Original Article

Efficacy and Safety of Empagliflozin versus Linagliptin as Add on Therapy to Insulin in Patients of Chronic Kidney Disease and Type 2 Diabetes Mellitus: A Randomised Controlled Trial

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ABSTRACT

Introduction: Patients with an eGFR of less than 60 ml/min have a limited selection of medication alternatives for glycaemic management. Most oral anti-diabetic medications are either not recommended or require dose decrease to prevent kidney damage, which would reduce their effectiveness and result in poor glycaemic control. Finding a medication that is quick acting, safe, and successful in attaining correct glycaemic control and so postponing the beginning and progression of CKD is crucial.

Aims/ objective: To compare the efficacy and safety of empagliflozin and linagliptin as add-on therapies to insulin in patients with Type 2 Diabetes Mellitus (T2DM) and chronic kidney disease.

Materials and Method: Following screening and application of the inclusion and exclusion criteria, 120 patients were randomly assigned, with 60 patients in each group using web-generated random numbers. Patients in the empagliflozin group received 10 mg of empagliflozin once daily in addition to their regular insulin medication, while those in the linagliptin group received 5 mg of linagliptin once daily. HbA1c, fasting blood sugar, eGFR, urine protein-creatinine ratio (UPCR) was recorded at baseline, 3 months, 6 months and 12 months of follow-up and compared between two groups.

Results: At 6 month and 12 months of follow up, HbA1c was lower in patients receiving empagliflozin than patients receiving linagliptin with statistically significant difference ($p<0.05$). Both the groups showed significant decline in mean HbA1c from baseline and end of the study ($p<0.05$). There was no statistically significant decline in eGFR in patients receiving linagliptin or empagliflozin ($p>0.05$). The decline in UPCR was better in patients receiving empagliflozin than patients receiving linagliptin with statistically significant difference ($p<0.05$). Gastrointestinal adverse effects were limiting adverse events in linagliptin pharmacotherapy whereas hypoglycaemia and urinary tract infection were frequent adverse effect associated with empagliflozin.

Conclusion: Empagliflozin has been demonstrated to be more efficacious than linagliptin when added to background insulin treatment. By reducing the amount of insulin needed to achieve the ideal blood glucose level, oral hypoglycaemic medications might reduce the risk of hypoglycaemia and weight gain associated with insulin therapy.

Keywords: Linagliptin, Empagliflozin, Diabetes Mellitus, Chronic Kidney Disease, HbA1c, Albuminuria.

INTRODUCTION

One of the main causes of chronic kidney disease (CKD) worldwide is diabetic kidney disease (DKD).[1] Albuminuria and a lower eGFR are frequent findings in DKD and have a significant role in the pathogenesis of end-stage kidney disease (ESKD), cardiovascular problems, and mortality.[2] In a small number of patients with type 2 diabetes mellitus (T2DM), there have also been reports of limited or no albuminuria linked with decreased eGFR, as well as further reports of microvascular and macrovascular problems connected to type 2 diabetes mellitus in these patients. [3, 4] The histological results of kidney biopsy reports varied, and some of the results were consistent with the non-diabetic pathophysiology of CKD. [5]

In order to accomplish a goal HbA1c level of 6.5 to 8.0% in patients of non-dialysis dependent CKD, medication should be scheduled, according to the diabetic work group of KDIGO (Kidney Disease: Improving Global Outcomes).[6] The American Diabetes Association (ADA) has recommended an ideal level of less than 7.0% for the majority of diabetic patients with little to no risk or complication and no more than 8.0% for patients with a shorter life expectancy or with a greater likelihood of complications, but has not provided specific HbA1c targets for patients with type 2 diabetes mellitus and chronic kidney disease.[7]

Patients with an eGFR of less than 60 ml/min have a limited selection of medication alternatives for glycaemic management. The majority of oral anti-diabetic medications are either not recommended or require dose decrease to prevent kidney damage, which would reduce their effectiveness and result in poor glycaemic control. [8] For glycaemic control in chronic kidney disease, insulin treatment is the safest and most effective option. The most frequent adverse drug reaction (ADR) connected to insulin therapy is hypoglycaemia, which can be fatal if not treated.[9]

Weight gain, which can increase morbidities in obese and elderly diabetic patients, is another typical adverse medication reaction linked to insulin therapy. There have also been some reports of electrolyte abnormalities such as hypokalaemia, and in the majority of these cases, other medicines that also cause hypokalaemia were used concurrently. Some adverse drug reactions (ADRs) are related to the subcutaneous mode of administration, including injection site discomfort and lipodystrophy at the injection site, which are frequently connected to routine subcutaneous injections.[10] Another issue with administering insulin subcutaneously is inadequate compliance and peripheral hyperinsulinemia. Poor compliance might cause patients to stop taking their insulin prescription and have poor glycaemic control.

According to the most recent scientific research, linagliptin is safe to utilise and well tolerated in patients with moderate, severe, and mild CKD as well as those receiving dialysis.[11-14] According to recent scientific literature, linagliptin not only lowers blood sugar levels but also has a positive impact on albuminuria. It is thought that this action is a result of linagliptin ability to inhibit myofibroblast transformation, hinder podocyte destruction, and decrease kidney inflammation as a result of decreased levels of glucagon-like peptide-1 (GLP-1).[15] Blood glucose levels affect how much postprandial insulin is released and how much is inhibited. [16,17] So there is a low likelihood of hypoglycaemia. 16 According to the results of numerous investigations, linagliptin is also weight neutral.16

Because SGLT2 is expressed more frequently in type 2 diabetes patients, the kidneys may reabsorb glucose from the bloodstream more readily.[18] A high potency selective SGLT2 inhibitor called empagliflozin has been authorised for use in the treatment of type 2 diabetes mellitus.[19] It lowers the rate of reabsorption of glucose that has been filtered, which results in increased urine glucose excretion, a drop in fasting and postprandial blood glucose levels, and a decreased risk of hypoglycemia.[20-22]

Empagliflozin pharmacotherapy also causes weight loss and a drop in blood pressure; it is hypothesised that these outcomes are brought about by the loss of carbohydrates from urine and osmotic diuresis.[18,21,22] The EMPA-REG renal outcome trial demonstrated a 46 percent reduction in the relative probability of the incidence of the composite of poor renal outcomes. 23 The trial's findings showed empagliflozin to have a lower incidence of serious adverse renal events than placebo in individuals with type 2 diabetes mellitus who are also at higher risk for cardiovascular problems and for delaying the advancement of CKD. [23]

Finding a medication that is quick acting and successful in attaining correct glycaemic control and so postponing the beginning and progression of CKD is crucial.[24,25] The current research was designed to compare the efficacy and safety of empagliflozin and linagliptin as add-on therapies to insulin in patients with Type 2 Diabetes Mellitus (T2DM) and chronic kidney disease, keeping in mind the results of previous studies and strengthening the evidence for their use in higher grades of chronic kidney disease. In the group receiving empagliflozin plus linagliptin, the major goal was to measure and compare improvements in HbA1c from the start of treatment to one year later. Secondary goals included measuring changes in eGFR, albuminuria, the incidence of hypoglycaemia, and other adverse events.

MATERIALS AND METHODS

The study was open label randomized controlled trial with 1:1 parallel allocation in tertiary care hospital of India. The International Conference on Harmonization's (ICH-GCP) good clinical practise criteria were followed when this study was launched, along with institutional ethics committee permission. Participant Information sheet was provided and explained to the patients fulfilling eligibility criteria and written informed consent was taken. The trial ran from October 2021 to September 2022 for 12 months.

Inclusion Criteria:

- Patients with diagnosis of type 2 diabetes mellitus of age greater than 18 years of either sex [26]
- Patients with diagnosis of chronic kidney disease [27]
- Patients with HbA1c of 7.5-10.0 %
- Patients with eGFR less than 60 ml/min per 1.73 m^2
- Patients on any insulin regimen as per target to attain proper glycaemic control

Exclusion Criteria:

- Patients with eGFR less than 15 ml/min per 1.73 m^2
- Patients with history of renal transplant
- Patients with requirement of dialysis
- Patients with diagnosis of urinary tract or any other systemic infections
- Patients with debilitating illness that may adversely affect renal function
- Patients with BMI less than 18.5 kg/m^2

Based on the serum creatinine values, we calculated eGFR using the algorithm below. The value calculated using this formula was multiplied by 0.85 for female patients:

eGFR = (140 − age) x Weight (kg)/ Serum Creatinine (mg/dl) x 72

With an expected HbA1c decrease of 1.9% ± 0.3% in patients receiving empagliflozin and 1.7% in patients receiving linagliptin, the lowest sample size required with 90% power and an alpha value of 0.05 was calculated to be 94. As a result, 120 patients were included in the study while accounting for a 20% potential dropout rate.

Following screening and application of the inclusion and exclusion criteria, 120 patients were randomly assigned, with 60 patients in each group using web-generated

random numbers. Patients in the empagliflozin group received 10 mg of empagliflozin once daily in addition to their regular insulin medication, while those in the linagliptin group received 5 mg of linagliptin once daily.

Primary outcome measure: Mean change in HbA1c from baseline to each follow-up.

Secondary outcome measure: Mean change in fasting blood sugar (FBS) from baseline to each follow-up, Mean change in eGFR (estimated by the Cockcroft-Gault formula) from baseline to each follow-up, Mean change in Urine Protein-Creatinine ratio (UPCR) from baseline to each follow-up, Incidence of hypoglycaemia and other adverse events during the study period.

Patients' prescriptions, laboratory test results, and interviews were obtained to gather information on the primary and secondary outcome measures at baseline, three months, six months, and twelve months of follow-up.

Statistical analysis

Data obtained from the patients at baseline and each follow-up visits were presented in tabular form and analysed using Microsoft Excel 365. Unpaired t-test was used to determine statistical significance of difference between two groups with respect to continuous variables like age, duration of diabetes, HbA1c, FBS, eGFR and UPCR which were expressed as mean ± SD (standard deviation). Determination of statistical significance of difference within group at different follow-up was done using repeated measure ANOVA. Chi-square test was used to determine statistical significance of difference between two groups with respect to categorical variables like gender, concurrent medication and incidence of adverse drug events. P-value less than 0.05 was taken as measure of statistical significance.

RESULTS

60 patients were enrolled in each group. After enrolment, 6 patients in linagliptin group and 9 patients in empagliflozin group were lost to follow up.

There was no statistically significant difference between two groups with respect to age, gender, duration of diabetes, and background anti-hypertensive medications ($p>0.05$). So, both groups were similar with respect to baseline demographic and clinical characteristics. [Table 1]

Table 1: Comparison of baseline demographic and clinical characteristics between two groups

Variables	Linagliptin Group (n = 54)	Empagliflozin Group (n = 51)	P-Value
Age in years (Mean ± SD)	64.41 ± 8.56	62.69 ± 8.63	0.31 (Unpaired t test)
Gender			
Male	24	25	
Female	30	26	
Duration of Diabetes in Years (Mean ± SD)	14.18 ± 4.94	13.65 ± 6.03	0.63
Taking anti-hypertensive drugs			
ACE inhibitors or ARB	41	40	
Beta blockers	19	19	
Loop diuretics	2	3	
Thiazide diuretics	14	16	
Calcium channel blockers	18	16	

Table 2: Comparison of Mean HbA1c at Different Follow-up between Two Groups

Time	Mean HbA1c (%) in Linagliptin Group ± SD	Mean HbA1c (%) in Empagliflozin Group ± SD	P-Value (Unpaired t-test)
Baseline	8.53 ± 1.23	8.56 ± 1.31	0.90
3 Months	8.01 ± 1.42	7.72 ± 1.32	0.28
6 Months	7.82 ± 1.18	7.38 ± 1.11	**0.05**
12 Months	7.51 ± 0.91	7.14 ± 0.95	**0.04**
P-Value (ANOVA)	<0.0001	<0.0001	

There was no statistically significant difference between two groups with respect to HbA1c at baseline and 3 months of follow-up. At 6 month and 12 months of follow up, HbA1c was lower in patients receiving empagliflozin than patients receiving linagliptin with statistically significant difference ($p<0.05$). Both the groups showed significant decline in mean HbA1c from baseline and end of the study ($p<0.05$). [Table 2] [Figure 1]

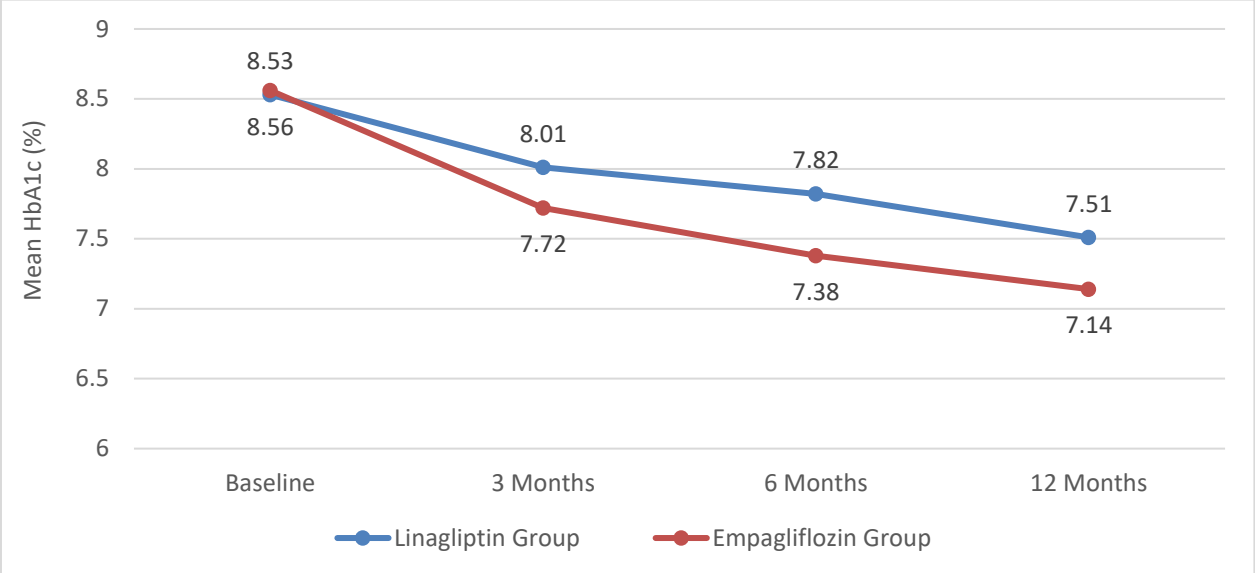

Figure 1: Comparison of Mean HbA1c between Two Groups

Table 3: Comparison of Mean Fasting Blood Sugar at Different Follow-up between Two Groups

Time	Mean FBS (mg/dl) in Linagliptin Group ± SD	Mean FBS (mg/dl) in Empagliflozin Group ± SD	P-Value (Unpaired t-test)
Baseline	181.36 ± 51.44	185.24 ± 53.56	0.71
3 Months	161.65 ± 48.54	148.36 ± 41.36	0.14
6 Months	151.73 ± 45.69	132.41 ± 39.81	**0.02**
12 Months	141.33 ± 33.68	125.28 ± 26.74	**0.01**
P-Value (ANOVA)	<0.0001	<0.0001	

There was no statistically significant difference between two groups with respect to FBS at baseline and 3 months of follow-up. At 6 month and 12 months of follow up, FBS was lower in patients receiving empagliflozin than patients receiving linagliptin with statistically significant difference ($p<0.05$). Both the groups showed significant decline in mean FBS from baseline and end of the study ($p<0.05$). [Table 3]

Table 4: Comparison of Mean eGFR at Different Follow-up between Two Groups

Time	Mean eGFR (ml/min) in Linagliptin Group ± SD	Mean eGFR (ml/min) in Empagliflozin Group ± SD	P-Value (Unpaired t-test)
Baseline	41.85 ± 12.33	42.43 ± 13.68	0.82
3 Months	40.34 ± 12.13	39.86 ± 12.54	0.84
6 Months	40.16 ± 11.87	37.47 ± 12.11	0.26
12 Months	39.78 ± 10.76	38.08 ± 11.67	0.44
P-Value (ANOVA)	0.10	0.12	

There was no statistically significant decline in eGFR in patients receiving linagliptin or empagliflozin ($p>0.05$). There was no statistically significant difference between two groups with respect to eGFR at baseline, 3 month, 6 month and 12 month of follow-up ($p>0.05$). [Table 4]

Table 5: Comparison of Mean Urine Protein-Creatinine Ratio (UPCR) at Different Follow-up between Two Groups

Time	Mean UPCR (mg/mg) in Linagliptin Group ± SD	Mean UPCR (mg/mg) in Empagliflozin Group ± SD	P-Value (Unpaired t-test)
Baseline	1.11 ± 0.21	1.08 ± 0.19	0.44
3 Months	0.96 ± 0.19	0.92 ± 0.20	0.30
6 Months	0.91 ± 0.17	0.83 ± 0.15	**0.01**
12 Months	0.85 ± 0.17	0.77 ± 0.13	**0.01**
P-Value (ANOVA)	<0.0001	<0.0001	

There was statistically significant improvement in both the groups with respect to decline in UPCR (P<0.05). The decline in UPCR was better in patients receiving empagliflozin than patients receiving linagliptin with statistically significant difference (p<0.05).

Table 6: Comparison of incidence of adverse drug events between two groups

Adverse Events	**Linagliptin Group (n = 54)**		**Empagliflozin Group (n = 51)**	
	Number of adverse events	**% of adverse events**	**Number of adverse events**	**% of adverse events**
Nausea	26	48.15	11	21.57
Hypoglycaemia	17	31.48	22	43.14
Respiratory Tract Infection	12	22.22	3	5.88
Abdominal pain	10	18.52	4	7.84
Weight gain	9	16.67	1	1.96
Urinary Tract Infection	7	12.96	30	58.82
Diarrhoea	6	11.11	0	0.00
Hypokalaemia	2	3.70	4	7.84

Incidence of gastrointestinal adverse effects such as nausea, abdominal pain and diarrhoea was greater in patients receiving linagliptin. However, incidence of urinary tract infection and hypoglycaemia was greater in patients receiving empagliflozin. There was greater incidence of respiratory tract infections in patients receiving linagliptin.

DISCUSSION

In this open-label, randomized controlled trial, we have compared the efficacy and safety of empagliflozin versus linagliptin as on to existing insulin regimen in patients of chronic kidney disease and type 2 diabetes mellitus. We found that empagliflozin was more efficient than linagliptin in reducing HbA1c, FBS, and albuminuria without causing the occurrence of any significant drug-related adverse events in the long-term follow-up period of one year. This result is remarkably comparable to the results of previous researches. However, there was no discernible difference in the eGFR change.

The decline in GFR was significantly lower in patients who received empagliflozin in comparison to patients who received linagliptin in a trial by Lee et al. that assessed and compared adverse events associated with renal functions in patients with type 2 diabetes being given either empagliflozin or linagliptin.[28] Additionally, they noted that patients who received empagliflozin experienced a lower risk of acute kidney damage (AKI) than those who received linagliptin.[28] From these results, we can infer that empagliflozin medication may be more effective than linagliptin therapy in arresting the advancement of diabetic nephropathy. Therefore, using empagliflozin in a real-world setting can support the results of the trials.

The effectiveness of linagliptin in reducing albuminuria has been compared with placebo in patients with type 2 diabetes over a 6-month period in a randomised controlled trial (MARLINA) carried out by Groop et al., but there was no statistically significant difference between two group with respect to reduction of albuminuria.[29] But linagliptin has been shown to be superior to placebo in decreasing albuminuria in a different randomised controlled trial (CARMELINA) with a 2 year study period.[30] Different trials have demonstrated the long-term usefulness of linagliptin in slowing the course of albuminuria, however there is debate over how well it works in short term reduction of albuminuria.[31,32]

In a retrospective review of four randomised controlled trials, it was discovered that linagliptin significantly decreased albuminuria over the course of the 2-year research period. [15] It was discovered that there was no statistically significant difference between the patients on empagliflozin and patients on linagliptin with regard to the decrease in albuminuria after 40 weeks of therapy in a randomised controlled trial carried out by Han et al. on patients with eGFR between 15 and 59 ml/min.[33]

In addition to the EMPA-REG trial and a cohort analysis with 379,033 patients, where empagliflozin's effectiveness was proven in reversing the loss of eGFR and reducing the risk of serious adverse renal events, further studies have been carried out to determine its efficacy in reducing albuminuria.[34,35] A reduction in albuminuria as evaluated by the UACR (urine albumin-creatinine ratio) was noted in a study by Cherney et al. that showed the effectiveness of empagliflozin in reducing albuminuria throughout a study period of 1.5 years, which is comparable to our study's findings.[36] In addition, a post hoc analysis of the EMPA-REG OUTCOME trial found a persistent decrease in UACR during the course of the trial's 3 year research period.[37]

In the EMPA-REG study, where early thirty percent decreases in UACR led to fewer instances of adverse cardiovascular events, an association between low albuminuria and lower risk of bad cardiovascular outcome was discovered.[38] Therefore, the primary goal of therapy should be to minimise albuminuria as soon as possible. In addition to helping patients' hemodynamic conditions,

SGLT-2 inhibitors can have histopathologic effects that may reduce albuminuria. When empagliflozin was administered to diabetic mice in an experiment by Klimontov et al., there was a reduction in renal hypertrophy, thickness of the basement membrane, mesangial enlargement, and podocytopathy of the glomerulus. They discovered a decline in UACR as well.[39] These results can help to explain why empagliflozin is effective in treating diabetic nephropathy.

Patients with proteinuria less than 1 g/g spent less time in grade 3-5 CKD than patients with proteinuria larger than or equal to 1 g/g, according to a research by Ku E. et al. [40]

Our study also has certain limitations. Since patients were sourced from an outdoor facility, we were unable to fully guarantee their adherence to medication. It was not investigated whether patients might be taking medicines that interact with other drug classes. Studies with a larger sample size should be conducted in order to strengthen the evidence for the efficacy and safety of empagliflozin in patients with CKD and T2DM.

CONCLUSION

Empagliflozin has been demonstrated to be more efficacious than linagliptin when added to background insulin treatment. However, both drugs were effective in reducing HbA1c and albuminuria. Gastrointestinal adverse effects were limiting adverse events in linagliptin pharmacotherapy whereas hypoglycaemia and urinary tract infection were frequent adverse effect associated with empagliflozin. By reducing the amount of insulin needed to achieve the ideal blood glucose level, oral hypoglycaemic medications might reduce the risk of hypoglycaemia and weight gain associated with insulin therapy. Improved glycaemic management can slow the progression of albuminuria and chronic renal disease.

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