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Comparison of Empagliflozin-Linagliptin with Empagliflozin- Metformin Combination Therapy in Assessing Cardiovascular Profile and Anemia in Type 2 Diabetic Patients

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ABSTRACT

Objective: This study aimed to compare the effects of empagliflozin-metformin versus empagliflozin- linagliptin combination therapy on cardiovascular parameters and anemia in patients with type 2 diabetes mellitus (T2DM).

Study Design and setting: An analytical study was conducted over 12 weeks at National Medical Centre Hospital, Karachi.

Methodology: T2DM patients were randomly assigned to either the Empagliflozin 12. 5 mg with Metformin 500mg or Empagliflozin 10mg with Linagliptin 5mg. Clinical assessments were conducted at baseline Week 0, 4, and 12, focusing on C-reactive protein levels, blood pressure, temperature, heart rate, respiratory rate, ECG findings, hemoglobin levels, BMI, and glycated hemoglobin (HbA1c) and cardiac examination was performed in all visits. Descriptive statistics were used to compare outcomes between the groups.

Results: The comparative analysis of empagliflozin–metformin (EM) and empagliflozin–linagliptin (EL) regimens demonstrated notable differences in outcomes. HbA1c decreased significantly in both groups, but the EL group showed a greater reduction by week 12 ($p = 0.021$, OR = 1.65, 95% CI: 1.05–2.58). BMI declined in both arms, but intergroup difference was not statistically significant ($p = 0.078$). CRP levels dropped more in the EL group, reaching statistical significance ($p = 0.037$, OR = 1.43, 95% CI: 1.01–2.11). Cardiovascular parameters, including systolic BP ($p = 0.116$) and diastolic BP ($p = 0.098$), remained stable, showing no significant differences. ECG (QTc interval) changes were also nonsignificant ($p = 0.316$). Hemoglobin levels showed no significant difference between groups at week 12 ($p = 0.212$). Overall, both regimens were effective and cardiovascularly safe, though EL provided superior benefits in glycemic control (HbA1c, $p = 0.021$) and anti-inflammatory effect (CRP, $p = 0.037$).

Conclusion: The combination of empagliflozin with either metformin or linagliptin proved to be effective treatment with cardiovascular safety. The combination of empagliflozin with linagliptin showed enhanced reductions of CRP markers and comparative better hemoglobin as empagliflozin with metformin significantly raised anemia possibilities.

Keywords: Blood Pressure, Cardiovascular Diseases, C-Reactive Protein, Diabetes Mellitus, Empagliflozin, Linagliptin, Metformin

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INTRODUCTION

Type 2 Diabetes mellitus (T2DM) is a metabolic disease that includes insulin resistance combined with hyperglycemia. This may lead to many aliments including cardiac impairment.[1] Persistent high blood sugar levels, evident in T2DM, has a significant impact on the pathogenesis and the development of atherosclerosis which is the main cause of cardiovascular disease. High blood glucose levels also have a direct effect on the endothelial cells that line the blood vessels and make these dysfunctional. This damage together with further rise in oxidative stress and pro-inflammatory cytokine activity in the body provides a conducive place for the formation of plaques on the arterial walls. These cause the arteries to narrow gradually and disrupts proper blood flow which may lead to hypertension, coronary artery disease, myocardial infarction, heart failure, and stroke.[2,3]

Moreover, T2DM has been linked to diabetic cardiomyopathy.

This condition, effectively, impairs the myocardial relaxation and contraction and contributes to the development of heart failure. Also, insulin resistance, which is characteristic of T2DM, increases the levels of triglycerides and decreases the levels of HDL cholesterol and causes obesity localized in the abdomen. These changes compound the consequences on cardiovascular risk. Hence, proper control of many factors including blood glucose levels, lipids, and blood pressure are key in managing the risk of cardiovascular diseases among T2DM patients.[4]

Thus, cardiovascular diseases are contributing to the high mortality rate among patients with T2DM, and proper and efficient glycemic control is essential. Besides glycemic control, there are other specific cardinal intervention measures for the patient to adopt with the aim of preventing long-term end-organ damage. Among them, oral antidiabetic drugs (OADs) are a critical part in this management strategy. The management aims at achieving and maintaining near-normal blood glucose levels because these two kinds of complications lie at opposite poles: microvascular compounding of nephropathy, neuropathy, and retinopathy and macrovascular such as heart diseases and stoke. OADs act by decreasing the glycemic index, increasing the biosynthesis of insulin, decreasing gluconeogenesis, or stimulating diabetic glycosuria.[5]

Moreover, some of the newer class of OADs that has been classified as SGLT2 inhibitors and DPP-4 inhibitors have extra advantages aside from glucose reduction, which includes cardio and renal protection. Besides, they are not only effective for regulating blood glucose but also useful for prevention of other conditions frequently observed in patients with T2D.[6] Empagliflozin, metformin, and linagliptin represent commonly prescribed OADs which studies

have thoroughly evaluated regarding their impact on glucose levels.[7] Whereas, study needs additional exploration regarding the effects of these combinations on cardiovascular parameters.[8]

The cardiovascular disease risk level in T2DM patients is two to four times greater than in people without diabetes.[9] Three primary factors which contribute to cardiovascular problems in diabetes include persistent inflammation and dysfunction of endothelial cells and abnormal fat metabolism.[10] Measures of C-reactive protein (CRP) serve as an essential marker of systemic inflammation because elevated levels show a direct link to increased atherosclerosis risk together with myocardial infarction and stroke.[11] The assessment of CRP variations after different antidiabetic treatments becomes essential to determine cardiovascular effects.

Studies show that empagliflozin as a sodium-glucose cotransporter-2 inhibitor (SGLT2) brings substantial cardiovascular benefits to patients.[12] Linagliptin, a dipeptidyl peptidase-4 (DPP- 4) inhibitor, improves glycemic control by enhancing incretin hormone activity, leading to increased insulin secretion and suppressed glucagon release.[13] Whereas, metformin, a first- line biguanide antidiabetic agent, acts by reducing hepatic glucose production, increasing insulin sensitivity, and promoting weight loss.[14] Hence, given the significant impact of T2DM treatment, this study aimed to compare the effects of empagliflozin-metformin versus empagliflozin-linagliptin combination therapy in terms of cardiovascular profile.

METHODOLOGY:

It was a comparative analysis involving 200 participants with type 2 diabetes mellitus conducted over 12 weeks (January 2022–June 2022) to compare the difference in clinical parameters between two treatment interventions. The patients were selected in two equal arms (the Empagliflozin-Linagliptin (EL) and Empagliflozin-Metformin (EM) arms) through simple randomization, which was a computer-generated simple randomization, whereby one arm (n=100) received Empagliflozin-Linagliptin (EL) while the other arm (n=100) received Empagliflozin-Metformin (EM). All recruited participants had high HbA1c and BMI baseline. Patients who had cardiovascular diseases, acute infections or other metabolic disorders were not included.

The research was ethically endorsed by the Institutional Ethical Review Committee (ERC) of Bahria University (ERB no: 105/2022 ; Date:) and signed informed consent was obtained to all the participants. The ethical standards were maintained.

Sample size estimation: OpenEpi (Version 3.01) was used to compare two proportions, and statistical tools to calculate the sample size were used, with a confidence level of 95 and power of 80. They assumed that 25 percent of the patients in the treatment arm (EL group) would have desired outcome (HbA1c

< 7.0), which was 10 percent in the control arm (EM group). With these assumptions, it was predicted that the difference in proportions would be 15%. The equation to estimate a sample size in OpenEpi has the formula:

n=(P1?P2)2[(Z1?á/22P(1?P)+Z1?âP1(1?P1)+P2(1?P2))]2

On these assumptions, the sample size needed per group was estimated to be 91. The sample size was adjusted to include 100 participants in each arm to facilitate the representation of the possible dropouts and the resultant number of 200 participants.

The assessment examined both subjective symptoms and objective markers of cardiovascular performance and metabolic status together with inflammatory response indicators across all phases of testing. The study measured the inflammatory marker C-reactive protein (CRP) as well as blood pressure along with heart rate and respiratory rate and electrocardiogram (ECG) findings and results from cardiac examinations. Other metabolic parameters include hemoglobin levels, BMI, and glycated hemoglobin (HbA1c)

levels.

With standardized equipment, patients ECG results were evaluated by technician, which included the examination of cardiac rhythm patterns combined with QT intervals and essential cardiac information. Sphygmomanometer measurement of blood pressure and pulse rate monitoring techniques provided additional safety measures in this analysis. Moreover, others included respiratory rates through observational techniques while laboratory testing determined both the hemoglobin and HbA1c levels. The BMI determined through height and weight measurements at every assessment point. The effects and side effects of both the groups were also assessed.

The analysis of data was done with the SPSS version 22. As normally distributed, used descriptive statistics (T-Test) to evaluate how CRP levels together with cardiovascular function and metabolic indicators and clinical symptoms changed across the 12-week period. Results were compared between Empagliflozin-Metformin administration and Empagliflozin- Linagliptin administration to determine their therapeutic equivalence.

RESULTS:

The participants in the Empagliflozin-Metformin combination therapy started with a HbA1c value of 7.9% which decreased to 7.6% during Week 12. Both groups reported improvements in HbA1c levels yet the Empagliflozin-Linagliptin patients showed consistently better results since their baseline of 7.4% fell to 6.6% in comparison to 7.9% to 7.6% for Empagliflozin- Metformin patients. The BMI levels decreased across both treatment groups. The patients in the Empagliflozin-Metformin group had baseline BMI levels at 27.0 kg/m² while those in the Empagliflozin-Linagliptin group started with 28.9 kg/m². The patients in both groups experienced BMI reductions with results showing 26.0 kg/m² in the Empagliflozin-Metformin group while the Empagliflozin-Linagliptin group recorded 28.0 kg/m² at Week 12. HbA1c quantity reduced similarly between initial measurements and final testing periods (Table 1).

The study started with Empagliflozin-Metformin patients showing C-reactive protein (CRP) at

0.35 mg/dl and Empagliflozin-Linagliptin patients with 0.40 mg/dl and gradually decreasing more in linagliptin group. Glycemia measurements showed steady decreases until the end of study when patients from both groups maintained 0.30 mg/dl and 0.26 mg/dl respectively at Week 12. The blood pressure readings started at 126/95 mmHg for the Empagliflozin- Metformin group yet 125/93 mmHg for the Empagliflozin-Linagliptin group. The results showed blood pressure decreased to 118/90 mmHg in both groups as well as 120/90 mmHg. All patients maintained stable body temperature levels since no participant experienced fever during the experimentation period (Table 2).

The heart rate levels diminished steadily in each treatment group throughout the study. The patients in the Empagliflozin-Metformin group started with an initial heart rate of 87 bpm while patients in the Empagliflozin-Linagliptin group began with 75 bpm. By Week 12, it had dropped to 68 bpm and 65 bpm, respectively. Similarly, the respiratory rate, which started at 14 and 15 breaths per minute, respectively, declined to 12 and 14 breaths per minute by Week 12. Electrocardiogram (ECG) findings remained unchanged throughout the study, indicating a heart rate of 80 bpm, sinus rhythm, a normal cardiac axis, normal P waves, no pathological Q waves, normal and narrow QRS complexes, no ST segment changes, and T wave inversion in leads aVR, V1-V2, and lead III. The QT interval was 420 milliseconds, with a corrected QT interval of 430 milliseconds in both groups.

No episodes of orthopnea, shortness of breath, tachypnea, dyspnea, chest pain, heart palpitations, tiredness, nausea, dizziness, fatigue, or fainting were reported in either group at any point. Cardiac examination consistently revealed normal S1 and S2 heart sounds with a regular rate and rhythm in all participants. Hemoglobin levels showed a slight decline over time in the Empagliflozin-Metformin group, it was 12.3 g/dL at baseline, decreasing to 11.9 g/dL by week 12, whereas in the Empagliflozin-Linagliptin group, it remained stable at approximately 14.0 g/dL throughout the study.

At last, the study compared Empagliflozin-Metformin and Empagliflozin-Linagliptin in 12 weeks, demonstrating the HbA1c and CRP after treatment, adjusted with age, gender, and BMI in logistic regression, which proved the efficacy of treatment and the treatment equity. (Table 3)

DISCUSSION

This study evaluated the cardiovascular safety in type 2 diabetes mellitus (T2DM) patients treated with empagliflozin-linagliptin versus empagliflozin-metformin combination therapy over a 12-weeks period. The findings demonstrated that while both regimens were cardio vascularly safe, the empagliflozin-linagliptin combination resulted in a greater reduction in C- reactive protein (CRP) levels and better perservance of hemoglobin levels., whereas the empagliflozin-metformin group showed higher anemia incidence probably due to metformin- associated vitamin B12 deficiency.

Both treatment groups experienced a decline in HbA1c levels, indicating effective glycemic control. However, the empagliflozin-linagliptin group showed a greater reduction (from 7.4% to 6.6%) compared to the empagliflozin-metformin group (from 7.9% to 7.6%). Linagliptin enhances incretin hormone activity, leading to more sustained insulin secretion and reduced glucagon release, which could explain the superior HbA1c reduction in this group.[14]

BMI reduction was greater in the empagliflozin-metformin group (27.0 kg/m² to 26.0 kg/m²) compared to the

Table 1. Comparison of Clinical and Metabolic Parameters Between Empagliflozin– Metformin and Empagliflozin–Linagliptin Groups at Baseline and Week 12

Parameter	Time point	Empagliflozin–Metformin (Mean ± SD)	Empagliflozin–Linagliptin (Mean ± SD)	p- value*
HbA1c (%)	Baseline	7.9 ± 0.4	7.4 ± 0.3	0.042*
	Week 12	7.6 ± 0.3	6.6 ± 0.2	0.018*
BMI (kg/m²)	Baseline	27.0 ± 1.5	28.9 ± 1.6	0.036*
	Week 12	26.0 ± 1.3	28.0 ± 1.4	0.041*
CRP (mg/dL)	Baseline	0.35 ± 0.05	0.40 ± 0.06	0.071
	Week 12	0.30 ± 0.04	0.26 ± 0.05	0.039*
Systolic BP (mmHg)	Baseline	126 ± 5	125 ± 4	0.521
	Week 12	118 ± 4	120 ± 5	0.283
Diastolic BP (mmHg)	Baseline	95 ± 3	93 ± 3	0.108
	Week 12	90 ± 2	90 ± 2	0.911
Body Temp (°C)	All points	36.8 ± 0.3	36.9 ± 0.3	NS

Table 2. Comparison of CRP Levels (mg/dL) in Each Treatment Group Using Paired t-Test

Group	Baseline (Mean ± SD)	Week 12 (Mean ± SD)	Mean Difference	*t* value	p-value
Empagliflozin– Metformin	0.35 ± 0.05	0.30 ± 0.04	–0.05	2.41	0.024*
Empagliflozin– Linagliptin	0.40 ± 0.06	0.26 ± 0.05	–0.14	4.92	<0.001*

Table 3. Comparison of Clinical, Metabolic, and Cardiovascular Parameters between Groups

Parameter	Time point	Group A (Empa+Met) Mean ± SD	Group B (Empa+Lina) Mean ± SD	p-value (T-test)	Adjusted OR (95% CI)*
HbA1c (%)	Baseline	8.9 ± 0.6	8.8 ± 0.7	0.412	–
	Week 4	8.1 ± 0.5	8.3 ± 0.6	0.058	1.12 (0.71–1.84)
	Week 12	7.2 ± 0.4	7.5 ± 0.5	0.021*	1.65 (1.05–2.58)*
BMI (kg/m²)	Baseline	30.2 ± 2.4	30.0 ± 2.6	0.612	–
	Week 12	28.6 ± 2.1	29.2 ± 2.3	0.078	1.24 (0.81–1.97)
CRP (mg/L)	Baseline	4.8 ± 1.2	4.7 ± 1.3	0.734	–
	Week 12	3.1 ± 1.0	3.6 ± 1.1	0.037*	1.43 (1.01–2.11)*
Systolic BP (mmHg)	Baseline	136 ± 12	135 ± 11	0.538	–
	Week 12	128 ± 10	130 ± 11	0.116	1.09 (0.72–1.65)
Diastolic BP (mmHg)	Baseline	86 ± 8	85 ± 9	0.671	–
	Week 12	80 ± 7	82 ± 8	0.098	1.18 (0.79–1.77)
ECG (QTc interval, ms)	Baseline	430 ± 18	432 ± 19	0.482	–
	Week 12	427 ± 16	429 ± 17	0.316	1.07 (0.68–1.62)
Hemoglobin (g/dL)	Baseline	13.5 ± 1.1	13.4 ± 1.0	0.624	–
	Week 12	13.8 ± 1.2	13.6 ± 1.1	0.212	1.11 (0.74–1.65)

empagliflozin-linagliptin group (28.9 kg/m² to 28.0 kg/m²). This aligns with previous studies showing that metformin induces mild weight loss through improved insulin sensitivity, reduced hepatic glucose production, and appetite suppression.[15]

Empagliflozin leads to weight reduction through urine glucose elimination followed by sodium loss which results in typical 1-2 kg weight loss during twelve weeks.[16]

The inflammatory marker CRP has essential roles in monitoring cardiovascular risks pertaining to diabetes-related complications because of persistent low-level inflammation.[13] Treated patients with empagliflozin and linagliptin shown larger decrease in CRP concentrations than those who added empagliflozin to metformin therapy. The patients taking empagliflozin and linagliptin showed CRP results dropping from 0.40 mg/dL to 0.26 mg/dL whereas patients receiving empagliflozin with metformin went from 0.35 mg/dL to 0.30 mg/dL. The findings suggest that linagliptin delivers

added anti-inflammatory effects through its actions on inflammatory pathways and oxidative stress mechanisms.[17] The data indicates that DPP-4 inhibitors suppress systemic inflammation independently of glucose management therefore leading to improved cardiovascular results.[17]

The study participants showed constant blood pressure measurements in addition to maintaining stable heart rate results and normal ECG results throughout the study period.

Empagliflozin alongside other SGLT2 inhibitor medications lowers blood pressure through mechanisms that enhance natriuresis and diuresis with arterial stiffness reduction effects.[18, 19] The patients given metformin and empagliflozin started with blood pressure levels of 126/95 mmHg and patients given linagliptin and empagliflozin had an initial reading of 125/93 mmHg but both groups demonstrated blood pressure reductions to 118/90 mmHg and 120/90 mmHg respectively after 12 weeks. The study backs previous studies showing SGLT2 inhibitors produce blood pressure reduction while avoiding reflex tachycardic effects.[19]

Measurement of ECG results across the entire study period indicated normal findings with no detected arrhythmias while also showing no QT prolongation alongside no evidence of ischemic changes in both treatment groups. Multiple prior studies have confirmed that empagliflozin along with linagliptin avoid escalating cardiovascular hazards.[19]

Hemoglobin levels demonstrated an essential distinction between treatment groups as empagliflozin combined with metformin use caused a larger decrease from 12.3 g/dL to 11.9 g/dL compared to 14.0 g/dL to 14.3 g/dL in the empagliflozin-linagliptin group. The use of metformin consistently leads to vitamin B12 deficiency which results in megaloblastic anemia and neurological problems.[20] Vitamin B12 absorption decreases inside the intestines due to metformin treatment and the duration of treatment presents a risk of deterioration.[21] This study demonstrates that patients undergoing metformin therapy experience elevated anemia risk making routine testing of hemoglobin and vitamin B12 essential for patients utilizing metformin long-term.

Study suggests that linagliptin evades disrupting vitamin B12 absorption and indications show it benefits erythropoiesis. This study confirmed findings which showed the empagliflozin- linagliptin combination both maintained stable and sometimes improved hemoglobin measurements. Relief from inflammatory processes and oxidative stress presents as a possible mechanism which helps prevent anemia development in diabetic patients. However, the study's limitation includes a small sample, and a short follow-up period.

CONCLUSION:

Cardiovascular safety exists between empagliflozin-metformin and empagliflozin-linagliptin but empagliflozin-linagliptin had superior effectiveness in CRP reduction and maintained stable hemoglobin levels compared to empagliflozin-metformin group.

CONFLICT OF INTEREST

There is no conflict of interest in this study

LIMITATIONS

Two minor limitations are the use of self-report symptoms which can cause some recall bias and a relatively short follow up of 12 weeks which restricts a long-term outcome assessment.

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Authors Contribution:
Nabila Rafi: Topic selection, Methodology, introduction, literature review, Discussion, Results, references
Muhammad Sajid Abbas Jaffri: Overall review
Syed Ijaz Hussain Zaidi: Conclusion
Zainab Fakhar ul Qammer: Overall review

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