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Efficacy and Safety Comparison between Empagliflozin and Linagliptin among Type 2 Diabetes Mellitus Patients : A Systematic Review and Meta-Analysis

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Abstract: Introduction: Empagliflozin and linagliptin are two commonly used medications for the management of Type 2 Diabetes Mellitus (T2DM). However, direct comparison of their efficacy and safety profiles remains limited. This study aims to compare efficacy and safety of empagliflozin and linagliptin in T2DM patients. Methods: Systematic review was done according to the PRISMA statements. Searching was conducted among multiple databases with specific keywords. Selection of studies were done by set of inclusion and exclusion criteria. Included studies were appraised using the Cochrane RoB2.0 critical appraisal tools. Analysis was done qualitatively and quantitatively, with assistance of RevMan 5.4. Heterogeneity analysis was done to determine the effects model used. *P* value of <0.05 was determined as statistical significance. Results: Four studies with low risk of bias and involving 420 subjects were included. Analysis showed that empagliflozin resulted in significantly greater reductions in HbA1c (MD = 0.71%, 95% CI = 0.43–0.99%) and fasting blood glucose (MD = 47.61 mg/dl, 95% CI = 25.57–69.65 mg/dl) compared to linagliptin. In terms of safety, there were no significant differences in the incidence of hypoglycemia (OR = 0.73, 95% CI = 0.38–1.38) or urinary tract infections (OR = 0.68, 95% CI = 0.37–1.25) between the two treatments. Conclusion: Empagliflozin provided better glycemic control over linagliptin among T2DM patients with satisfactory safety profile.

Keywords: diabetes, empagliflozin, glucose, linagliptin, safety

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a long-standing global health burden, affecting millions of individuals worldwide. Effective management of blood glucose levels is critical to reducing the risk of complications associated with T2DM, including cardiovascular diseases, kidney failure, and neuropathy.[1,2] A variety of pharmacological agents are available to control

[1] Lu, X., Xie, Q., Pan, X., Zhang, R., Zhang, X., Peng, G., et al. (2024). Type 2 diabetes mellitus in adults: Pathogenesis, prevention and therapy. *Signal Transduction and Targeted Therapy*, *9*(1), 1–25.

blood glucose, with newer classes of medications providing additional benefits beyond glycemic control. Among these, sodium-glucose cotransporter-2 inhibitors (SGLT2is) and dipeptidyl peptidase-4 inhibitors (DPP-4is) have gained significant attention due to their promising effects on both glycemic control and cardiovascular outcomes.[3]

Empagliflozin, an SGLT2 inhibitor, works by reducing glucose reabsorption in the kidneys, leading to increased glucose excretion in the urine. In addition to its glycemic-lowering effect, empagliflozin has demonstrated cardiovascular and renal protective properties in large-scale clinical trials, particularly in patients with established cardiovascular disease.[4] Conversely, linagliptin, a DPP-4 inhibitor, enhances endogenous incretin activity by inhibiting the enzyme responsible for the degradation of glucagon-like peptide-1 (GLP-1). This results in increased insulin secretion and decreased glucagon levels, which together help lower blood glucose levels in a glucose-dependent manner.[5]

Despite their distinct mechanisms of action, both empagliflozin and linagliptin have become integral components of modern T2DM treatment regimens.[3,6] However, the comparative efficacy and safety of these two agents remain an area of active investigation. While both drugs have shown efficacy in reducing HbA1c and improving glucose control, they differ in their additional effects on weight, blood pressure, and potential risks, such as hypoglycemia, dehydration, and renal function decline. This study aims to compare efficacy and safety profiles of empagliflozin and linagliptin in patients with T2DM to help clinicians make evidence-based decisions to improve patient outcomes.

METHODS

A systematic review with meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) Statement.[7] Searching was conducted on PubMed, ScienceDirect, ProQuest, EBSCOHost, and through hand-searching; using the keywords of "("Diabetes") AND ("Linagliptin " OR "Tradjenta" OR "Trajenta")) AND ("Empagliflozin" OR "Jardiance")". Articles found among searching were assessed using set of criteria. These inclusion criteria were applied: (1) Randomized clinical study; (2) Have intervention and comparator of empagliflozin and linagliptin; (3) Done among patients with type 2 diabetes mellitus; (4) Having outcome of clinical outcome and/or safety profile. In addition, following exclusion criteria were applied to omit articles: (1) No full paper available; (2) Written in other than English language.

Selected studies were included and appraised using Cochrane risk of bias assessment tool.[8] Studies further extracted for characteristics and outcome. Characteristics extracted as

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[2] Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., et al. (2020). Pathophysiology of type 2 diabetes mellitus. *International Journal of Molecular Sciences, 21*(17), 6275.

[3] Gaggini, M., Sabatino, L., Suman, A. F., Chatzianagnostou, K., & Vassalle, C. (2025). Insights into the roles of GLP-1, DPP-4, and SGLT2 at the crossroads of cardiovascular, renal, and metabolic pathophysiology. *Cells, 14*(5), 387.

[4] Scheen, A. J. (2012). DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials. *Diabetes & Metabolism, 38*(2), 89–101.

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follows: (1) First author; (2) Time of publication; (3) Place of study; (4) Study design; (5) Subject size; (6) Gender; (7) Age; (8) Other comorbidities. Outcomes extracted as follows: (1) Glucose profiles; (2) Hypoglycemia; (3) Other safety profiles. Outcomes were assessed qualitatively and quantitatively. Quantitative analysis was carried through RevMan 5.4. Data were analyzed of heterogeneity using the Cochrane I^2 test and Higgins' test. Data with $I^2 \geq 50\%$ and/or $P < 0.05$ were considered heterogeneously-distributed. Homogenously-distributed data were analyzed using the fixed-effect measure, whereas heterogeneously-distributed data were analyzed using the random-effect measure. P value of < 0.05 was determined as determinant to statistical significance.

RESULT AND DISCUSSION

Result

Four randomized studies were included after thorough searching and selection (Figure 1). All studies were considered good after critical appraisal with low risk of bias (Figure 2). Studies were conducted among Asian and American populations with total sample size of 420 subjects. Most of subjects were women. Three studies reported studies among adults, whereas one study by Laffel et al reported intervention results among adolescents. No baseline differences between groups were noted among all studies (Table 1).

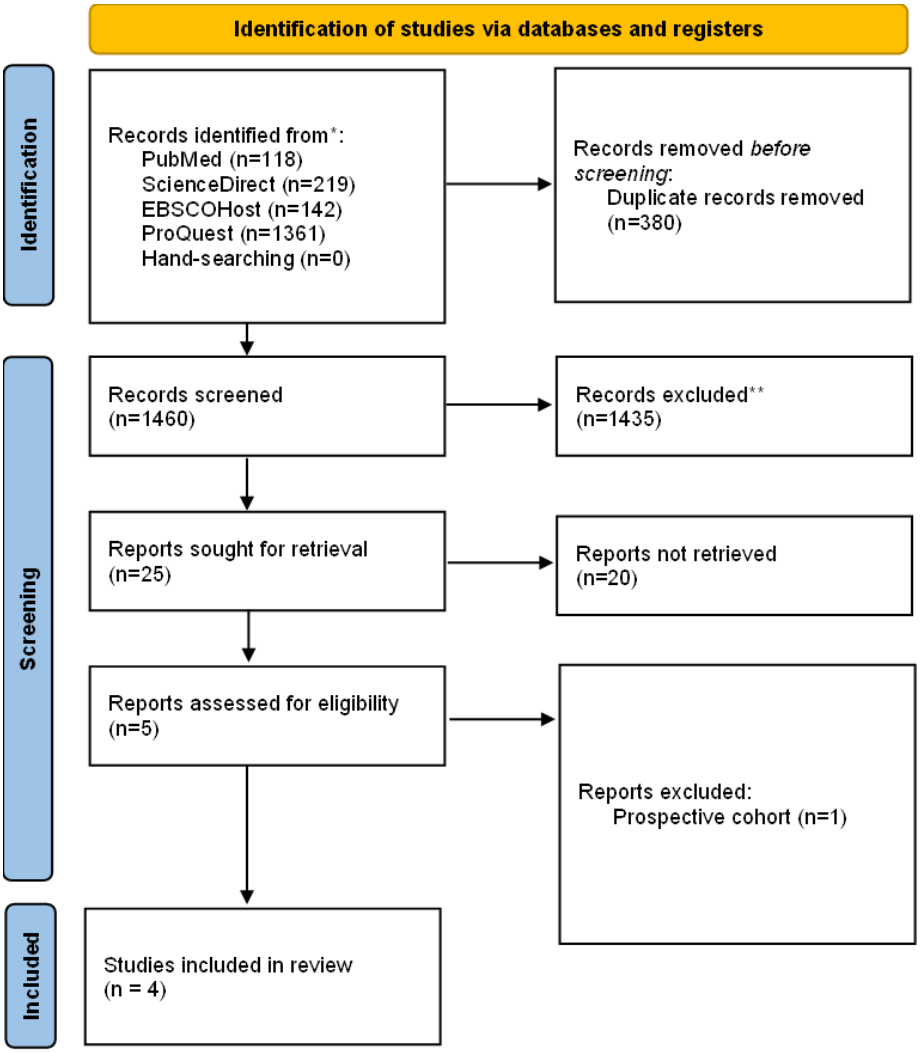

Figure 1. Searching flow of included studies.

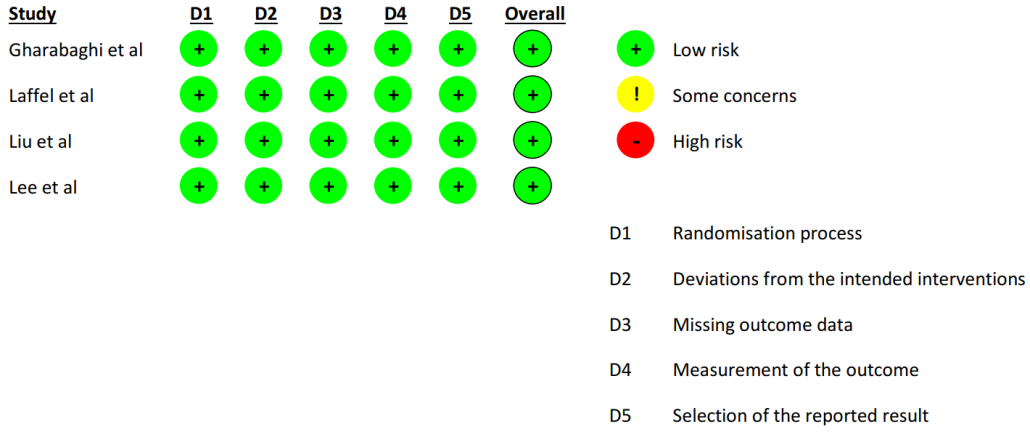

Figure 2. Risk of bias appraisal results.

Table 1. Baseline characteristics of each included studies.

First author	Publication year	Place of study	Study design	Follow up (weeks)	Regiments	Subject size	Male (%)	Age (years)
Gharabaghi et al[9]	2022	Iran	RCT	12	I: Linagliptin 5 mg OD II: Empaglifozin 10 mg OD	I: 30 II: 30	I: 30 II: 30	I: 56.8 (8.2) II: 60.9 (7.2)
Laffel et al[10]	2023	Multinational (America)	RCT	52	I: Linagliptin 5 mg OD II: Empaglifozin 10 mg OD III: Placebo	I: 52 II: 52 III: 53	I: 57.7 II: 63.5 III: 64.2	I: 14.5 (10-17) II: 13 (10-17) III: 14 (11-17)
Zeng et al[11]	2022	Taiwan	ROLT	24	I: Linagliptin 5 mg OD II: Empaglifozin 25 mg OD	I: 51 II: 46	I: 27.5 II: 50	I: 58.7 (10.2) II: 58.9 (9.9)
Liu et al[12]	2021	Taiwan	ROLT	24	I: Linagliptin 5 mg OD II: Empaglifozin 25 mg OD	I: 53 II: 53	I: 28.3 II: 49.1	I: 59.1 (10.2) II: 58 (10.4)

Abbreviations: RCT = Randomized-controlled study; ROLT = Randomized, open-label study; OD = Once daily

Analysis found that there was significantly greated HbA1c reduction among patients receiving empagliflozin (MD = 0.71%; 95% CI = 0.43–0.99%). In addition, similar finding was found among reduction of fasting blood glucose, as empagliflozin showed better reduction compared to linagliptin (MD = 47.61 mg/dl; 95% CI = 25.57–69.65 mg/dl). In accordance to the safety profile, there was no significant difference of hypoglycemia nor urinary tract infection between linagliptin and empagliflozin with odds ratio (OR) of 0.73 (95% CI = 0.38–1.38) and 0.68 (95% CI = 0.37–1.25), respectively (Figure 3). There was no case of diabetic ketoacidosis among two studies using linagliptin, even though there was a case in empagliflozin arm found among two studies, deemed insignificant for analysis.

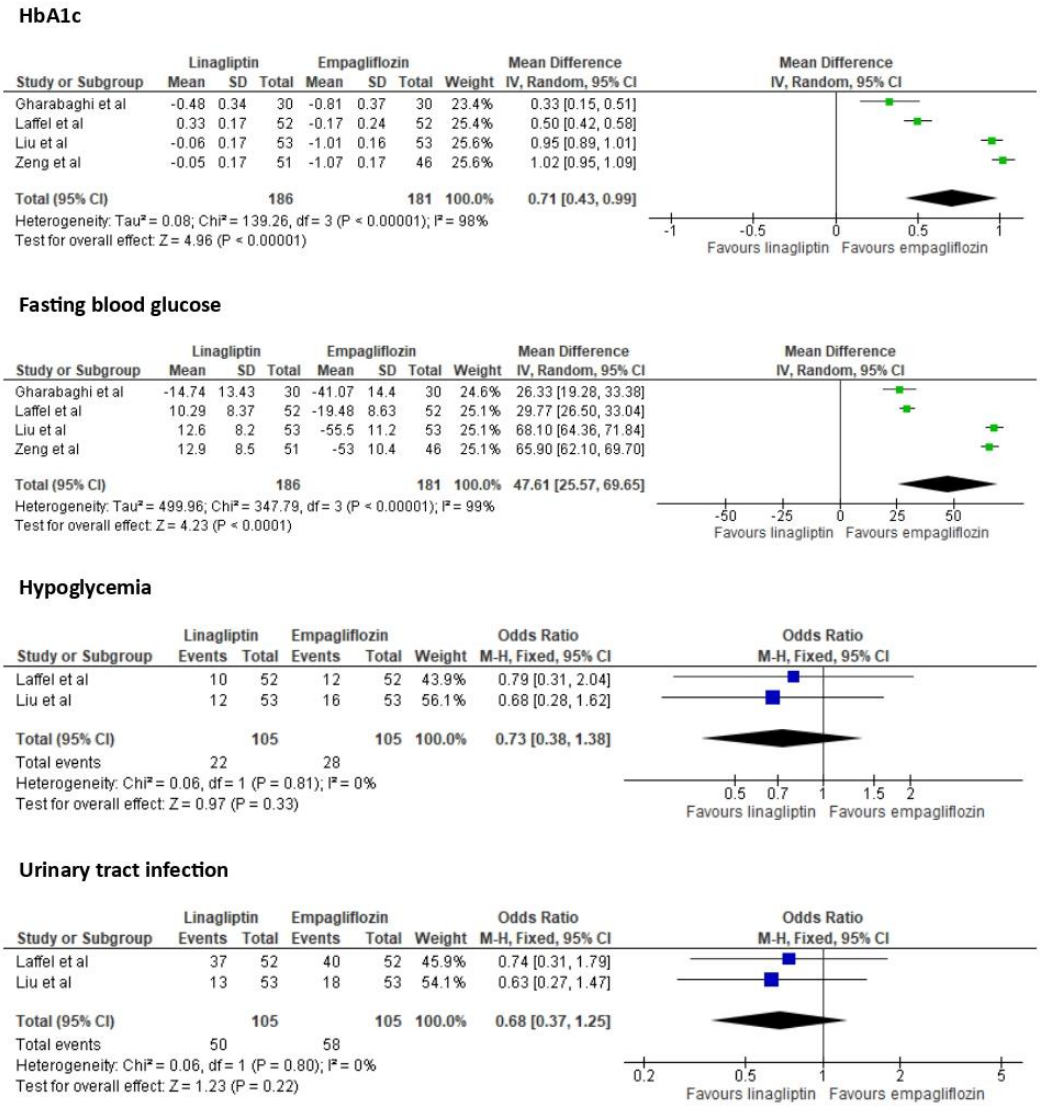

Figure 3. Analysis of included studies' outcome.

Discussion

This study indicated that empagliflozin was associated with significantly greater reductions in both HbA1c and fasting blood glucose compared to linagliptin, both of which reflect its potent glycaemic-lowering effects. These findings are consistent with previous studies that highlight the robust efficacy of SGLT2 inhibitors, such as empagliflozin, in reducing blood glucose levels and improving long-term glycaemic control, which benefited T2DM patients.[9,10] The ability of empagliflozin to reduce blood glucose through renal glucose excretion offers a complementary mechanism to the insulin-based therapies typically used in T2DM, further enhancing its therapeutic value.[4,11]

[9] Wanner, C., Inzucchi, S. E., Lachin, J. M., Fitchett, D., von Eynatten, M., Mattheus, M., et al. (2016). Empagliflozin and progression of kidney disease in type 2 diabetes. *The New England Journal of Medicine, 375*(4), 323–334.

[10] Zinman, B., Wanner, C., Lachin, J. M., Fitchett, D., Bluhmki, E., Hantel, S., et al. (2015). Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *The New England Journal of Medicine, 373*(22), 2117–2128.

[11] Rascher, J., Cotton, D., Haertter, S., & Brueckmann, M. (2024). Clinical pharmacokinetics and pharmacodynamics of empagliflozin in patients with heart failure. *British Journal of Clinical Pharmacology, 90*(9), 2215–2222.

In contrast, linagliptin, a DPP-4 inhibitor, demonstrated less potent reductions in both HbA1c and fasting blood glucose. While linagliptin effectively increases insulin secretion and decreases glucagon levels in a glucose-dependent manner, its impact on HbA1c is typically less pronounced compared to SGLT2 inhibitors.[12,13] Linagliptin's milder effect on glycaemic control may be attributable to its mechanism, which enhances insulin secretion only in response to elevated blood glucose levels, limiting its ability to achieve as significant a reduction in HbA1c as empagliflozin.[5,14]

Empagliflozin also provided better renal outcome. A study by Lee et al suggested that there was less acute kidney injury occurred among empagliflozin arm when compared to linagliptin arm. T2DM patients underwent empagliflozin has 40% less risk of developing acute kidney injury. In addition, T2DM patients aged more than 65 years who took empagliflozin demonstrated more renal benefits and less risk of acute kidney injury, with a significantly smaller reduction of filtration rate observed on empagliflozin arm.[15]

In terms of safety, both drugs were similarly well-tolerated, with no significant differences in the incidence of hypoglycaemia or urinary tract infections. Empagliflozin has been proven as a safe approach towards T2DM through previous studies, as reciprocated in this study.[16,17] Importantly, neither drug led to a significant increase in the incidence of hypoglycemia, an advantage given the risk of low blood sugar with other anti-diabetic agents. However, urinary tract infections, though a known side effect of SGLT2 inhibitors, did not differ significantly between empagliflozin and linagliptin, indicating that the risk of UTIs might not be substantially greater with empagliflozin in this population.

A notable finding in this study was the occurrence of diabetic ketoacidosis (DKA) in one patient treated with empagliflozin, though this was deemed insignificant for analysis due to the small number of cases. DKA is a well-documented, albeit rare, side effect of SGLT2 inhibitors.[18] The absence of DKA in the linagliptin group suggests that DPP-4 inhibitors do not carry the same risk. Nevertheless, the overall incidence of DKA remains low in clinical practice, and patients receiving SGLT2 inhibitors should be monitored appropriately for signs of this condition.

This study was the first to directly compare efficacy and safety of linagliptin and empagliflozin using data from randomized trials, which improve the strength and quality of findings to be applied in clinical practice. However, small subject size gathered and less representations from other continents than Asia and America made study's applicability

[12] Scheen, A. J. (2012). DPP-4 inhibitors in the management of type 2 diabetes: A critical review of head-to-head trials. *Diabetes & Metabolism*, *38*(2), 89–101.

[13] Gallwitz, B. (2013). Emerging DPP-4 inhibitors: Focus on linagliptin for type 2 diabetes. *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy*, *6*, 1–9.

[14] Graefe-Mody, U., Retlich, S., & Friedrich, C. (2012). Clinical pharmacokinetics and pharmacodynamics of linagliptin. *Clinical Pharmacokinetics*, *51*(7), 411–427.

[15] Lee, Y. T., Hsu, C. N., Fu, C. M., Wang, S. W., Huang, C. C., & Li, L. C. (2021). Comparison of adverse kidney outcomes with empagliflozin and linagliptin use in patients with type 2 diabetic patients in a real-world setting. *Frontiers in Pharmacology*, *12*, 781379.

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limited and need to be confirmed. Therefore, more high-quality studies should be conducted to improve the strength of findings on this study, hence more applicable and relevant

CONCLUSION

Empagliflozin provided better glycemic control compared to linagliptin among patients with T2DM with decent safety profile, thus could be considered to be used in daily clinical practice.

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