion Criteria

Patients with type 1 or secondary diabetes, eGFR < 45 mL/min/1.73 m², non-diabetic kidney disease, recent cardiovascular events within the last 3 months, uncontrolled hypertension (> 160/100 mmHg), active urinary tract infection, chronic inflammation, pregnancy or planned pregnancy, prior use of SGLT2i or DPP4i within 3 months, insulin or other oral antidiabetic drugs except metformin, or severe hepatic impairment were excluded. Serum creatinine ≥ 1.3 mg/dl (women) or ≥ 1.4 mg/dl (men) also led to exclusion.

All patients received standard counseling on CKD care including dietary salt restriction, avoidance of nephrotoxins, and strict blood pressure control.

Interventions

Following a 2-week screening period for compliance assessment on stable metformin therapy, eligible patients were assigned to: • Group A (n = 47): Linagliptin 5 mg once daily + metformin • Group B (n = 47): Dapagliflozin 10 mg once daily + metformin.

No dose adjustments, rescue therapy, or addition of new antihypertensives were permitted during the study. Compliance was assessed by pill counts (> 85% threshold for continuation).

Assessments

Evaluations were conducted at baseline, week 12, and week 24. Blood pressure was measured using standardized sphygmomanometer (average of three readings). First-morning midstream urine samples were used for uACR, and fasting blood samples were collected for laboratory parameters.

Statistical Analysis

The modified intention-to-treat population (n = 88) was used for analysis. Primary between-group comparisons were performed using ANCOVA adjusted for baseline values, age, sex, diabetes duration, and BMI. Within-group changes were evaluated by repeated-measures ANOVA with Bonferroni correction. Missing data due to loss to follow-up were handled using last-observation-carried-forward in the modified intention-to-treat analysis. No adjustment for multiple secondary endpoints was performed as they were exploratory in nature.

Continuous variables are presented as mean ± SD or median with inter-quartile range. Between-group comparisons used independent t-tests or Mann-Whitney U test as appropriate. Within-group changes were analyzed by paired t-test. Categorical variables were compared using chi-square or Fisher's exact test. A p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS v27.0.

Results

In total, 145 patients were screened, of whom 94 met eligibility criteria and were allocated to the two study groups. Due to loss to follow-up and withdrawal, 88 patients completed the 24-week study protocol (Fig. 1).

Baseline Characteristics Baseline sociodemographic and clinical parameters are presented in Table 1.

Table 1
Baseline sociodemographic and clinical parameters of the study population

Variable	Total	Metformin + Linagliptin	Metformin + Dapagliflozin	p-value
Number of Patients (n)	94	47	47	0.65
Women (n)	40	20	20	0.26
Age (mean ± SD)	57.9 ± 4.6	57.4 ± 2.5	58.3 ± 3.6	0.87
Duration of diabetes (years), median (IQR)	3.7 (1.04–6.23)	3.56 (1.58–4.46)	3.97 (1.70–4.81)	0.54
Smoking (n)	44	21	23	0.85
Fasting plasma glucose (mg/dl)	178.7 ± 23.5	191.2 ± 19.4	172.8 ± 25.6	0.78
HbA1c (%)	8.65 ± 0.41	8.44 ± 0.57	8.86 ± 0.24	0.52
eGFR (mL/min/1.73 m^2)	72.2 ± 12.8	69.6 ± 15.6	78.3 ± 11.5	0.86
Serum creatinine (mg/dL)	1.06 ± 0.78	1.04 ± 0.53	1.08 ± 0.68	0.68
Urinary albumin-creatinine ratio (uACR) (mg/g)	176.56 ± 32.78	189.45 ± 35.34	167.45 ± 34.27	0.54
Serum Uric Acid (mg/dl)	7.45 ± 1.22	7.37 ± 1.8	7.63 ± 1.4	0.79
hs-CRP (mg/L)	1.52 ± 1.75	1.55 ± 1.78	1.48 ± 1.79	0.75
Systolic blood pressure	147.6 ± 14.5	148.2 ± 12.7	147.2 ± 12.7	0.45
Diastolic blood pressure	88.3 ± 4.7	87.5 ± 6.3	88.9 ± 5.2	0.56
Body Weight (Kg)	72.9 ± 1.7	72.57 ± 1.3	73.17 ± 2.3	0.06

The mean age was 58.28 ± 3.55 years in the dapagliflozin group and 57.4 ± 2.48 years in the linagliptin group, with no statistically significant difference ($p = 0.87$). Both groups were comparable with respect to eGFR, renal parameters, laboratory values, and concomitant medications. Gender distribution was balanced ($p = 0.26$), with women comprising 42.6% of the study population. Smoking status and family history of diabetes were also equally distributed ($p \geq 0.05$); data on coronary artery disease and peripheral arterial disease comorbidity were not systematically collected (see Study Limitations). There were no significant differences in age, sex, duration of diabetes, FPG, HbA1c, or BMI between the two groups.

Table 2
Effects of metformin and linagliptin on metabolic and renal parameters

Parameter/s	Baseline Mean ± SD	12 weeks Mean ± SD	24 weeks Mean ± SD	Change from Baseline to 24 weeks (95% CI)	F Statistics	p-value
Fasting blood Glucose (mg/dl)	191.2 ± 19.4	158.9 ± 23.1	172.5 ± 21.3**	-18.7 (-22.8, -6.9)	F (2,84) = 28.47	< 0.05
HbA1c (%)	8.44 ± 0.57	8.05 ± 0.47	7.65 ± 0.37**	-0.79 (-0.91,-0.54)	F (2,84) = 41.23	< 0.05
eGFR (ml/min/1.73 m^2)	73.12 ± 5.57	72.5 ± 4.9	72.09 ± 4.75	-0.97 (-1.42,-0.44)	F (2,84) = 1.89	0.67
Serum creatinine (mg/dl)	1.04 ± 0.76	1.01 ± 0.65	0.98 ± 0.64	-0.02 (-0.043,-0.015)	F (2,84) = 0.34	0.78
Urinary albumin-creatinine ratio (uACR) (mg/gm)	189.45 ± 35.34	167.7 ± 31.2	146.29 ± 29.34**	-43.16 (-74.76,-23.98)	F (2,84) = 18.56	< 0.001
Uric Acid (mg/dl)	7.03 ± 1.8	6.97 ± 1.4	6.91 ± 1.34	-0.12 (-0.25, -0.02)	F (2,84) = 3.12	0.57
hs-CRP (mg/L)	4.55 ± 1.78	3.2 ± 1.5	1.48 ± 1.54	-3.07 (-5.67,-2.36)	F (2,84) = 11.34	0.75
Systolic Blood pressure (mmHg)	148.2 ± 12.7	146.7 ± 12.8	145.5 ± 14.7	-2.7 (-4.62, -0.72)	F (2,84) = 4.56	0.65
Diastolic Blood pressure (mmHg)	87.5 ± 6.3	86.2 ± 5.7	85.11 ± 6.5	-2.39 (-3.54,-1.22)	F (2,84) = 7.89	0.78
Body Weight (Kg)	72.57 ± 1.3	72.1 ± 1.9	71.7 ± 2.1	-0.87 (-1.45, -0.55)	F (2,84) = 5.23	0.04***

‡ Repeated measures ANOVA with bonferroni post-hoc correction for multiple comparisons. All analyses adjusted for baseline values, age, sex, diabetes duration, and BMI

Data are means ± SD, or 95% CI. † $p < 0.05$ was considered significant. ‡ $p \geq 0.05$ was considered significant.

Changes from baseline and percent change from baseline are adjusted for age, sex, diabetes duration, BMI body mass index, and glucose control status (HbA1c difference). DPP-4 dipeptidyl peptidase 4, SGLT2 sodium glucose co-transporter 2, Haemoglobin A1C HbA1c.

* $p < 0.05$ (comparison between before treatment and after treatment in all subjects)

** p < 0.05 (comparison between before treatment and after treatment in each group)

*** p < 0.05 (comparison between DPP-4 inhibitor group and SGLT2 inhibitor group)

There were no statistically significant differences in age, sex, duration of diabetes, and other baseline laboratory findings, including the FPG, HbA1c levels, and the BMI between the two groups.

Changes in metabolic and renal parameters in the linagliptin group are detailed in Table 2. During the 24-week follow-up, addition of linagliptin to metformin produced significant improvements in glycemic control and renal parameters (Table 2).

Mean fasting plasma glucose decreased by 18.7 mg/dL (95% CI: − 22.8 to − 6.9; F(2,84) = 28.47, p < 0.001), falling from 191.2 ± 19.4 mg/dl at baseline to 172.5 ± 21.3 mg/dl at week 24.

HbA1c decreased by 0.79% (95% CI: − 0.91 to − 0.54; F (2,138) = 41.23, p < 0.001).

Urinary albumin-to-creatinine ratio (uACR) showed a significant reduction of 43.16 mg/g (95% CI: − 74.76 to − 23.98; F(2,138) = 18.56, p < 0.001), declining from 189.45 ± 35.34 mg/g to 146.3 ± 29.3 mg/g.

eGFR showed a minimal non-significant decline of 0.97 mL/min/1.73 m² (95% CI: − 1.42 to − 0.44; F(2,138) = 1.89, p = 0.15). Serum creatinine decreased minimally by 0.02 mg/dl (p = 0.71). Serum uric acid decreased significantly by 0.12 mg/dl (p = 0.048), and hsCRP decreased by 3.07 mg/L (p < 0.001).

Systolic and diastolic blood pressure decreased by 2.7 mmHg (p = 0.01) and 2.39 mmHg (p < 0.001) respectively. Body weight reduced by 0.87 kg (p = 0.007).

Table 3
Effects of metformin and dapagliflozin on metabolic and renal parameters

Parameter/s	Metformin + Dapagliflozin				F-statistic	p-value
	Baseline	12 weeks	24 weeks	Change from Baseline to 24 weeks (95% CI)		
Fasting blood Glucose (mg/dl)	178.3 ± 33.4	162.1 ± 27.5	149.9 ± 22.3**	-28.4 (-32.9,-15.4)	F(2,138) = 44.21	< 0.05
HbA1c (%)	8.86 ± 0.24	8.31 ± 0.35	7.75 ± 0.37**	-1.11 (-1.42,-0.56)	F(2,138) = 62.15	< 0.05
eGFR (ml/min/1.73 m^2)	71.12 ± 5.57	70.8 ± 5.0	70.32 ± 4.75	-0.8 (-1.32,-0.4)	F(2,138) = 1.56	0.67
Serum creatinine (mg/dl)	1.04 ± 0.76	1.05 ± 0.68	1.06 ± 0.64	-0.02 (-0.043,-0.015,)	F(2,138) = 0.28	0.78
Urinary albumin-creatinine ratio (uACR)	184.63 ± 35.34	155.8 ± 29.8	127.47 ± 24.24**	-57.18 (-67.86,-34.98)	F(2,138) = 26.84	< 0.001
Uric Acid (mg/dl)	7.03 ± 1.8	6.75 ± 1.5	6.52 ± 1.34**	-0.51 (-0.74,-0.2)	F(2,138) = 8.76	< 0.001
hs-CRP (mg/L)	4.86 ± 1.65	3.7 ± 1.42	2.56 ± 1.38	-2.3 (-4.68,-1.28)	F(2,138) = 9.12	< 0.001
Systolic Blood pressure (mmHg)	147.2 ± 12.7	145.5 ± 11.8	143.9 ± 12.6**	-3.3 (-5.62, -0.32)	F (2,138) = 5.34	< 0.05
Diastolic Blood pressure (mmHg)	88.94 ± 5.2	88.0 ± 4.8	87.2 ± 4.5	-1.74 (-2.46, -0.86)	F (2,138) = 6.78	< 0.001
Body Weight (Kg)	73.17 ± 2.3	71.98 ± 1.24	69.10 ± 2.1	-4.07 (-4.95, -0.55)	F (2,138) = 18.45	< 0.001

‡ Repeated measures ANOVA with bonferroni post-hoc correction for multiple comparisons. All analyses adjusted for baseline values, age, sex, diabetes duration, and BMI

Data are means ± SD, or 95% CI. $p < 0.05$ was considered significant. Changes from baseline and percent change from baseline are adjusted for age, sex, diabetes duration, BMI body mass index, and glucose control status (HbA1c difference). DPP-4 di-peptidyl peptidase 4, SGLT2 sodium glucose co-transporter 2, Haemoglobin A1C HbA1c

* $p < 0.05$ (comparison between before treatment and after treatment in all subjects)

** p < 0.05 (comparison between before treatment and after treatment in each group)

*** p < 0.05 (comparison between DPP-4 inhibitor group and SGLT2 inhibitor group)

Changes in the dapagliflozin group are presented in Table 3.

Addition of dapagliflozin to metformin resulted in significant improvements across metabolic and renal parameters (Table 3). Mean fasting plasma glucose decreased by 28.4 mg/dL (95% CI: − 32.9 to − 15.4; $F(2,138) = 44.21$, $p < 0.001$). HbA1c reduced by 1.11% (95% CI: − 1.42 to − 0.56; $F(2,138) = 62.15$, $p < 0.001$). uACR decreased by 57.16 mg/g ($p < 0.001$). eGFR declined minimally and non-significantly by 0.80 mL/min/1.73 m² ($p = 0.67$). Serum uric acid decreased significantly by 0.51 mg/dl ($p < 0.001$). Body weight reduction was 4.07 kg ($p < 0.001$).

Dapagliflozin showed significantly greater reductions in uACR, body weight, and serum uric acid (all $p < 0.05$), while the between-group difference in HbA1c remained non-significant ($p \geq 0.05$).

Dapagliflozin shows significantly greater reductions in uACR, body weight, and serum uric acid (all $p < 0.05$), while the between-group difference in HbA1c remains non-significant ($p \geq 0.05$).

Efficacy Outcomes

Renal Parameters

The reduction in uACR was greater in the dapagliflozin group compared with linagliptin (estimated treatment difference − 14.02 mg/g; 95% CI − 14.42 to − 13.86; $p < 0.05$) (Fig. 2). The decline in eGFR was slightly higher in the linagliptin group (estimated treatment difference − 0.46 mL/min/1.73 m²; $p \geq 0.05$) (Fig. 3).

Glycemic Control

Reduction in HbA1c was numerically greater with dapagliflozin (estimated treatment difference − 0.32%; $p \geq 0.05$) (Fig. 4). The decrease in fasting plasma glucose was also larger with dapagliflozin (estimated treatment difference − 9.70 mg/dl; $p \geq 0.05$) (Fig. 5).

Metabolic and Cardiovascular Parameters

Body weight reduction was significantly greater with dapagliflozin (estimated treatment difference − 3.20 kg; $p < 0.05$) (Fig. 6). Serum uric acid reduction was significantly greater in the dapagliflozin group (0.39 mg/dL; $p < 0.05$) (Fig. 7). Changes in systolic/diastolic blood pressure and hsCRP were non-significant in both groups.

Target Glycemic Control

At 24 weeks, 17% (8/47) of patients in the linagliptin group and 21.3% (10/47) in the dapagliflozin group achieved HbA1c < 7.0% (χ^2=0.65, p = 0.42) (Fig. 8).

Safety Outcomes

Safety data are summarized in Table 4. At least one adverse event occurred in 23.5% of the linagliptin group and 26.0% of the dapagliflozin group. All events were mild and resolved without intervention. No serious adverse events, deaths, or treatment discontinuations occurred. The most common adverse events were nasopharyngitis and headache. Hypoglycemia was reported in two patients in the dapagliflozin group only, and neither case led to discontinuation.

Table 4
Summary of Adverse Events reported and recorded during the 24 -week treatment period

Events	Group A	Group B
Any adverse event	23.5% (11/47)	26.0% (12/47)
Adverse events leading to drug discontinuation	0	0
Any serious adverse event	0	0
Hypoglycaemia	0	2
UTI	0	1
Nasopharyngitis	0	0
Genital fungal infection	0	1
Headache	2	1
Dizziness	1	1
Diarrhoea	1	1
Dyspepsia	2	1
Nausea	1	1
Abdominal pain	2	1
Back pain	1	1
Arthralgia	1	1

Discussion

Diabetic nephropathy remains a major cause of morbidity in type 2 diabetes mellitus (T2DM) patients and is a leading contributor to end-stage renal disease (ESRD) worldwide. This prospective, non-randomized study highlights the renal protective and glycaemic benefits of adding either dapagliflozin, a

sodium-glucose cotransporter-2 inhibitor (SGLT2i), or linagliptin, a dipeptidyl peptidase-4 inhibitor (DPP-4i), to metformin therapy in patients with uncontrolled T2DM and mild chronic kidney disease (CKD) (11).

Inadequate blood glucose control and Insulin resistance plays a pivotal role in the progression of kidney disease to end-stage renal disease (ESRD), which requires dialysis or kidney transplantation to sustain life (12).

Some oral anti-diabetic drug classes such as the SGLT-2 inhibitors and linagliptin, a DPP- 4 inhibitor have been observed to have reno-protective effects.

This non-randomized, prospective, open-label cohort study investigated the reno-protective and metabolic effects of dapagliflozin and linagliptin, as add-on treatment to metformin monotherapy, in patients with poorly controlled type 2 diabetes and mild (stage 2-3a) chronic kidney disease (CKD).

We investigated the effects of linagliptin and dapagliflozin in addition to metformin monotherapy on the progression of renal functions in patients with uncontrolled T2D.

Our primary finding was that both agents led to significant reductions in glycemic markers and albuminuria, with dapagliflozin demonstrating a larger reduction in HbA1c, fasting plasma glucose, urinary albumin-to-creatinine ratio, and body weight over the 24-week study period. However, while eGFR declined slightly in both groups, the change was not statistically significant.

Strict control of blood sugar alone has not been associated with preventing the deterioration of eGFR, urinary albumin excretion, or risk of progressing to dialysis in advanced CKD (13).

Until recently, reno-protective effects of drugs acting on the renin-angiotensin aldosterone system (RAAS) ACEIs and ARBs were thought to represent a major therapeutic strategy to halt the progression of renal disease (14). Despite the use of drugs acting on the RAAS, the renal disease may continue to progress, and many patients remain proteinuric even under treatment. These observations have highlighted the need to use different drugs especially in the management of diabetic patients with CKD.

All the patients in our study had stage 2-3a CKD on antihypertensive therapies and were equally distributed at the time of enrolment.

HbA1c levels in both the groups showcased a statistically significant change from the baseline. The comparison of change in mean HbA1c levels from baseline in both the groups ($p = 0.65$) were similar to the study by Del Prato et al. where the combination of an SGLT2i and metformin had superior efficacy in the long-term control of FPG levels and mean HbA1c compared to the DPP-4i and metformin (15).

Comparison of mean change in FPG and the HbA1c levels from the baseline in the linagliptin and dapagliflozin combination groups ($p = 0.59$) was similar to the study by Kumar et. al. (16).

This was in contrast to a study, where metformin and DPP-4i were effective compared to metformin and SGLT2i in reducing mean FPG and mean HbA1c levels (17).

Both the groups showed a statistically significant reduction in the mean uACR levels after 24 weeks of treatment, similar to the findings by Bae et. al. where the SGLT-2i combination group performed better to the DPP-4 inhibitor group in the improvement of uACR (18).

Dapagliflozin may lower albuminuria through hemodynamically by reducing in the intra-glomerular pressure by constriction of the afferent arterioles through the activated tubuloglomerular feedback (TGF) (19). Other non-hemodynamic effects include osmotic diuresis, natriuresis, enhanced insulin sensitivity, and direct actions on renal tubules (20).

Linagliptin may interrupt the interaction between DPP-4 and the M6P/IGF-IIR receptor, helping to alleviate microvascular inflammation and injury to the kidney's glomerular filtration barrier (21). A similar study by Groop et al. found non-significant reduction in albuminuria and eGFR with Linagliptin after 24 weeks of treatment (22).

The present study reveals the decline in eGFR by 0.97 and 0.80 in the linagliptin and dapagliflozin groups after 24 weeks therapy, respectively. Similar observations have been observed in another study where the SGLT-2 inhibitors showcased a favourable and a slower decline in the eGFR levels compared to the DPP- 4 inhibitors (19).

Our study noticed decrease in the serum uric acid and serum creatinine levels in the linagliptin group. Whereas, the dapagliflozin group showcased increase in the levels of serum creatinine and a significant reduction in the levels of serum uric acid, similar to an earlier study (23). The drug mechanism involved is the reduction of eGFR and a transient increase in serum creatinine levels.

The reduction in blood pressure and body weight in the dapagliflozin group was statistically significant consistent with another study done by Zhang et. al. (24)

In this study, we observed that the addition of either linagliptin of dapagliflozin to metformin in uncontrolled Type 2 Diabetes significantly improved the mean plasma HbA1c levels, FPG, uACR levels after 24 weeks of drug therapy. Whereas, significant reductions in the uric acid levels and body weight were observed after 24 weeks in the dapagliflozin group.

In contrast to other DPP-4 inhibitors, linagliptin is majorly eliminated by the biliary route. Hence, dose adjustment is not required in the patients of with CKD (24).

Renoprotective effect of linagliptin are probably also the result antioxidative and antiapoptotic effects due to the enhancement of active GLP-1 levels after inhibition of DPP-4 enzymes (25).

Other effects including modulation of osteopontin, cyclophilin A, stromal cell-derived factor-1 have postulated (26).

Both the linagliptin and the dapagliflozin combination groups showcased an improvement in renal progression at the end of 24 weeks follow-up. This study is among the first prospective comparative

evaluations from India in patients with stage 2 CKD and T2DM, offering insights into real-world physician-driven treatment choices in a resource-limited setting.

Study Limitations

1. Modest sample size (n = 94): Provided 85% power for primary outcome (HbA1c) but underpowered for secondary renal endpoints (eGFR change), limiting detection of small between-group differences.
2. Short duration (24 weeks): Insufficient to assess long-term hard renal outcomes (e.g., doubling creatinine, ESRD); CKD progression typically requires 2–5 years follow-up.
3. Stage 2-3a CKD only (eGFR 45–89 mL/min): Findings may not generalize to advanced CKD (eGFR < 45) where SGLT2i dosing/safety differs.
4. Open-label, non-randomized design: Physician judgement allocation risks selection/performance bias despite uACR stratification; larger RCTs needed.
5. Single-center: Limits external validity beyond urban Indian tertiary care; multicenter validation required.
6. No blinding: Potential observer bias in efficacy assessments, though objective labs (HbA1c, eGFR) minimized this.
7. Comorbidity data not collected: Coronary artery disease and peripheral arterial disease status were not systematically recorded at baseline, precluding assessment of their potential influence on renal and glycemic outcomes given the established relationship between diabetic CKD and macrovascular disease; this should be addressed in future study designs.

These limitations highlight the pilot nature—results justify larger, randomized, multicenter trials.

Conclusion

In patients with poorly controlled type 2 diabetes and stage 2-3a chronic kidney disease, the addition of either dapagliflozin or linagliptin to metformin therapy resulted in significant improvements in glycemic control and reductions in albuminuria over a 24-week period. Dapagliflozin produced significantly greater reductions than linagliptin in uACR, body weight, and serum uric acid (all $p < 0.05$), while between-group differences in glycemic parameters and eGFR were not statistically significant. Both agents were well tolerated with no major safety concerns observed. However, given the modest sample size, short duration, and restriction to stage 2-3a CKD, these findings should be interpreted with caution. Larger, long-term trials are warranted to confirm the sustained renoprotective effects and safety profiles of these therapies across the full spectrum of diabetic kidney disease. These results support the potential role of SGLT2 and DPP-4 inhibitors as important adjuncts in the management of diabetic nephropathy.

Declarations

Conflict of Interest: None declared

Funding: No external funding received

Ethics Approval: HIMSR/IEC/018/2021

Author Contributions

Dr. Shreshth Khanna: Conceptualization, methodology, data curation, formal analysis, writing-original draft, visualization, project administration, corresponding author.

Dr. Maynak Malik: Investigation, resources, data collection (patient recruitment/enrollment).

Dr. Bhaskar Malik: Investigation, data collection (clinical assessments, safety monitoring).

Dr. Razi Ahmad: Validation, supervision, review & editing, funding acquisition (none), ethics submission. All authors reviewed and approved the final manuscript and agree to be accountable for all aspects.

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Study medications (dapagliflozin, linagliptin) were sourced at standard rates through the institutional hospital pharmacy (HAHC Hospital). All personnel costs and lab analyses were covered by departmental resources at HIMSR as part of routine pharmacovigilance/clinical audit activities. No honoraria, consulting fees, or travel reimbursements were provided to authors.

Conflict of Interest

None declared.

Authors have no financial relationships with AstraZeneca (dapagliflozin), Boehringer Ingelheim (linagliptin), or related entities. No stock ownership, patents, or advisory roles.

Ethics Approval

The present study was approved by the Institutional Ethics Committee of Hamdard Institute of Medical Sciences and Research (HIMSR), Jamia Hamdard, New Delhi, India (Approval No: HIMSRIEC/018/2021; Date: March 19, 2021).

The study adhered to the ethical principles outlined in the Declaration of Helsinki (2013 amendment) and ICH-GCP guidelines. Written informed consent was obtained from all participants in English or Hindi after providing a detailed patient information sheet explaining study objectives, procedures, potential risks (e.g., mild AEs like headache, UTI), benefits (improved glycemic/renal monitoring), and right to

withdraw. Patient data was anonymized, stored securely, and accessible only to the research team. No vulnerable populations were included.

Clinical trial number: Not Applicable. This was a prospective observational cohort study with physician-preference treatment allocation (no randomization, intervention, or protocol deviation from routine care). Per ICMR guidelines (2023), CTRI registration is exempt for purely observational studies. Reported per CONSORT 2010 extension for non-randomized studies.

Consent: written informed consent obtained.

Study medications were sourced through hospital pharmacy at standard rates. No honoraria, consulting fees, or research grants were received.

All work was performed as part of standard academic responsibilities.

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Figures

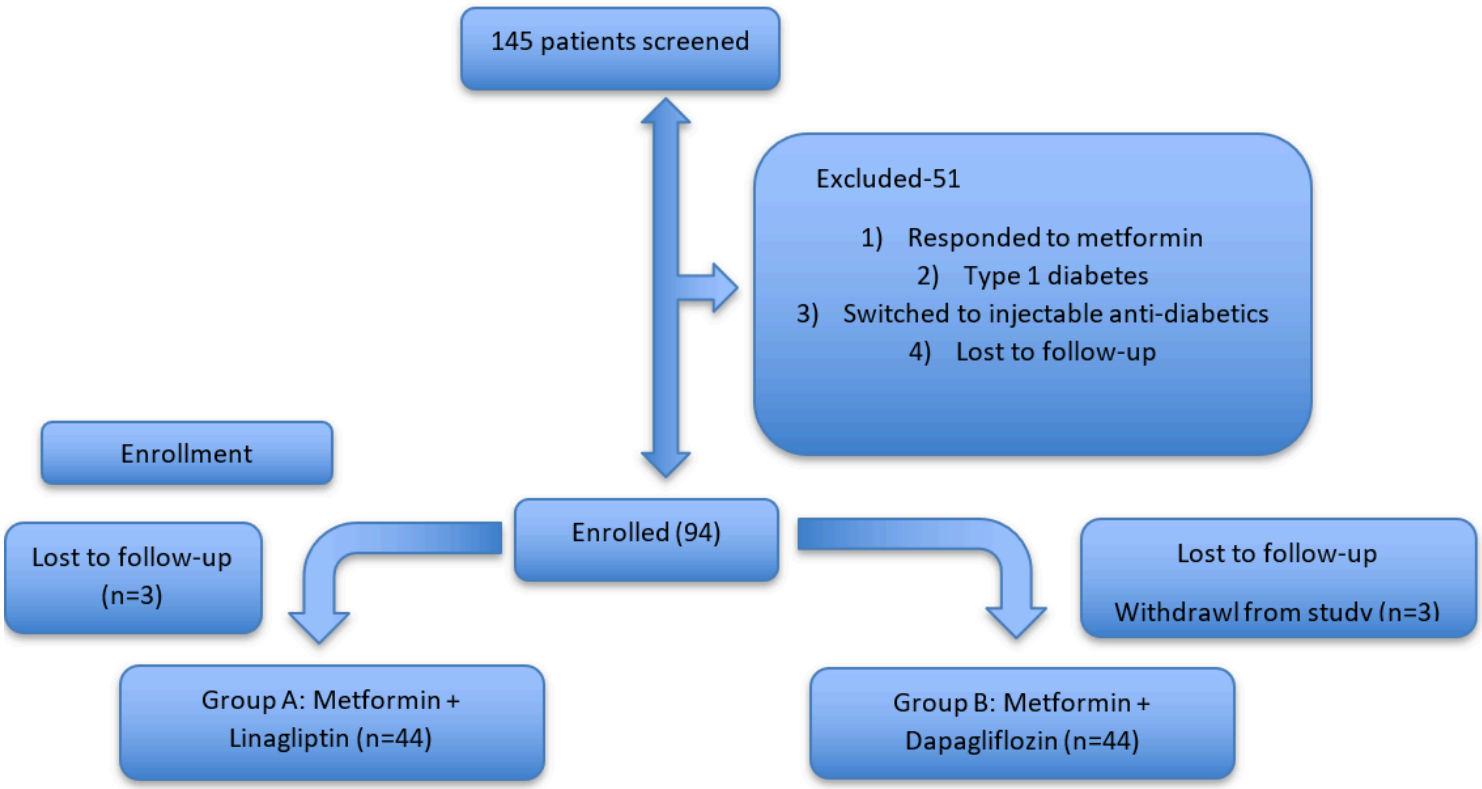


Figure 1

Physician-Preference Cohort: Dapagliflozin vs Linagliptin Add-on to Metformin in Indian T2DM with Stage 2 CKD

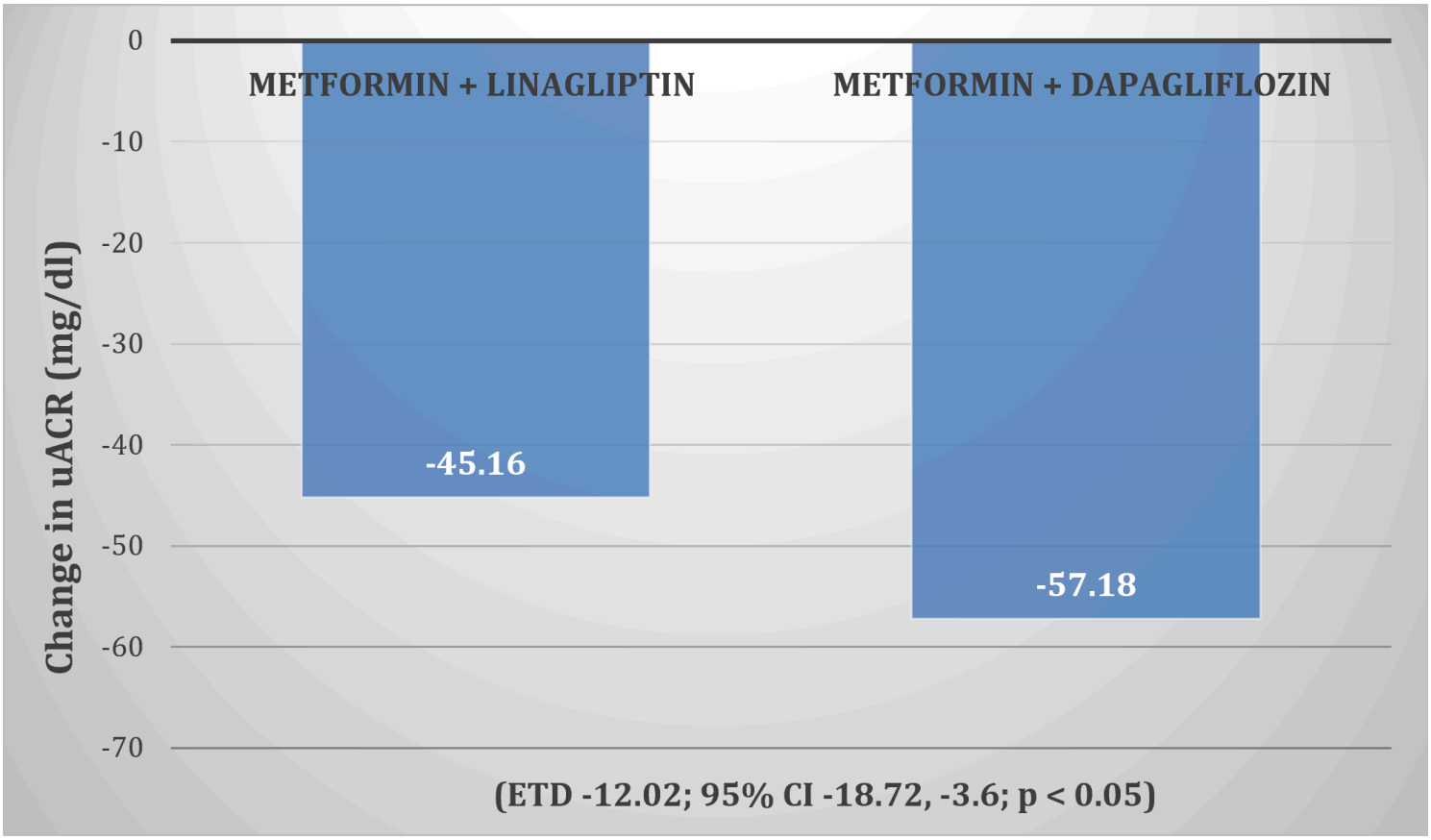


Figure 2

Comparison of improvement in uACR levels between the two groups

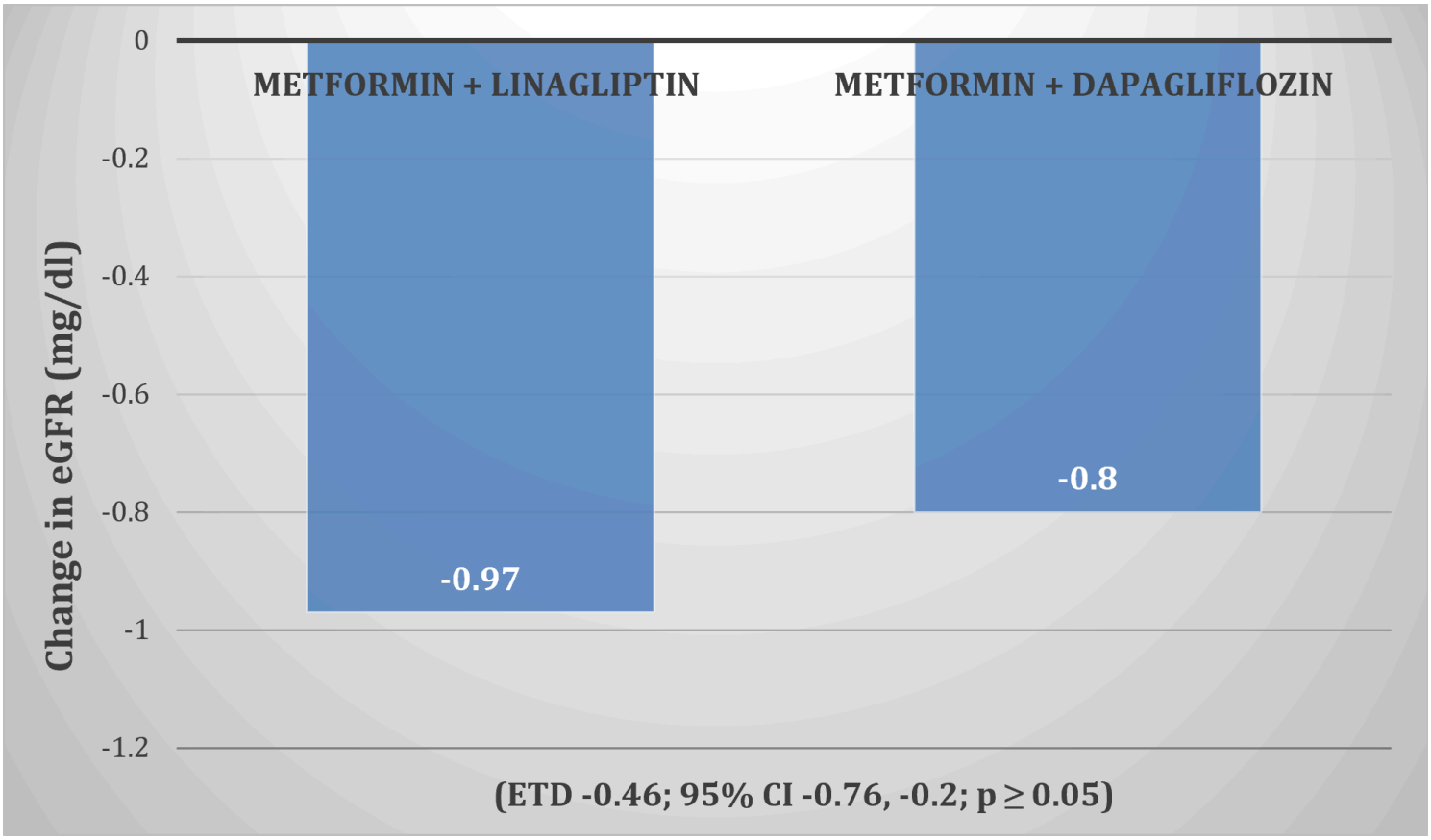


Figure 3

Comparison of decline in the eGFR levels between the two groups

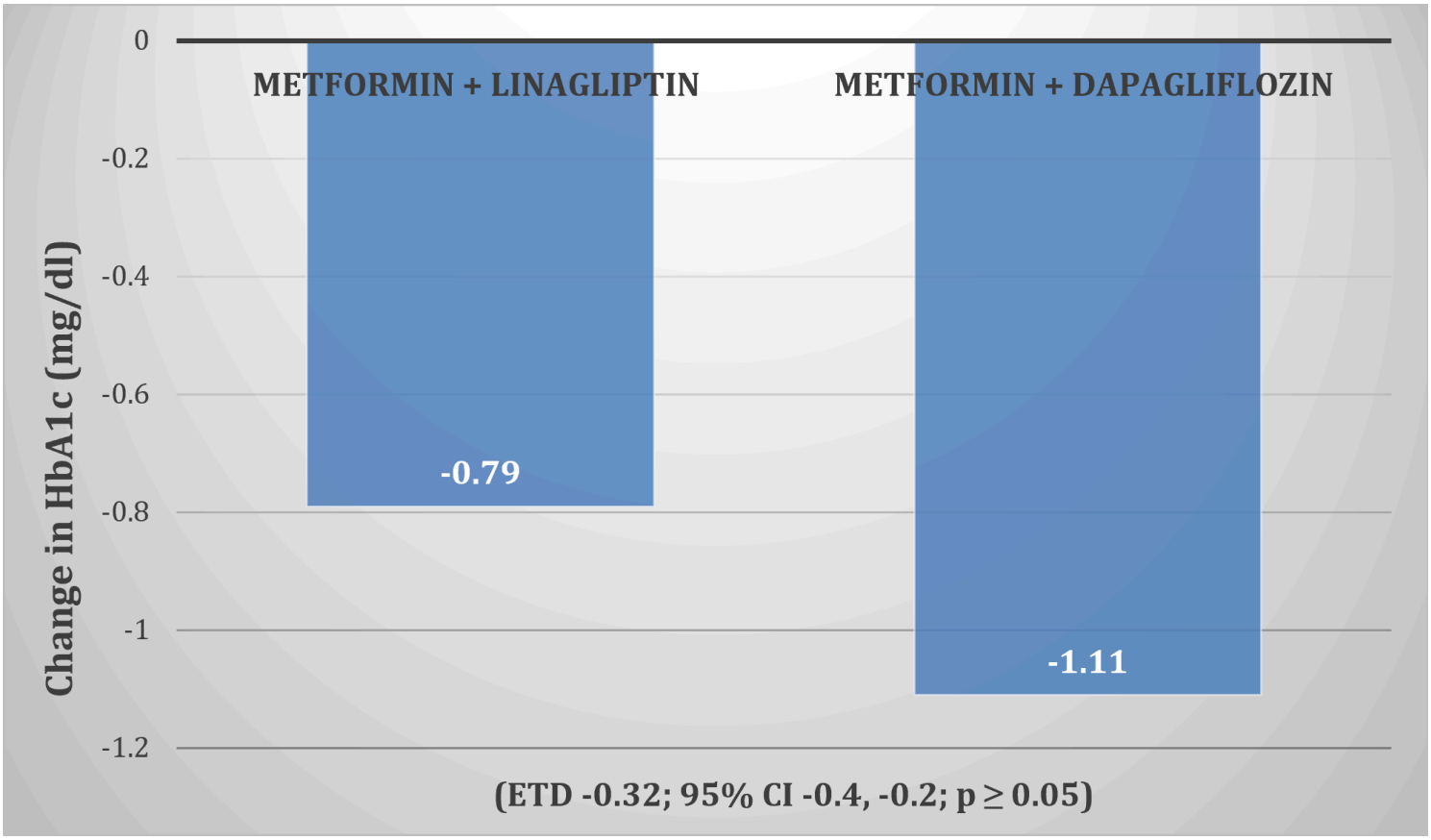


Figure 4

Comparison of reduction in the HbA1c levels between the two groups

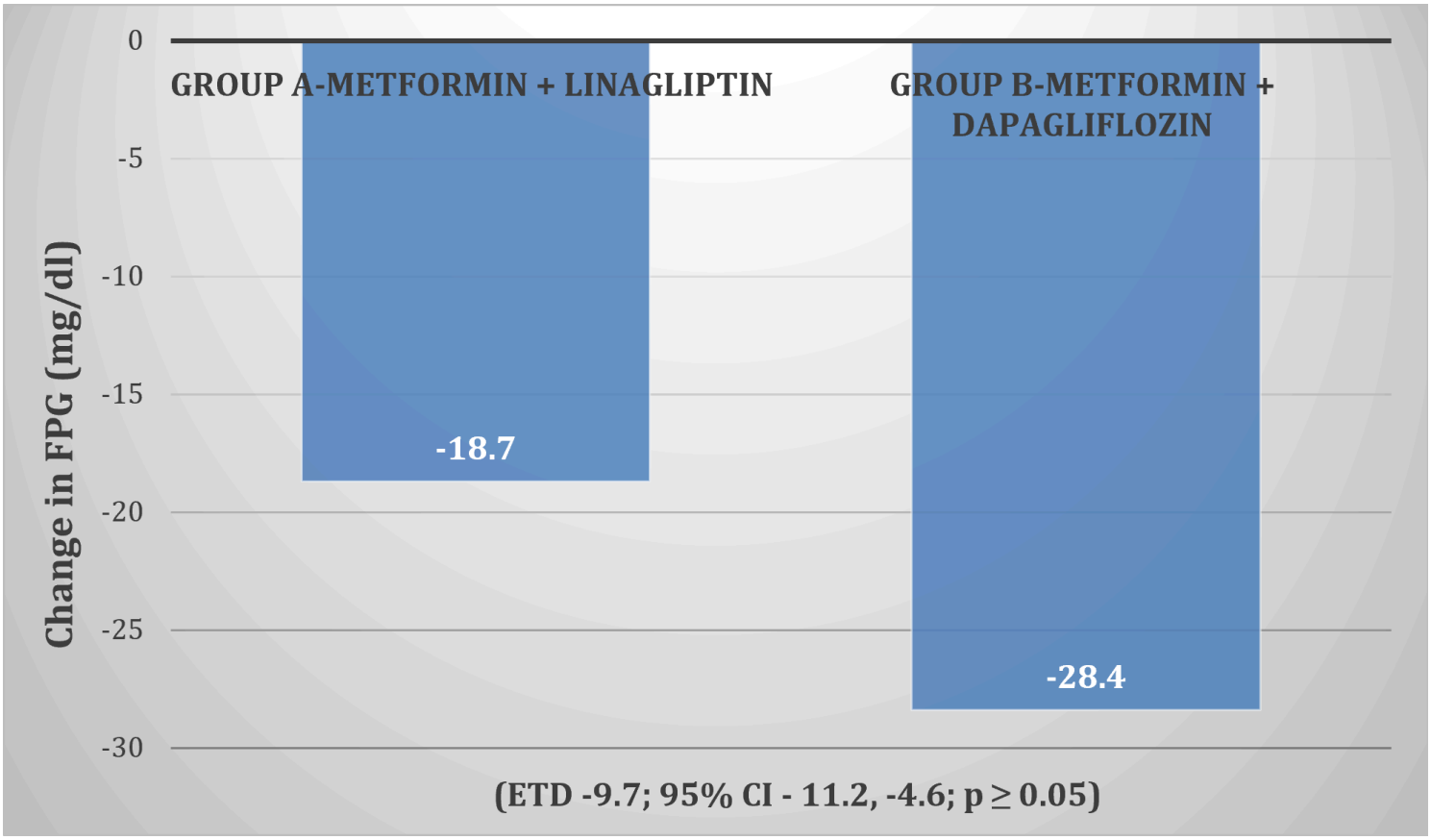


Figure 5

Comparison of reduction in the fasting plasma glucose between the two groups

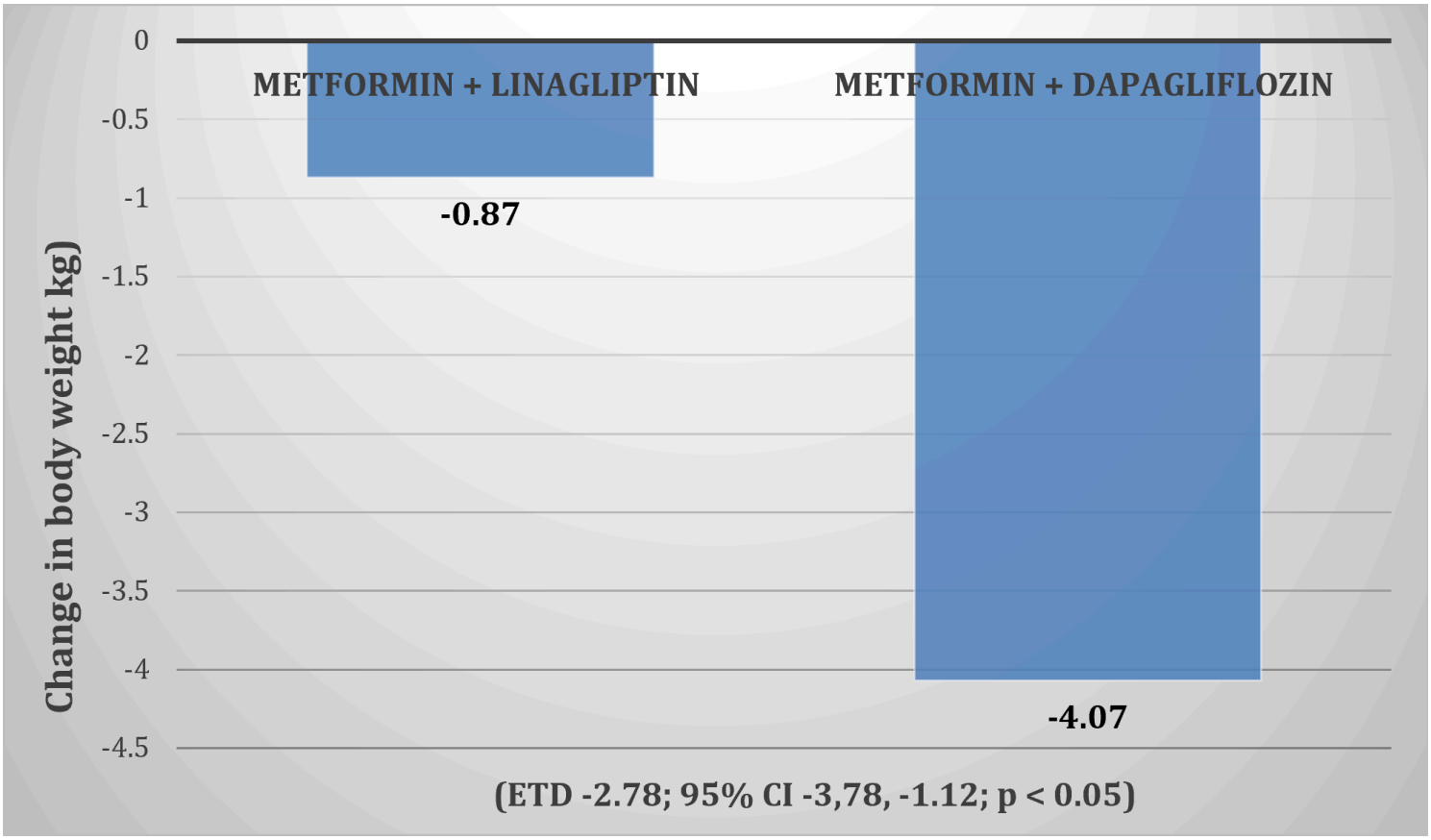


Figure 6

Comparison of change in body weight between the two groups

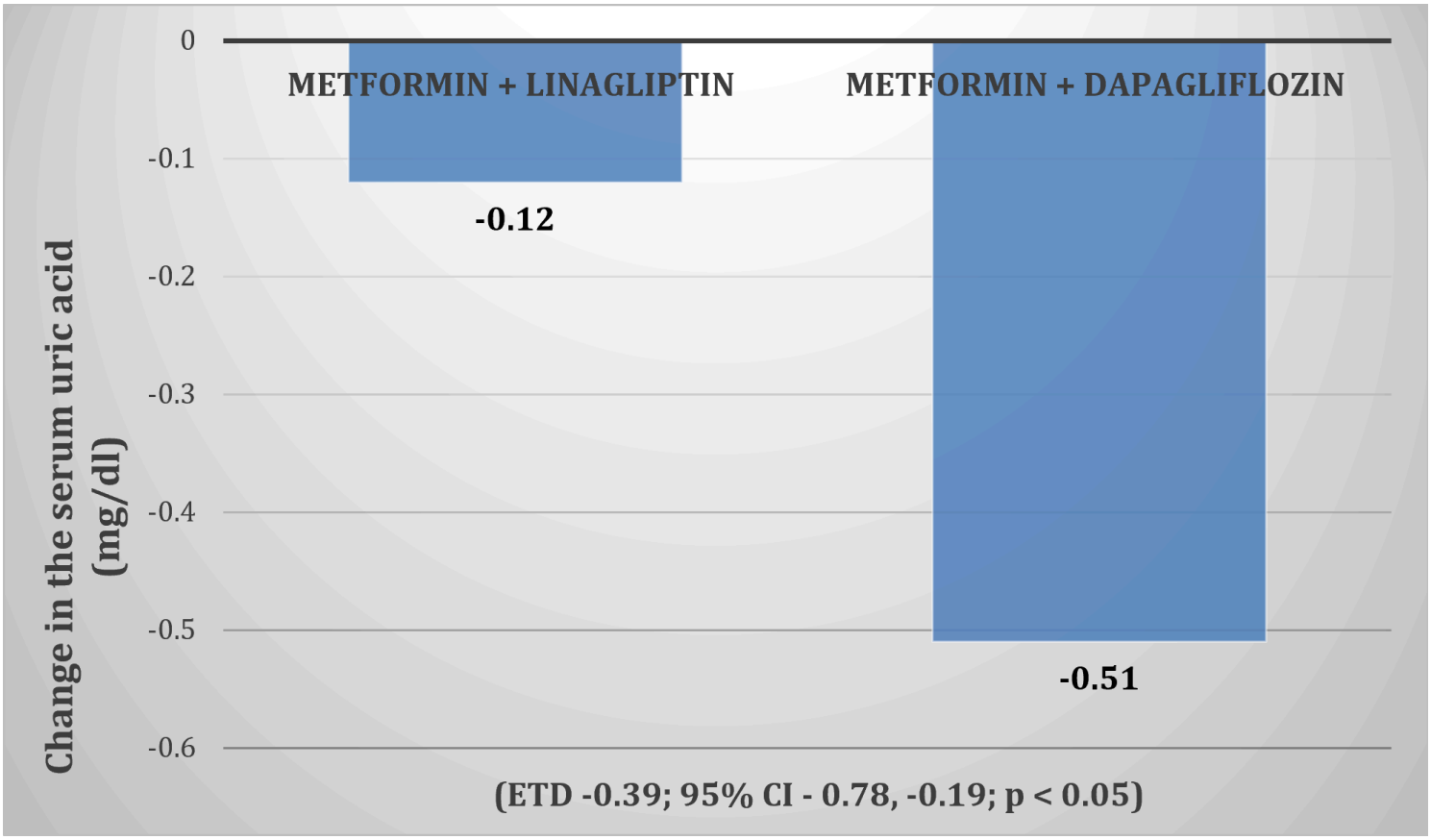


Figure 7

Comparison of change in the serum Uric acid between the two groups