Original Article

Comparative Study of Efficacy and Safety of Empagliflozin vs Linagliptin as Add on Therapy to Insulin in Patients of Type 2 Diabetes Mellitus and Chronic Kidney Disease in Tertiary Care Centre of Eastern India.

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ABSTRACT

Introduction: It is essential to find a pharmacotherapy that is fast acting and effective in achieving proper glycaemic control and thus delaying the onset and progression of chronic kidney disease. The options of drugs for glycaemic control in patients with eGFR<60 ml/min is limited and insulin therapy has low compliance as limiting factor. Empagliflozin decreases the reabsorption of filtered glucose leading to high excretion of urinary glucose and decrease in fasting and postprandial blood glucose level with a reduced risk of hypoglycaemia.

Aims/ objective: To compare the efficacy and safety of empagliflozin and linagliptin as add on therapy to insulin in patients of T2DM and CKD. The primary objective was to assess and compare change in HbA1c from baseline to 1 year in empagliflozin and linagliptin group while secondary objectives were to assess changes in eGFR, albuminuria and incidence of hypoglycaemia and other adverse event after therapy.

Materials and Method: Prescriptions, laboratory reports and interview were taken from patients at baseline, 3 months, 6 months, and 12 months of follow-up to collect data regarding primary outcome measure that was HbA1c and secondary outcome measures that were Fasting blood sugar (FBS), eGFR, Urine Protein-Creatinine ratio (UPCR), Hypoglycaemia and other adverse events. Comparison between two group was done using unpaired t test and comparison with group at different follow-up was done using repeated measure ANOVA.

Results: Both the groups showed significant decline in HbA1c values from baseline to end of trial. At 6 months and 12 months of follow-up, glycaemic control as HbA1c values was significantly better in empagliflozin group ($p<0.05$). As per FBS values, glycaemic control was better achieved with addition of empagliflozin to previous insulin therapy. At 6 month and end of trial, addition of empagliflozin to previous insulin therapy had significantly better control on albuminuria as per mean UPCR values ($p<0.05$).

Conclusion: Addition to empagliflozin to background insulin therapy was found more effective than addition of linagliptin. Better glycaemic control can help in halting the progression of chronic kidney disease and albuminuria.

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

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INTRODUCTION

Diabetic kidney disease (DKD) is one of the leading contributor of chronic kidney disease (CKD) globally.[1] Albuminuria and decreased estimated glomerular filtration rate (eGFR) are common findings in DKD and they have major role in pathophysiology of end-stage kidney disease (ESKD), cardiovascular complications, and death.[2] [3] There is also reports of minimal or no albuminuria associated with decreased eGFR in few patients of type 2 diabetes mellitus (T2DM) in whom there was also further reports of microvascular and macrovascular complications related to type 2 diabetes mellitus.[4] There was also findings of variation in histopathological findings in kidney biopsy reports and some of the findings had similarities with non-diabetic pathophysiology of CKD. [5]

The diabetes work group of KDIGO (Kidney Disease: Improving Global Outcomes) suggested that pharmacotherapy should be planned to achieve target HbA1c level of <6.5% to <8% in patients of non-dialysis-dependent CKD.[6] However, specific HbA1c goals was not suggested by the ADA (American Diabetes Association) for patients of type 2 diabetes mellitus and CKD but has suggested a target level of <7% for most of diabetic patients with minimal risk or complication and <8% for patients with a decreased life expectancy or with high risk of complications.[7]

The options of drugs for glycaemic control in patients with eGFR<60 ml/min is limited. Most of the oral anti-diabetic drugs are contraindicated or dose-reduction is mandatory to avoid renal damage leading to reduced efficacy and poor glycaemic control. [8] Insulin therapy is safest and most preferred for glycaemic control in CKD. The commonest adverse drug reaction (ADR) associated with insulin therapy is hypoglycaemia that can be life threatening if ignored.[9] The other common adverse drug reaction associated with insulin therapy is weight gain that can add to morbidities in obese and elderly diabetic patients. There are also some reports of electrolyte disturbances like hypokalaemia and in most cases, there was also concomitant use of other drugs causing hypokalaemia. Some ADRs are related to subcutaneous route of administration such as injection site pain and lipodystrophy at injection site commonly associated with daily subcutaneous injections.[10] Low compliance and peripheral hyperinsulinemia are other problems associated with subcutaneous route for insulin administration. Low compliance can lead to patient's non-adherence to insulin therapy and poor glycaemic control.

As per current scientific evidences, it is safe to use linagliptin is well tolerated in mild, moderate, and severe CKD and in patients undergoing dialysis. [11-14] In addition to blood glucose lowering effect, linagliptin also has albuminuria lowering effect and it is hypothesized that prevention of podocyte damage, improvement in inflammation of kidney due to reduced level of glucagon like peptide -1 (GLP-1) and inhibition of myofibroblast transformation by linagliptin has a role in this action as per current scientific literature.[15] Enhancement of release of postprandial insulin and inhibition of release of is dependent on blood glucose level. [16,17] Thus, chance of hypoglycaemia is low. [16] Linagliptin is also weight neutral as per findings of many studies.[16]

In patients of type 2 diabetes mellitus, the kidneys has increased capacity to reabsorb glucose due to increase in expression of SGLT2.[18] Empagliflozin is a selective inhibitor of SGLT2 with high potency approved for pharmacotherapy of type 2 diabetes mellitus.[19] It decreases the reabsorption of filtered glucose leading to high excretion of urinary glucose and decrease in fasting and postprandial blood glucose level with a reduced risk of hypoglycaemia.[20-22] Pharmacotherapy with empagliflozin also leads to weight loss and decrease in blood pressure and these effects are hypothesized to be due to loss of calories from urine and osmotic diuresis.[18,21,22] A decrease in 46% in relative risk of occurrence of the composite of adverse renal outcomes was reported in the EMPA-REG renal outcome trial. [23] The results of the trial confirmed that empagliflozin is effective in patients with type 2 diabetes mellitus and at increased risk of cardiovascular complications and in suspending the progression of CKD with low incidence of clinically significant adverse renal events in comparison to placebo. [23]

It is essential to find a pharmacotherapy that is fast acting and effective in achieving proper glycaemic control and thus delaying the onset and progression of CKD.[24,25] Keeping these findings of earlier researches in mind and to further strengthen the evidence for the use of empagliflozin or linagliptin in higher grades of CKD, this study was planned to compare the efficacy and safety of empagliflozin and linagliptin as add on therapy to insulin in patients of T2DM and CKD. The primary objective was to assess and compare change in HbA1c from baseline to 1 year in empagliflozin and linagliptin group while secondary objectives were to assess changes in eGFR, albuminuria and incidence of hypoglycaemia and other adverse event after therapy.

MATERIALS AND METHODS

This was an open label, single centred, randomised controlled trial with 1:1 allocation ratio. This study was started according to good clinical practice guidelines of International Conference on Harmonisation (ICH-GCP) after getting approval from institutional ethics committee and taking written informed consent from the patients. The duration of study was 1 year from October 2021 to September 2022.

Inclusion Criteria: Diagnosed case of T2DM of age greater than 18 years of either sex[26], diagnosed case of CKD[27], HbA1c of 7.5-10%, eGFR <60 ml/min per 1.73 m^2, Patients on any insulin regimen as per requirement to achieve their glycaemic control

Exclusion Criteria: eGFR <15 ml/min per 1.73 m^2, renal transplant, patients on dialysis, Patients having urinary tract or other systemic infections, haematuria, decompensated heart failure, liver failure, debilitating illness that may adversely affect renal function, BMI < 18.5 kg/m^2

We used following formula to calculate eGFR based on the serum creatinine levels. For female patients, value obtained using this formula was multiplied by a factor of 0.85:

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

With anticipated 1.9% ± 0.3 decrease in HbA1c in empagliflozin group and 1.7% decrease in linagliptin group, minimum sample size needed with 90% power and alpha value of 0.05 was found to be 94, so 120 patients were recruited in the study keeping in mind 20% possible attrition rate.

After screening and applying the inclusion and exclusion criteria, 120 patients were randomised using web generated random numbers to empagliflozin and linagliptin group with 60 patients in each group. Patients in empagliflozin were given empagliflozin 10 mg once daily in addition to background insulin therapy and patients in linagliptin group were given linagliptin 5 mg once daily in addition to background insulin therapy.

Primary outcome measure: HbA1c (Glycated Haemoglobin)

Secondary outcome measure: Fasting blood sugar (FBS), eGFR (estimated by the Cockcroft -Gault formula), Urine Protein-Creatinine ratio (UPCR), Hypoglycaemia and other adverse events.

Prescriptions, laboratory reports and interview were taken from patients at baseline, 3 months, 6 months and 12 months of follow-up to collect data regarding primary and secondary outcome measures.

Statistical analysis

Data obtained from the patients were presented in tabular form and analysed using Microsoft excel 365. Mean and standard deviation was calculated for continuous variables**.** Comparison between two group was done using unpaired t test and comparison with group at different follow-up was done using repeated measure ANOVA. Chi-square test was used to compare categorical data. P-value <0.05 was considered as measure of statistical significance.

RESULTS

60 patients were enrolled in each group. After enrolment, 5 patients in linagliptin group and 8 patients in empagliflozin group were lost to follow up.

Table 1: Comparison of baseline demographic and clinical characteristics

Parameters	Linagliptin Group (n=55)	Empagliflozin Group (n=52)	P- Value
Age in years (Mean ± SD)	63.32 ± 7.47	61.58 ± 7.52	0.2327 (Unpaired t-test)
Gender			
Male	26	24	0.9076 (Chi-square test)
Female	29	28	
Duration of diabetes in years (Mean ± SD)	13.67 ± 5.13	13.16 ± 5.69	0.6270 (Unpaired t-test)
Taking anti-hypertensive drugs			
ACE inhibitors or ARB	43	39	0.9381 (Chi-square test)
β-Blockers	18	20	
Loop diuretics	3	2	
Thiazide diuretics	13	15	
Calcium channel blockers	20	17	

Both groups were comparable according to various demographic and clinical parameters ($p < 0.05$). [Table 1]

Table 2: Comparison of mean HbA1c at each follow-up between two groups

Time	Mean HbA1c (%) in Linagliptin Group ± SD (n=55)	Mean HbA1c (%) in Empagliflozin Group ± SD (n=52)	P- Value (Un-paired t-test)
Baseline	8.42 ± 1.12	8.47 ± 1.23	0.8263
3 Months	7.95 ± 1.34	7.63 ± 1.41	0.2314
6 Months	7.73 ± 1.07	7.32 ± 1.04	**0.0472**
12 Months	7.42 ± 0.84	7.08 ± 0.89	**0.0446**
P-Value (ANOVA)	<0.0001	<0.0001	

There was not significant difference between two groups at baseline and 3 months of follow-up regarding HbA1c values ($p>0.05$). Both the groups showed significant decline in HbA1c values from baseline to end of trial. At 6 months and 12 months of follow-up, glycaemic control as HbA1c values was significantly better in empagliflozin group ($p<0.05$). [Table 2]

Table 3: Comparison of mean FBS at each follow-up between two groups

Time	Mean FBS (mg/dl) in Linagliptin Group ± SD (n=55)	Mean FBS (mg/dl) in Empagliflozin Group ± SD (n=52)	P- Value (Un-paired t-test)
Baseline	172.27 ± 47.33	176.13 ± 49.67	0.6814
3 Months	156.86 ± 51.12	135.49 ± 45.24	**0.0245**
6 Months	148.62 ± 46.47	131.38 ± 42.76	**0.0488**
12 Months	139.97 ± 32.57	123.19 ± 28.83	0.0058
P-Value (ANOVA)	<0.0001	<0.0001	

As per FBS values, glycaemic control was better achieved with addition of empagliflozin to previous insulin therapy.

Table 4: Comparison of mean eGFR at each follow-up between two groups

Time	Mean eGFR (ml/min) in Linagliptin Group ± SD (n=55)	Mean eGFR (ml/min) in Empagliflozin Group ± SD (n=52)	P- Value (Un-paired t-test)
Baseline	40.94 ± 11.42	41.32 ± 12.77	0.8713
3 Months	39.23 ± 11.22	38.97 ± 11.65	0.9066
6 Months	38.79 ± 10.98	36.58 ± 11.29	0.3071
12 Months	39.11 ± 9.89	37.17 ± 10.78	0.3339
P-Value (ANOVA)	0.095	0.122	

There was no significant difference between two groups regarding eGFR values. Decline in eGFR values from baseline to end of trial was not significant in both groups.

Table 5: Comparison of mean Urine Protein-Creatinine Ratio (UPCR) at each follow-up between two groups

Time	Mean UPCR (mg/mg) in Linagliptin Group ± SD (n=55)	Mean UPCR (mg/mg) in Empagliflozin Group ± SD (n=52)	P- Value (Un-paired t-test)
Baseline	1.07 ± 0.16	1.04 ± 0.15	0.3200
3 Months	0.92 ± 0.14	0.88 ± 0.16	0.1711
6 Months	0.87 ± 0.13	0.79 ± 0.11	**0.0009**
12 Months	0.81 ± 0.13	0.73 ± 0.09	**0.0004**
P-Value (ANOVA)	<0.0001	<0.0001	

Decline in mean UPCR was extremely significant in each group. At 6 month and end of trial, addition of empagliflozin to previous insulin therapy had significantly better control on albuminuria as per mean UPCR values ($p<0.05$).

Table 6: Frequency of adverse drug events in two groups

Adverse Events	Number of adverse events in Linagliptin Group (%) n=55	Number of adverse events in Empagliflozin Group (%) (n=52)
Hypoglycaemia	16 (29.09)	23 (44.23)
Weight gain	8 (14.55)	2 (3.85)
Nausea	27 (49.09)	10 (19.23)
Diarrhoea	7 (12.73)	0 (0)
Abdominal pain	11 (20)	3 (5.77)
Urinary tract infection	6 (10.91)	31 (59.62)
Respiratory tract infection	13 (23.64)	4 (7.69)
Hypokalaemia	2 (3.64)	5 (9.62)
Acute pancreatitis	1 (1.82)	0 (0)

Hypoglycaemia and urinary tract infection were more frequently reported in empagliflozin group. Gastrointestinal adverse events and respiratory tract infection were more frequently reported in linagliptin group. 1 case of acute pancreatitis was detected in linagliptin group while patients in empagliflozin group had no serious drug related adverse events.

DISCUSSION

In this open label, randomized clinical trial comparing the efficacy and safety of empagliflozin vs linagliptin as add-on to background insulin therapy in patients with T2DM and CKD, we found that empagliflozin was more effective with respect to reduction in HbA1c, FBS, and albuminuria without occurrence of any serious drug related adverse event in the long term follow up of 12 months which is very much similar to findings of earlier studies. Although, there was no significant difference with respect to change in eGFR. In a study conducted by Lee et al. in which adverse event related to renal functions was evaluated and compared in patients of T2DM receiving either empagliflozin or linagliptin, reduction in GFR was much less in patients who were given empagliflozin in comparison to patients who were given linagliptin.[28] They also reported

that there was decreased risk of acute kidney injury (AKI) in patients who were given empagliflozin as compared to patients who were given linagliptin.[28] From these findings, we can conclude that pharmacotherapy with empagliflozin might be better than linagliptin therapy in halting progression of diabetic nephropathy. So, utilization of empagliflozin in real-world situation can confirm the finding of trials.

In a randomised controlled trial (MARLINA) conducted by Groop et al. in which efficacy of linagliptin in lowering the albuminuria was compared with placebo in patients of T2DM in 6 months, there was no significant difference in reduction of albuminuria between two groups.[29] But, in another randomised controlled trial (CARMELINA) with 26 months study duration, linagliptin was found superior to placebo in lowering albuminuria.[30] Although, efficacy of linagliptin in halting the progression of albuminuria in long term is proved in different studies, there is controversy regarding its effectiveness in lowering albuminuria in short duration.[31,32] A retrospective analysis four randomised controlled trial was done in which it was found that linagliptin had significant effect in reduction of albuminuria in study period of 2 years.. [15] In a randomised trial conducted by Han et al. on patients of eGFR from 15 to 59 ml/min in which efficacy of empagliflozin was compared with linagliptin, it was found that there was no statistically significant difference between two group with respect to reduction in albuminuria after 40 weeks.[33]

Apart from EMPA-REG trial and a cohort study in 379,033 patients in which efficacy of empagliflozin in halting the decline of eGFR and lowering risk of major renal adverse events was confirmed, other studies have also been conducted to asses its effectiveness in lowering albuminuria.[34,35] In a study conducted by Cherney et al. in which efficacy of empagliflozin in lowering albuminuria in study period of 30 months, reduction of albuminuria measured by UACR (urine albumin-creatinine ratio) was reported in short duration of 3 months which is similar to finding of our study.[36] Apart from this, sustained lowering of UACR in study period of 36 months was reported in a post hoc analysis of the EMPA-REG OUTCOME trial.[37]

Association of low albuminuria with lower risk of adverse cardiovascular outcome was found in EMPA-REG trial where early 30% reduction in UACR lead to less outcome of adverse cardiovascular events.[38] So, treatment goal should be aimed to reduce albuminuria as early as possible. Apart from improvement in haemodynamic status of patients, SGLT-2 inhibitors also have histopathologic effects that could help in lowering albuminuria. In a study conducted by Klimontov et al. in which empagliflozin was given to diabetic mice, decrease in renal hypertrophy, thickening of basement membrane, mesangial expansion and podocytopathy of glomerulus was reported. They also found reduction in UACR.[39] These findings can explain the efficacy of empagliflozin in diabetic nephropathy

In a study conducted by ku E et al., It was found that patients with proteinuria <1 g/g spent lesser time in grade 3-5 CKD than patients with proteinuria ≥1 g/g. [40]

Our study had certain limitation also. Patients were recruited from outdoor unit hence we were unable to completely ensure compliance of patients to drugs. Drug interactions with other groups of drugs that patients might be taking was not evaluated. For strengthening evidences for efficacy and safety of empagliflozin, studies with more sample size should be performed.

CONCLUSION

Addition to empagliflozin to background insulin therapy was found more effective than addition of linagliptin. Addition of oral hypoglycaemic drugs can minimize the dose of insulin required to achieve optimum blood glucose level thus minimizing adverse effects of insulin therapy such as hypoglycaemia and weight gain. Better glycaemic control can help in halting the progression of chronic kidney disease and albuminuria.

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