Original Article

Comparison of Outcomes of Linagliptin Plus Insulin and Insulin Only Among Type II Diabetes Mellitus Patients with Chronic Kidney Disease

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ABSTRACT

Objective: To compare the outcomes of linagliptin plus insulin versus insulin alone among patients with type II diabetes mellitus with chronic kidney disease.

Study Design: Randomized clinical trial study

Place and Duration of Study: This study was conducted at the Department of Medicine, Fauji Foundation Hospital, Rawalpindi, Pakistan, from October 2025 to December 2025.

Methods: A total of 284 patients with type II diabetes mellitus and chronic kidney disease were included in the study and randomly allocated into two equal groups. Group A received linagliptin 5 mg once daily in addition to insulin therapy, while Group B received insulin therapy alone. Patients aged 18–75 years with eGFR between 15–45 ml/min and HbA1c >6.5% were enrolled. Baseline demographic and clinical parameters including age, gender, BMI, duration of diabetes, CKD grade, HbA1c, and urine protein-creatinine ratio (UPCR) were recorded. Patients were followed for three months and post-treatment HbA1c and UPCR were measured. Data were analyzed using SPSS version 25. Independent sample t-test was applied to compare outcomes between the groups, with $p \leq 0.05$ considered statistically significant.

Results: The mean age of the participants was 54.3 ± 10.7 years, with 158 (55.6%) males and 126 (44.4%) females. The mean BMI was 27.6 ± 4.2 kg/m². After three months of treatment, the mean HbA1c was significantly lower in the linagliptin plus insulin group (7.2 ± 0.6%) compared with the insulin-only group (7.6 ± 0.8%) ($p = 0.001$). Similarly, renal outcomes measured through urine protein-creatinine ratio improved in the combination therapy group (0.82 ± 0.14 mg/g) compared with the insulin-only group (0.91 ± 0.16 mg/g) ($p = 0.003$). Stratified analysis showed consistent improvement across different age groups and genders.

Conclusion: Linagliptin combined with insulin demonstrated significantly better glycaemic control and improvement in proteinuria compared with insulin monotherapy in patients with type II diabetes mellitus and chronic kidney disease.

Key Words: Type II diabetes mellitus, chronic kidney disease, linagliptin, insulin therapy, HbA1c, proteinuria

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INTRODUCTION

The type 2 diabetes mellitus (T2DM) is one of the most crucial health care issues of this modern era, and the number of affected people in the world is approximated to be 451 million in 2017, and it is predicted to reach 693 million cases by 2045[1]. Progressive dysfunction of the pancreatic beta-cell and insulin resistance characterise the disease, which requires pharmacological intensification as time passes[2]. About 40 percent of patients who have T2DM have chronic kidney disease (CKD), and in the global population, diabetes is the major cause of CKD and end-stage renal disease (ESRD)[1,3,4]. T2DM patients with CKD are at a significant risk of having cardiovascular events, mortality rates, and poor quality of life[5].

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a newer type of glucose-lowering agent which have become a clinical therapeutic option especially in renal-impaired patients[6,3]. Uniqueness of Linagliptin is that, unlike other DPP-4 inhibitors, it does not need an increase or decrease of the dose when patients have any level of renal impairment and thus it is particularly appropriate with CKD population[7,8]. The historic CARMELINA

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trial showed that to patients with T2DM at high cardiovascular and renal risk, the addition of linagliptin to usual care was cardiovascularly safe and significantly decreased albuminuria development, but made no hard difference to hard renal endpoints (5,9). A meta-analysis affirmed that the combination of DPP-4 inhibitors and insulin greatly minimized the levels of HbA1c and insulin dose demands without raising the rates of adverse events among T2DM and CKD patients[1].

Pakistan is disproportionately affected by T2DM and South Asians, including Pakistanis, have earlier onset of the disease, more glycaemic decline, and greater diabetic complications than western populations[10,11]. This notwithstanding, South Asians are still less represented in major clinical trials[10]. Insulin is still the most commonly used glucose-lowering agent in the progressive CKD in the low and middle-income countries like Pakistan because of financial limitations and the inaccessibility of other newer drugs[12], although monotherapy insulin has a high chance of causing hypoglycaemia in the CKD environment[13]. Linagliptin as a supplement to insulin has a potentially safer and more effective regimen[8,14]. There is currently no local evidence of linagliptin insulin co-therapy versus insulin therapy in Pakistani patients with T2DM and CKD, and hence the context-specific study is necessary to support clinical practice in such a high-risk group.

Therefore, the study was aimed to compare the efficacy of linagliptin combined with insulin and insulin alone in enhancing the glycaemic control and renal outcomes of type II diabetes mellitus patients with chronic kidney disease.

METHODS

The study was a randomized clinical trial done at the Department of Medicine at Fauji Foundation Hospital (FFH), Rawalpindi, Pakistan. The research was conducted during three months between October of 2025 and December of 2025. The institutional research ethics committee gave ethical approval prior to the study and signed informed consent was given to all the participants.

The WHO sample size calculator was used to compare two population means taking a 5% level of significance and 80% power of test to calculate the sample size. According to the parameters that were previously reported, there were 284 patients in total, 142 patients per group. Non-probability consecutive sampling in the outpatient of the medicine unit was used to select patients. The study participants had to be diagnosed with type II diabetes mellitus on insulin therapy and must have had chronic kidney disease with an estimated glomerular filtration rate (eGFR) of 15 to 45 ml/min calculated using the cockroft-gault formula and needed to have a HbA1C above 6.5.

Patients who had used other oral antidiabetic agents in the past three months, those with temporary ischemic attacks, heart attacks, or stroke, kidney transplantation, urinary tract infection, liver failure, malignancy, immunocompromised conditions or hypersensitivity to linagliptin were not allowed. The patients that were lost to follow-up also were not included in the analysis.

Following the enrollment process, demographic and clinical information such as age, gender, body mass index, duration of diabetes, duration of chronic kidney disease, smoking status, CKD grade, baseline HbA1C and baseline urine protein-creatinine ratio (UPCR) were captured into a structured proforma. The lottery method was used in assigning the participants into two groups randomly. Group A was supplied with insulin therapy plus 5 mg of linagliptin 1 time daily whereas Group B was only given insulin therapy. The patients were followed up over a period of three months and repeat HbA1C and UPCR were determined in the end of treatment to evaluate the level of glycemic control and renal functioning.

The SPSS version 25 was used to analyze data. Quantitative variables were in form of mean and standard deviation and categorical variable was in form of frequencies and percentages. The independent sample t-test was used to compare the post-treatment mean HbA1C and UPCR in both groups. Potential confounders such as age, gender, BMI, CKD grade, and duration of disease, were stratified. The p-value of 0.05 was taken to be statistically significant.

RESULTS

A total of 284 patients diagnosed with type II diabetes mellitus with chronic kidney disease were included in the study. Patients were randomized into two equal groups: Group A (Linagliptin plus insulin) and Group B (insulin only), with 142 patients in each group. The overall mean age of the participants was 54.3 ± 10.7 years. There were 158 (55.6%) males and 126 (44.4%) females. The mean BMI was 27.6 ± 4.2 kg/m². The mean duration of type II diabetes mellitus was 8.4 ± 3.1 years, while the mean duration of chronic kidney disease was 3.6 ± 1.5 years (Table 1).

Smoking status, CKD grade distribution, and diabetes control status were also analyzed. Overall, 82 (28.9%) patients were smokers. CKD stage 3 was the most common stage observed in the study population. Uncontrolled diabetes (baseline HbA1C ≥9%) was present in 126 (44.4%) patients (Table 2).

Baseline biochemical parameters were comparable between the two groups. The mean baseline HbA1C was 8.9 ± 1.2% in Group A and 8.8 ± 1.1% in Group B. Similarly, the mean baseline urine protein-creatinine ratio (UPCR) was 0.95 ± 0.18 mg/g in Group A and 0.96 ± 0.17 mg/g in Group B (Table 3).

Table No. 1: Demographic and Baseline Characteristics of Study Population (n=284)

Variable	Group A (Linagliptin + Insulin) n=142	Group B (Insulin Only) n=142	Total
Age (years), mean ± SD	53.9 ± 10.5	54.7 ± 10.9	54.3 ± 10.7
Male	79 (55.6%)	79 (55.6%)	158 (55.6%)
Female	63 (44.4%)	63 (44.4%)	126 (44.4%)
BMI (kg/m²), mean ± SD	27.4 ± 4.1	27.8 ± 4.3	27.6 ± 4.2
Duration of T2DM (years), mean ± SD	8.2 ± 3.0	8.6 ± 3.2	8.4 ± 3.1
Duration of CKD (years), mean ± SD	3.5 ± 1.4	3.7 ± 1.6	3.6 ± 1.5

Table No. 2: Clinical Characteristics of Study Participants

Variable	Group A n=142	Group B n=142	Total
Smoking	40 (28.2%)	42 (29.6%)	82 (28.9%)
Non-smokers	102 (71.8%)	100 (70.4%)	202 (71.1%)
CKD Grade 3	86 (60.6%)	88 (62.0%)	174 (61.3%)
CKD Grade 4	56 (39.4%)	54 (38.0%)	110 (38.7%)
Controlled diabetes	78 (54.9%)	80 (56.3%)	158 (55.6%)
Uncontrolled diabetes	64 (45.1%)	62 (43.7%)	126 (44.4%)

After three months of treatment, significant improvement in glycemic control was observed in the Linagliptin plus insulin group. The mean HbA1C after treatment was 7.2 ± 0.6% in Group A compared with 7.6 ± 0.8% in Group B. The difference between the groups was statistically significant (p = 0.001). Similarly, renal function assessed through UPCR showed improvement in Group A with a mean UPCR of 0.82 ± 0.14 mg/g compared with 0.91 ± 0.16 mg/g in Group B (p = 0.003) (Table 4).

Table No. 3: Baseline Laboratory Parameters

Parameter	Group A (Linagliptin + Insulin)	Group B (Insulin Only)	p-value
Baseline HbA1C(%)	8.9 ± 1.2	8.8 ± 1.1	0.46
Baseline UPCR (mg/g)	0.95 ± 0.18	0.96 ± 0.17	0.58

Table No. 4: Comparison of Post-Treatment Outcomes Between Groups

Outcome	Group A (Linagliptin + Insulin)	Group B (Insulin Only)	p-value
HbA1C after 3 months (%)	7.2 ± 0.6	7.6 ± 0.8	0.001
UPCR after 3 months (mg/g)	0.82 ± 0.14	0.91 ± 0.16	0.003

Stratification analysis was performed to evaluate the effect of age, gender, BMI, CKD grade, and smoking status on treatment outcomes. The improvement in HbA1C and UPCR remained consistently greater in the Linagliptin plus insulin group across most stratified subgroups, indicating that the observed treatment benefit was independent of baseline demographic and clinical characteristics (Table 5).

Table No. 5: Stratified Analysis of Post-Treatment HbA1C and UPCR

Stratification Variable	Outcome	Group A Mean ± SD	Group B Mean ± SD	p-value
Age ≤55 years	HbA1C	7.1 ± 0.5	7.5 ± 0.7	0.004
Age >55 years	HbA1C	7.3 ± 0.7	7.7 ± 0.8	0.008
Male	UPCR	0.83 ± 0.13	0.92 ± 0.17	0.005
Female	UPCR	0.81 ± 0.15	0.90 ± 0.16	0.007

DISCUSSION

The present study demonstrated that linagliptin combined with insulin produced significantly superior glycaemic and renal outcomes compared to insulin monotherapy in patients with T2DM and CKD, with post-treatment HbA1c of 7.2 ± 0.6% versus 7.6 ± 0.8% (p = 0.001) and UPCR of 0.82 ± 0.14 versus 0.91 ± 0.16 mg/g (p = 0.003), respectively.

Regarding glycaemic outcomes, Zhou et al. conducted a meta-analysis of randomized controlled trials and

confirmed that DPP-4 inhibitor and insulin combination therapy significantly reduced HbA1c and insulin dose requirements in patients with T2DM and CKD without increasing adverse events (1). Our findings are consistent with this evidence, further corroborating the additive glycaemic benefit of linagliptin when combined with insulin. Similarly, Deacon reported that the addition of DPP-4 inhibitors to insulin therapy improved glycaemic control without increasing hypoglycaemia risk, including in patients with CKD[14].

Concerning renal outcomes, Karimifar et al. conducted a randomized double-blind clinical trial and demonstrated that linagliptin produced a significantly higher percentage of improvement in microalbuminuria compared to placebo[15]. In our research, there was also a considerable decrease in UPCR with the use of linagliptin in combination with insulin, which indicates that three months of intervention might be enough to identify significant renal improvement in this group. The second study by Perkovic et al., which reported secondary analyses of the landmark CARMELINA trial, established that linagliptin made a significant reduction in albuminuria progression in all eGFR categories with no risk of higher hypoglycaemia[5]. Daza-Arnedo et al. further emphasized that the pleiotropic renal actions of linagliptin such as; antioxidant, antipharmacologic, and antifibrotic action, are more applicable to CKD patients since all DPP-4 inhibitors do not necessitate an increase in dose[3].

The Hoe et al. observed that among patients under insulin monotherapy there was the highest rate of rapid CKD progression than in the patients under DPP-4 inhibitors that demonstrated a significant improvement in proteinuria[16]. This is consistent with our observation that insulin alone treatment was linked to worse renal prognoses. Kawanami et al. also affirmed through meta-analysis that DPP-4 inhibitors have a significant effect in reducing the risk of microalbuminuria and macroalbuminuria in comparison to controls[17].

Our stratified analysis revealed that the treatment effect of linagliptin and insulin was similar between both sexes and age groups and this supported the strength of the observed effects. This is in line with Gomez-Peralta et al. where the combination therapy of DPP-4 inhibitors and basal insulin was found to be highly effective and safe in patients with different patient subgroups such as the elderly and different levels of renal impairment[8].

The study was carried out in one center and had a rather short term of follow up of three months, which could restrict the generalizability of the findings. Multicenter studies are needed over the long period to further test the long-term renal and glycaemic effects of linagliptin in chronic kidney disease patients.

CONCLUSION

Linagliptin added to insulin therapy produced better glycaemic control and reduction in proteinuria compared with insulin alone in patients with type II diabetes mellitus and chronic kidney disease. The findings suggest that combination therapy may provide improved metabolic and renal outcomes in this high-risk population.

Author's Contribution:

Concept & Design or acquisition of analysis or interpretation of data:	Shumaila Ahmed Khan, Nayyar Yaqoob
Drafting or Revising Critically:	Naseem Ullah, Sana Hassan
Final Approval of version:	All the above authors
Agreement to accountable for all aspects of work:	All the above authors

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