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Comparison of Metformin combined with Empagliflozin or Sitagliptin on Glycemic Status, Renal Function, and Albumiuria in Patients with Type 2 Diabetes Mettitus

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ABSTRACT

Background: Type 2 diabetes mellitus is frequently complicated by insulin resistance and early renal impairment, including albuminuria. Metformin is still the first-line treatment, but other drugs like sodium–glucose cotransporter-2 inhibitors and dipeptidyl peptidase-4 inhibitors are often needed as well. There is still not enough comparative evidence about how they affect the kidneys and metabolism in everyday clinical practice.

Aims: The objective of this study was to evaluate the effects of metformin in conjunction with empagliflozin or sitagliptin on glycemic control, insulin resistance, renal function, and albuminuria in individuals with type 2 diabetes mellitus.

Patients and Methods: In this cross-sectional comparative study, 133 individuals with type 2 diabetes mellitus were chosen and divided into two groups based on their current treatment: metformin combined with empagliflozin (n = 67) or metformin combined with sitagliptin (n = 66). We looked at glycemic indices, insulin levels, insulin resistance, beta cell function, renal function parameters, estimated glomerular filtration rate, and urinary albumin-to-creatinine ratio.

Results: Patients taking metformin and empagliflozin had much lower fasting serum glucose (p=0.005), insulin levels (p=0.002), and insulin resistance (p=0.001) than those taking metformin and sitagliptin. This shows that their insulin sensitivity improved. The studied groups had similar levels of HbA1c, beta cell function, and estimated glomerular filtration rate. The urinary albumin-to-creatinine ratio was significantly lower in the empagliflozin group (p = 0.03). In both groups, urinary albumin-to-creatinine ratio had a positive correlation with insulin resistance and a negative correlation with estimated glomerular filtration rate.

Conclusion: Both combinations had similar effects on HbA1c, but metformin plus empagliflozin worked better at lowering insulin resistance and albuminuria. This suggests that metformin plus empagliflozin has an improved early renoprotective profile for people with T2DM.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a progressive metabolic disease that is characterized by insulin resistance and impaired function of pancreatic beta cells, that worsen over time, making it difficult to manage with one only therapy. Recent guidelines suggest combination therapies to achieve optimal control and prevent long-term complications (1,2). Metformin remains the gold-standard and also considered the first-line treatment of T2DM; however, it is still not enough as its own. Therefore, to obtain optimal glycemic control, many patients need to have further medications such as dipeptidyl peptidase-4 (DPP4) inhibitors or sodium-glucose cotransporter-2 (SGLT2) inhibitors (3,4). Empagliflozin, a SGLT2 inhibitor, enhances the excretion of glucose at renal proximal tubule and has been increasingly recognized for its pleiotropic effects, including the protection of cardiac and renal tissues in addition to weight loss effects (5). Sitagliptin, on the other hand, is a DPP4 inhibitor that works by boosting the body's natural incretin system to release insulin in a way that depends on glucose (6). Both agents are commonly prescribed as second-line treatments, but their advantages surpass glycemic control and significantly differ in their impact on renal physiology. In standard clinical practice, healthcare professionals frequently choose these agents based on their availability or glycemic effectiveness, rather than on comparative data concerning renal protection (7). Chronic kidney disease and albuminuria are prevalent complications of type 2 diabetes mellitus (T2DM), often resulting in significant deterioration of renal function and life-threatening consequences. While extensive cardiovascular outcome trials have shown that SGLT2 inhibitors protect the kidneys, there are still not many direct comparisons with DPP-4 inhibitors, especially in real-world patients who are already taking metformin. This study aims to assess the potential differences between two treatment strategies, empagliflozin plus metformin and sitagliptin plus metformin, regarding glycemic status, alterations in estimated glomerular filtration rate (eGFR), and urinary albumin-to-creatinine ratio (UACR) as an early indicator of renal impairment.

AIM AND OBJECTIVES

STUDY DESIGN, SETTING, AND ETHICAL APPROVAL

This cross-sectional comparative study was performed at the consultation unit of Al-Wafaa Center for Diabetes and Endocrine Disorders, located in Mosul, Nineveh Province, from October to December 2025. The Nineveh Health Directorate's local ethics committee reviewed and approved the study protocol (approval code: 2025248). Everyone who took part in the study knew what it was for and how it would work, and they all signed a form saying they understood and agreed to it before they signed up. Consultant doctors did a clinical evaluation on each patient to make sure they were eligible and to rule out any conditions that could affect the results of the study.

STUDY PARTICIPANTS

A total of 133 individuals with T2DM were enrolled consecutively and divided into two treatment groups based on their current antidiabetic therapy and inclusion criteria. Group 1 (metformin plus empagliflozin group) had 67 patients (33 men and 34 women) who were taking metformin at a dose of 1000 mg/day along with empagliflozin 25 mg once a day. Group 2

(metformin plus sitagliptin group) comprised 66 patients (32 males and 34 females) administered metformin 1000 mg/day in conjunction with sitagliptin 50 mg twice daily.

EXCLUSION CRITERIA

Patients undergoing insulin therapy or any antidiabetic agents outside the examined combinations were excluded. Additional exclusion criteria included the presence of chronic systemic diseases, use of medications known to affect glucose metabolism or renal function, pregnancy, lactation, or any condition that could interfere with glycemic or renal parameters.

LABORATORY INVESTIGATIONS

Five milliliters of venous blood were obtained from each participant following an overnight fast, utilizing sterile disposable syringes. Two milliliters of blood were put into EDTA tubes so that glycated hemoglobin (HbA1c) could be measured using the turbidimetric inhibition immunoassay (TINIA) method on a Cobas c111 autoanalyzer (Roche Diagnostics, Germany). The rest of the blood sample was put in plain tubes, let to clot, and then spun at 3000 rpm for 10 minutes to get serum. Photometric methods on the Cobas c111 analyzer with Roche kits that are available for sale were used to measure fasting serum glucose, serum urea, and serum creatinine. We used a sandwich enzyme-linked immunosorbent assay (ELISA) according to the manufacturer's instructions to find out the levels of insulin in the blood.

Insulin resistance and β-cell function were estimated using the homeostasis model assessment indices, calculated as HOMA-IR and HOMA-β, respectively. Renal function was assessed by calculating the estimated glomerular filtration rate (eGFR) using the CKD-EPI equation. For assessment of albuminuria, a spot urine sample was collected from each participant. Urinary albumin-to-creatinine ratio (UACR) was measured using the immunoturbidimetric method, which is commonly employed for routine clinical evaluation of albuminuria.

STATISTICAL ANALYSIS

Statistical analysis was performed using GraphPad Prism 8.4.2. Continuous variables are presented as mean ± standard deviation (SD), while categorical variables are expressed as frequencies. Comparisons between the two study groups were carried out using the unpaired (independent samples) t-test for continuous variables and the chi-square test for categorical variables. Correlation analyses were performed using Pearson's correlation coefficient (r) to assess the relationships between UACR and indices of insulin resistance and the eGFR, within each treatment group. A p value $\leq$ 0.05 was considered statistically significant.

RESULTS

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

The baseline demographic and clinical characteristics of the study participants are presented in Table A total of 133 patients with T2DM were included in the analysis (67 patients in group 1 vs 66 patients in group 2), with comparable distributions of age (49.4±9.2 years in group 1 vs 48.1±9.6 years in group 2), sex (33 males and 34 females in group 1 vs 32 males and 34 females in group 2), body mass index (BMI; 29.4±4.2 kg/m^2 in group 1 vs 29.1±7.9 kg/m^2 in group 2), duration of diabetes (11.2±3.2 months in group 1 vs 11.9±3.4 months in group 2), duration of treatment (4.6±1.1 months in group 1 vs 4.5±1.1 months in group 2), and family history (27 patients has positive family

history in group 1 vs 28 patients in group 2) between the two treatment groups. No statistically significant differences were observed between the metformin plus empagliflozin group and the metformin plus sitagliptin group for any of the baseline parameters, indicating adequate matching between the groups.

Continuous variables are presented as mean ± SD and were compared using the unpaired t-test. Categorical variables were compared using the chi-square test. Non-significant difference was noticed between the two groups. M: male, F: female, Y: yes, N: no, BMI: body mass index. Group 1: Empagliflozin+ metformin. Group 2: Sitagliptin + metformin.

GLYCEMIC AND METABOLIC PARAMETERS

The comparison of glycemic and metabolic indices between the two groups is summarized in Table 2. Patients receiving metformin combined with empagliflozin showed significantly lower fasting serum glucose (FSG; 127.5±28.5 mg/dl) levels compared with 145.1±41.4 mg/dl in those treated with metformin plus sitagliptin ($p = 0.005$). Serum insulin levels (14.1±6.3 µU/ml in group 1 vs 18.1±8.8 µU/ml in group 2) and HOMA-IR (4.6±2.8 in group 1 vs 6.7±4.5 in group 2) were also significantly lower in the empagliflozin group ($p = 0.002$ and $p = 0.001$, respectively), reflecting improved insulin sensitivity. In contrast, no significant differences were observed between the two groups with regard to HbA1c (7.4±1.2 % in group 1 vs 7.5±1.4 % in group 2) levels or HOMA-β (95.9.7±69.8 in group 1 vs 92.6±51.5 in group 2), suggesting comparable long-term glycemic control and β-cell function between the treatment strategies.

Data are expressed as mean±SD, and are significant when p value is ≤0.05, using unpaired t.test. Group 1: Empagliflozin+ metformin. Group 2: Sitagliptin + metformin. FSG: Fasting serum glucose; HbA1c: Glycated hemoglobin; HOMA-IR: Homeostatic model assessment of insulin resistance; HOMA-B: Homeostasis model assessment of β-cell function.

RENAL FUNCTION AND ALBUMINURIA

Renal function parameters are presented in Table 3. Serum creatinine (0.78±0.19 mg/dl in group 1 vs 0.83±0.22 mg/dl in group 2), blood urea levels (26.6±4.6 mg/dl in group 1 vs 27.7±7.2 mg/dl in group 2), and eGFR (102±16 ml/min/1.73m^2 in group 1 vs 98±17 ml/min/1.73m^2 in group 2) did not differ significantly between the two groups. However, the metformin plus empagliflozin group demonstrated a significantly lower log-transformed UACR (1.37±0.48 mg/g) compared with the metformin plus sitagliptin group (1.46±0.56 mg/g) at $p = 0.03$, indicating a more favorable effect on albuminuria.

Data are expressed as mean±SD, and are significant when p value is ≤0.05, using unpaired t.test. Group 1: Empagliflozin+ metformin. Group 2: Sitagliptin + metformin. S. Creatinine: serum creatinine; eGFR: Estimated glomerular filtration rate; UACR: Urinary albumin-creatinine ratio.

CORRELATION ANALYSES

Correlation analyses were performed to explore the relationship between albuminuria and markers of insulin resistance and renal function within each treatment group (Figure 1). In the metformin and empagliflozin group, UACR showed a significant positive correlation with HOMA-IR (Figure 1A). A significant negative correlation was also observed between UACR and eGFR in this group (Figure 1C). Similarly, in the metformin plus sitagliptin group, UACR

was positively correlated with HOMA-IR (Figure 1B), and a significant inverse relationship was found between UACR and eGFR (Figure 1D).

Analysis was performed using Pearson's correlation and are significant were indicated when $p \leq 0.05$. (A) Correlation between UACR and HOMA-IR in group 1. (B) Correlation between UACR and HOMA-IR in group 2. (C) Correlation between UACR and eGFR in group 1. (D) Correlation between UACR and eGFR in group 2.

DISCUSSION

This study aimed to assess the glycemic status and renal function markers in patients with T2DM receiving combination therapy of sitagliptin or empagliflozin as add-ons to metformin to aid the local healthcare practitioners with proper decision when prescribing the correct therapy for T2DM patients.

BASELINE CHARACTERISTICS OF THE STUDY POPULATION

The baseline characteristics of both groups in the present study were matching regarding age, gender, duration of diabetes, duration of treatment and BMI, excluding any effect of these variables on the obtained results.

GLYCEMIC AND METABOLIC PARAMETERS

When comparing the result of the treatment options in this study, it was noted that the combination of metformin with empagliflozin may provide better protection potential to the body compartments than the metformin and sitagliptin combination. Metformin and empagliflozin represented a more pronounced synergistic effect, due to not only its ability in managing blood sugar more efficiently, but it also provided much stronger protection for the kidneys. This effect is recently reported by Salankar and co-workers in their comparative study that was carried out in India during 2024. The study confirmed that while both agents improve glycemic control similarly, superior synergistic benefit regarding metabolic parameters and weight reduction was obtained from metformin and empagliflozin combination in comparison to metformin and sitagliptin. This outcome is attributed to more caloric loss mechanism through glycosuria and enhanced insulin sensitivity (8). Such an action is regarded as a vital advantage for any T2DM person to halt the complications of the disease, making it a highly effective strategy for long-term therapy (9). Additionally, evaluating HOMA-B together with HOMA-IR is considered essential test , as it permits for the differentiation between changes in insulin sensitivity and pancreatic beta cell secretory function, both of which are important component of pathophysiology of T2DM (10,11). It is well approved that insulin resistance represents a highest priority for clinician when managing T2DM. This is because when the insulin resistance is not properly controlled, the patient eventually may develop numerous complications, including renal impairment. Data analysis of the present study revealed that patients using the empagliflozin and metformin combination had a significantly lower levels of both insulin resistance and blood sugar than sitagliptin group. These results are in line with those of Talebi et al. (2024), who reported in a non-randomized, prospective observational study that patients receiving sitagliptin (100 mg) and empagliflozin (10 mg) once daily for 12 weeks had better glycemic profile when metformin is combined with empagliflozin (12). This could be explained by the mechanism that lowering blood sugar and

insulin levels effectively could make the body much more sensitive to its own insulin and helping the body to use insulin correctly (13). Similarly, the Alsarkhi and colleagues in 2025 highlighted a superior metabolic effect of empagliflozin, which is often focused on a significant reduction in intrahepatic lipid content, which correlates directly with improved insulin sensitivity of hepatic tissues (11). . In contrast, a randomized controlled trial that was performed by Hiruma et al. in 2023 on 44 Japanese patients with T2DM and non-alcoholic fatty liver disease (NAFLD) reported no significant difference between using empagliflozin or sitagliptin in regard of the changes of insulin sensitivity in the muscle, liver, or adipose tissues. This disagreement could be attributed to the selected criteria of their study, which only included patients with non-alcoholic fatty liver disease, and the obtained results might be explained by more tissue localized rather than systemic effect (14). Interestingly, although FSG and insulin resistance are significantly different between the two studied groups, analyzing HbA1c data in the current study revealed no statistically significant difference, suggesting that more time is needed for this parameter to be affected significantly and the high baseline level of HbA1c in both groups. This observation aligns with the findings of Mishriky et al., who, in a randomized trial, indicated that although SGLT2 inhibitors provide unique hemodynamic advantages, their efficacy in reducing glucose levels may not above that of DPP-4 inhibitors in patients with elevated baseline HbA1c levels (15). These results align with previous systematic reviews showing that the difference between empagliflozin therapy and sitagliptin is not constantly the same. Even when considering that SGLT2 inhibitors are generally higher at reducing fasting glucose levels in blood, but this fact decreases or even disappears in patients with a higher baseline level of HbA1c and this is in agreement with many studies (16–18).

RENAL FUNCTION AND ALBUMINURIA

Concerning renal function effects of the studied groups, the present study's results showed that metformin plus empagliflozin group demonstrated a significantly lower urinary albumin leakage, measured as UACR, in comparison to metformin plus sitagliptin group. This result is in line with the results of a recent study (19), which examined twenty-one T2DM patients with nephropathy and nineteen without nephropathy. Each group obtained empagliflozin (10 mg/day) as an add-on to the traditional treatment. After 16 weeks, empagliflozin significantly reduced HbA1c and UACR in the nephropathy group. This represented a significant improve in renal outcome when SGLT2 inhibitors are used in comparison to DPP4 inhibitors, a results that also agree with Kaneko et al. study (9). Moreover, the data of the present study revealed a significant correlation between HOMA-IR and UACR, this supports the hypothesis were metabolic insulin resistance and renal endothelial dysfunction progress concurrently. These results are in line with a large-scale REACTION study conducted by Gu and co-workers in 2020, which established that HOMA-IR shows positive association with urine albumin levels even after controlling other potential confounders. Their work suggested that insulin resistance is not simply a metabolic defect, but a driver of renal vascular damage, reporting that the presence of insulin resistance may predict the progression of microalbuminuria likely through mechanisms involving oxidative stress and podocyte injury (20). This

pathophysiological link is validated through further investigation by Hsu et al., in which a long-term follow-up confirmed that the elevated baseline HOMA-IR values as independent risk factors for microalbuminuria development, which further reinforcing the concept that systemic insulin resistance precedes and accelerates organ dysfunction (21). Conversely, the present study observed a negative relationship between UACR and eGFR, which can perfectly reflect how diabetic kidney disease progress. As UACR increases, it acts as a red flag for a drop in eGFR, leading to the first signal that the kidneys lose, which is filtration; a result that is in agreement with a recent study (22). Consistently, Ju and colleagues in 2025 conducted a retrospective cohort study, which established that although sitagliptin shows minimal impact on renal function, empagliflozin significantly slows eGFR worsening, supporting the empagliflozin role in maintaining sustained glomerular filtration function in diabetic nephropathy (23). Likewise, the American diabetes association recommends that it is advisable to use SGLT2 inhibitors for individuals with type 2 diabetes and CKD (24) .

LIMITATIONS AND RECOMMENDATIONS FOR FUTURE WORK

While the findings of the current study provide valuable insights for clinical practice, certain limitations should be considered when interpreting the results and planning the directions for future research. Although the duration of treatment is sufficient to reflect changes in glycemic status and renal function, this duration may be considered short in some clinical settings to predict the exact long-term renoprotective effects of both treatments. Also, to confirm and strengthen the findings of the study, expanding the inclusion of patients on multicenter bases is needed to produce more conclusive evidence. Therefore, future research should be performed on large-scale and multicenter bases with extended follow-up periods.

CONCLUSION

1. Combinations of empagliflozin with metformin and sitagliptin with metformin have almost the same impact on HbA1c levels.
2. Empagliflozin and metformin combination has a better ability in reducing systemic insulin resistance and proteinuria compared to metformin and sitagliptin.
3. When treating patients with type 2 diabetes, choosing the treatment options should not be based only on controlling the blood glucose levels, but should also target insulin resistance in order to provide earlier renoprotective effects.

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CONFLICT OF INTEREST

The authors have no conflict to declare

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TABLES

Table 1. Baseline Characteristics of the Study Group

Variable	Group 1	Group 2
Number (M/F)	67 (33/34)	66 (32/34)
Age (years)	49.4±9.2	48.1±9.6
Duration of Diabetes (months)	11.2±3.2	11.9±3.4
Duration of treatment (months)	4.6±1.1	4.5±1.1
Family history (Y/N)	27/40	28/38
BMI (kg/m^2)	29.4±4.2	29.1±7.9

Table 2. Glycemic status of the studies groups

Parameter	Group 1	Group 2	P-value
FSG (mg/dl)	127.5±28.5	145.1±41.4	**0.005**
HbA1c (%)	7.4±1.2	7.5±1.4	0.68
Insulin (µU/ml)	14.1±6.3	18.1±8.8	**0.002**
HOMA-IR	4.6±2.8	6.7±4.5	**0.001**
HOMA-B	95.9.7±69.8	92.6±51.5	0.76

Table 3. Renal function parameters in the studied groups

Parameter	Group 1	Group 2	P-value
S. Creatinine (mg/dl)	0.78±0.19	0.83±0.22	0.18
Urea (mg/dl)	26.6±4.6	27.7±7.2	0.3
eGFR (ml/min/1.73m^2)	102±16	98±17	0.15
Log UACR (mg/g)	1.37±0.48	1.46±0.56	**0.03**

FIGURES

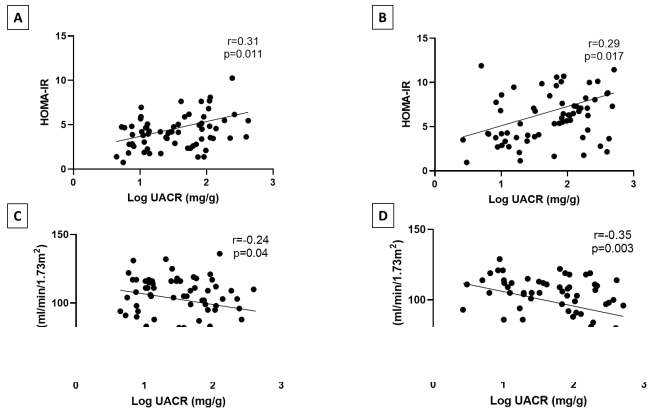

Figure 1. Correlation analyses between urinary albumin-to-creatinine ratio (UACR) and metabolic and renal paramete