

## Research Article

# Integrative Diabetes and Cardiovascular Diseases

## Gemigliptin in Diabetic Kidney Disease in Asian Indians with Type 2 Diabetes in Real-Life Scenarios- Insights from Gem Study

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### Abstract

Diabetic Kidney disease is strongly associated with cardiovascular events, premature mortality and ESRD. Gemigliptin can be used without dose adjustment in patients with renal failure. The current study aimed to assess the possible renoprotective effects of gemigliptin, using albuminuria and eGFR as indicators. This was a multi-center real-world retrospective analysis of 146 DPP-4 inhibitor naïve type 2 diabetic patients with established moderate DKD (eGFR between 30 to 45 ml/min/1.73 m<sup>2</sup> over last 3 months) with diabetic retinopathy who received gemigliptin 50 mg once daily for 24 weeks in addition to anti-hyperglycemic, anti-hypertensive's and statins. Goodness of fit was examined using SPSS statistics 20 and ANOVA was conducted to interpret the results. Baseline characteristics were: 71 (48.6%) males and 75 (51.4%) females, the mean age was 60.81 ± 7.42 years, mean duration was 11.92 ± 3.3 years, mean BMI was 26.54 ± 2.59 kg/m<sup>2</sup>. Gemigliptin showed significant improvements in glycaemia, renal and lipid parameters with no deterioration in retinopathy, liver enzymes and with no hypoglycemic episodes and was weight neutral. In the present study, gemigliptin reduced albuminuria independent of age, gender, duration of diabetes, HbA1c, eGFR and SBP. It could ameliorate diabetic nephropathy by reducing urine albumin excretion and mitigating the reduction of eGFR in diabetic patients.

**Keywords:** Diabetic kidney disease, Urinary albumin excretion, Glomerular filtration rate, Type 2 diabetes mellitus

### Introduction

Diabetic kidney disease (DKD) is a leading cause of end-stage renal disease in India and worldwide, and is a risk factor for the development of cardiovascular complications [1]. Prevalence of DKD varies from 10% to 40% for both type 1 and type 2 diabetes patient groups depending on definition of disease used [2]. Renal risk is more in type 2 diabetes mellitus as compared to type 1 [3].

DKD is defined as the presence of increased urinary  
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albumin excretion ([UAE] a ratio of urinary albumin to creatinine 30 mg/g or more), decreased glomerular filtration rate ([GFR] less than 60 mL/min/1.73 m<sup>2</sup>), or both [4]. Kidney function assessment is done by calculating estimated glomerular filtration rate (eGFR) from the serum creatinine while kidney damage assessment is done by measurement of proteinuria. It is a known fact that measures of kidney function are associated with increased risk for mortality and cardiovascular disease [5] and also that both diabetes and chronic kidney disease are risk factors for cardiovascular mortality and morbidity and that risk increases with the progression of

renal dysfunction in diabetic patients [6].

Both modifiable and non-modifiable factors can be involved in the pathogenesis of DKD including altered expression of certain genes, hyperglycemia, hypertension, dyslipidemia, smoking, ethnicity, sex, age, and a long diabetes duration. The aim is to target modifiable risk factors [2].

Most important factor for the prevention of kidney function deterioration in patients with type 2 diabetes mellitus (T2DM) and advanced kidney disease is to control blood glucose levels. However, certain oral hypoglycaemic agents (OHAs) are contraindicated in patients with type 2 diabetes with CKD because of their side effect profiles. Recently, growing evidence suggests that two oral hyperglycemic agents, dipeptidyl peptidase 4 (DPP-4) inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors, exert reno-protective effects [7].

The dipeptidyl peptidase-4 (DPP-4) inhibitors have been recommended as a first-line or an add-on therapy after metformin due to their superior efficacy, weight-neutrality, low risk of hypoglycemia, and excellent tolerability [8,9]. DPP-4 enzyme inactivates incretin hormone glucagon-like peptide (GLP)-1 in the peripheral circulation. DPP-4 inhibitors inhibit DPP-4 enzyme in peripheral plasma and increases circulating intact GLP-1, thereby stimulating the release of insulin from  $\beta$ -cells and reducing glucagon secretion in a glucose-dependent manner. However, certain DPP-4 inhibitors that are eliminated mainly by the kidney require dose adjustments in patients with renal dysfunction. Pharmacokinetic and clinical trials have proved that DPP-4 inhibitor linagliptin and gemigliptin can be used safely without dose adjustment in patients with T2DM and renal impairment [10-13].

Gemigliptin was developed by LG Life Sciences (Seoul, Korea) and was approved by the Ministry of Food and Drug safety in June 2012 for the treatment of T2DM [14]. Gemigliptin is a potent, selective, competitive, and long-acting DPP-4 inhibitor with dual mode of excretion [15,16]. Additionally, the proportion of gemigliptin eliminated via urine is roughly equal to the proportion eliminated via faeces. Therefore, the drug can be used without dose adjustment in patients with T2DM and renal impairment [15]. Various studies have proven the efficacy and safety of gemigliptin for the treatment of T2DM, both as monotherapy as well as in combination with other anti-diabetic drugs.

In this article, we will review the recent clinical studies of gemigliptin and assess if gemigliptin has possible reno-protective effects of gemigliptin, using albuminuria and estimated glomerular filtration rate (eGFR) as indicators.

## Materials and Methods

### Study design

This was a multi-center real-world retrospective analysis of 146 DPP-4 inhibitor naïve type 2 diabetic patients with established moderate DKD (eGFR between 30 to 45 ml/min/1.73 m<sup>2</sup> over last 3 months) with diabetic retinopathy.

This clinical study was conducted in accordance with the Declaration of Helsinki, good clinical practice guidelines, and the standard operating procedures of the sponsors and local regulatory guidelines. The study was approved by the institutional review boards of the investigational site, and written informed consent was obtained from each patient before screening.

### Study subjects

A total of 146 patients who were adult patients with T2DM, DPP-4 Inhibitor naïve, patients with established DKD with eGFR persistent between 30 to 45 ml/min/1.73 m<sup>2</sup> over the last 3 months, patients with Diabetic Retinopathy, patients not on ACE inhibitors or ARB over the last 6 months and patients on background Insulin therapy were enrolled in the study. Patients with severe renal impairment, needing dialysis or already on dialysis and also patients with preexisting cardiovascular diseases were excluded from the study.

### Study interventions

Study subjects received gemigliptin 50 mg once daily for 24 weeks in addition to anti-hyperglycemic, anti-hypertensives and statins.

### Efficacy and safety assessments

Outcome data were noted at baseline visit and after 24 weeks. Data related to glycemic parameters viz., FPS, PPBS, HbA1c; lipid parameters viz., Total cholesterol, HDL, LDL, TGs; liver profile viz., SGOT, SGPT; kidney function viz., proteinuria, urine albumin creatinine ration (UACR), eGFR, serum creatinine and body weight and blood pressures were analyzed and compared at baseline and 24 weeks. Additionally, data related to retinopathy and neuropathy was analyzed. Any reported adverse event or any other recorded safety data was assessed and

analyzed.

## Statistical analysis

Data was collected and analyzed using IBM SPSS Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp. Besides descriptive statistics, repeated measures ANOVA was conducted and a  $p$ -value was reported (Significance < 0.001).

## Results

Data of 146 patients was extracted and analyzed. Baseline characteristics were: 71 (48.6%) males and 75 (51.4%) females, the mean age was  $60.81 \pm 7.42$  years, mean duration of diabetes was  $11.92 \pm 3.3$  years, mean BMI was  $26.54 \pm 2.59$  kg/m<sup>2</sup>. These patients were analyzed for efficacy and safety. Demographic data is presented in table 1. All patients were instructed for lifestyle modification in terms of dietary modification, physical activity and smoking cessation at the baseline as part of the routine advice. All adult T2DM patients with established DKD were on basal insulin; gemigliptin therapy was added to existing antidiabetic therapy to achieve glycemic control (Table 1).

Data expressed as mean  $\pm$  SD. FPG-Fasting Plasma Glucose; PPG-Postprandial Plasma Glucose; HbA1c-Glycated Hemoglobin; eGFR-estimated GFR; HDL-High density cholesterol; LDL-Low density cholesterol; TG-Triglycerides; SGPT-Serum glutamic pyruvate transaminase; SGOT-Serum glutamic oxaloacetic transaminase.

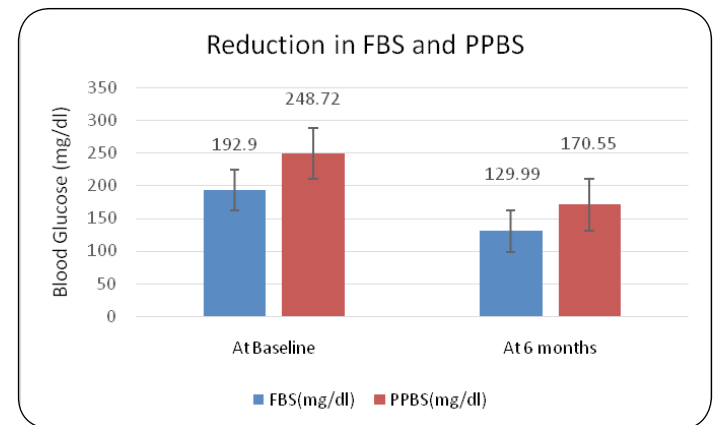
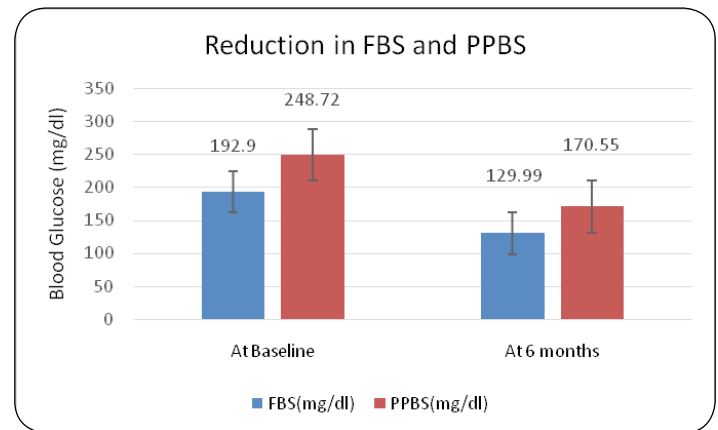
### Effect of gemigliptin on Glycemic parameters

Treatment with gemigliptin reported a significant reduction in FPG and PPG at 6 months. Compared to baseline, mean FPG was reduced by 62.91 mg/dl ( $p < 0.001$ ) at 6 months. Similarly, mean PPG was reduced by 78.71mg/dl ( $p < 0.001$ ) at 6 months (Figure 1). There was significant reduction of 1.5% ( $p < 0.001$ ) HbA1c at 6 months (Figure 2).

### Effect of gemigliptin on Renal parameters

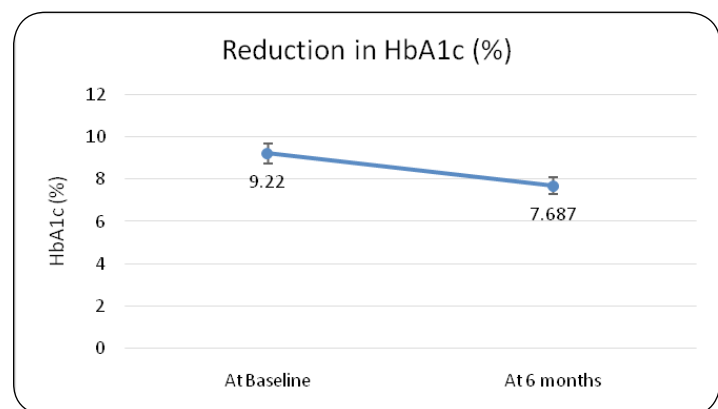
Significant improvement in eGFR was noted with Gemigliptin (Table 2 and Figure 3). At baseline, all patients had eGFR below 60 ml/min/1.73 m<sup>2</sup>. At 6 months of gemigliptin therapy, significant increase of eGFR was noted (37.57 vs. 41.76 ml/min/1.73 m<sup>2</sup>;  $p < 0.001$ ). eGFR was increased by 12%. Serum creatinine was reduced significantly at 6 months. Almost 8.8% reduction in Sr. creatinine was noted at 24 weeks. At baseline, all patients

had proteinuria. At 6 months, proteinuria was reduced significantly in 34.2% patients (Figure 4).



**Figure 1:** Reduction in fasting and postprandial glucose at 6 months.

\* $p < 0.001$  when compared with baseline;



**Figure 2:** Reduction in HbA1c at 6 months.

\* $p < 0.001$  when compared with baseline;

### Effect of gemigliptin on BMI, Blood Pressure, lipid variables and liver enzymes

Gemigliptin was found to weight neutral. At 6 months, there was significant reduction in SBP and DBP by 4.8% and 2.2% from baseline. Significant improvement in lipid

variables and liver enzymes was also reported during gemigliptin therapy (Table 3).

**Table 1:** Baseline patient characteristics.

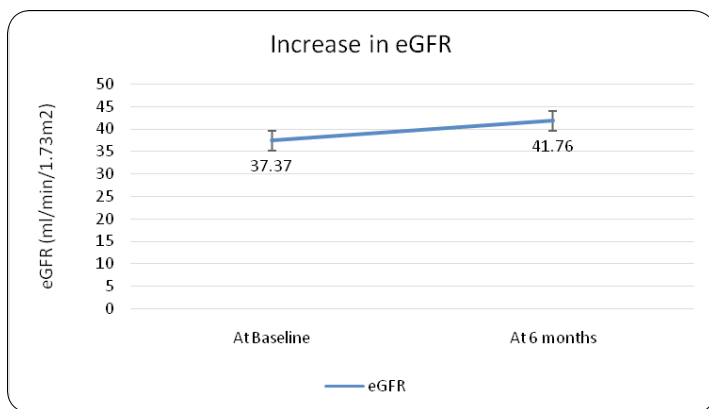
| Parameters                | At baseline    |
|---------------------------|----------------|
| BMI (kg/m <sup>2</sup> )  | 26.548 ± 2.59  |
| SBP (mm of Hg)            | 143.98 ± 17.61 |
| DBP (mm of Hg)            | 85.63 ± 6.69   |
| FBS (mg/dl)               | 192.90 ± 52.64 |
| PPBS (mg/dl)              | 248.72 ± 62.75 |
| HbA1c (%)                 | 9.22 ± 1.51    |
| Total cholesterol (mg/dl) | 201.9 ± 51.29  |
| HDL (mg/dl)               | 36.96 ± 6.64   |
| LDL (mg/dl)               | 137.43 ± 45.39 |
| TG (mg/dl)                | 182.94 ± 59.67 |
| SGPT (ALT) (U/l)          | 38.36 ± 12.57  |
| SGOT (AST) (U/l)          | 34.73 ± 11.05  |

of renal function. In a trial by UKPDS on newly diagnosed diabetic patients, direct relationship between the risks of diabetes related complications and level of glycaemia was identified.

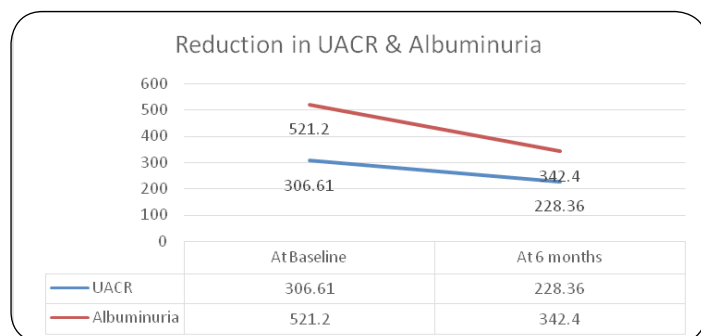
Kidney function assessment is done by calculating estimated glomerular filtration rate (eGFR) from the serum creatinine while kidney damage assessment is done by measurement of proteinuria. The first clinical evidence of DN is microalbuminuria (MA) defined as excretion in urine of 30 to 300 mg albumin/day or 20 to 200 µg/ml. One important cause of microalbuminuria is selective loss of nephrons expression by podocytes which is reversible with blockade of the renin angiotensin system (RAS) [17]. Albuminuria is a key predictor of cardiovascular complications both in diabetic and non-diabetic CKD populations.

While it is clear that measures of kidney function are associated with increased risk for mortality and cardiovascular disease [5] and also know the fact that both diabetes and chronic kidney disease are risk factors for cardiovascular mortality and morbidity, and that risk increases with the progression of renal dysfunction in diabetic patients [6]. Strict glucose control through lifestyle changes (i.e., diet, physical exercise, and weight loss) and antidiabetic pharmacotherapy is crucial for slowing the progression of DKD.

In management of T2DM patients, DPP-4 inhibitors have found to have two relevant benefits: negligible risk of severe hypoglycemia, particularly when compared with sulphonylureas [18,19] and weight neutrality, in contrast with the weight gain generally observed with insulin therapy, sulphonylureas, glinides, and thiazolidinediones [19,20]. DPP-4 inhibitors inhibit the DPP-4 enzyme, increasing the level of endogenous plasma glucagon-like peptide-1, which stimulate the release of insulin from β-cells and reduce glucagon levels in a glucose-dependent manner; thus, these drugs are associated with minimal risks of hypoglycemia and weight gain. Recent studies have reported that these peptides may have pleiotropic beneficial effects on vascular function in addition to improving glycemic control [21]. A prior study showed that gemigliptin improved glycemic control compared with placebo in patients with T2DM and moderate or severe renal impairment. 9 DPP-4 also cleaves substrates such as neuropeptide Y, high-mobility group protein B1, and meprin-β [22,23]. Recent studies suggest that DPP-4 inhibition is associated with pleiotropic effects on cardio renal protection. Apart from the glucose-lowering effect,



**Figure 3:** Increase in eGFR at 6 months.  
\**p* < 0.001 when compared with baseline;



**Figure 4:** Increase in UACR & Albuminuria at 6 months.  
\**p* < 0.001 when compared with baseline;

## Discussion

Hyperglycemia alters kidney architecture, by oxidative and inflammatory stress, and eventually progressive loss

**Table 2:** Effect of gemigliptin on Renal parameters.

| Parameters                        | At Baseline   | At 6 months    | % change from baseline | P-value              |
|-----------------------------------|---------------|----------------|------------------------|----------------------|
| UACR(mcg/min)                     | 306.61 ± 6.61 | 228.36 ± 45.85 | 25%                    | Significant (<0.001) |
| Albuminuria(mg/g)                 | 521.2         | 342.4          | 34.20%                 | Significant (<0.001) |
| eGFR (ml/min/1.73m <sup>2</sup> ) | 37.57 ± 5.86  | 41.76 ± 5.52   | 12%                    | Significant (<0.001) |
| S.Creatinine (mg/dl)              | 1.70 ± 0.23   | 1.55 ± 0.21    | 8.80%                  | Significant (<0.001) |

\*p < 0.001 when compared with baseline; data expresses as mean ± SD

**Table 3:** Effect of gemigliptin on BMI, SBP, DBP, lipid variables and liver enzymes.

| Parameters                | At Baseline    | At 6 months    | % change from baseline | P value              |
|---------------------------|----------------|----------------|------------------------|----------------------|
| BMI (kg/m <sup>2</sup> )  | 26.548 ± 2.59  | 26.5 ± 2.56    | 0.15%                  | Not significant      |
| SBP (mm of Hg)            | 143.98 ± 17.61 | 136.95 ± 12.75 | 4.80%                  | Significant (<0.001) |
| DBP (mm of Hg)            | 85.63 ± 6.69   | 83.67 ± 6.68   | 2.20%                  | Significant (<0.001) |
| Total cholesterol (mg/dl) | 201.9 ± 51.29  | 154.47 ± 35.16 | 23.50%                 | Significant (<0.001) |
| HDL (mg/dl)               | 36.96 ± 6.64   | 39.00 ± 5.31   | 5.50%                  | Significant (<0.001) |
| LDL (mg/dl)               | 137.43 ± 45.39 | 103.39 ± 28.60 | 25.03%                 | Significant (<0.001) |
| TG (mg/dl)                | 182.94 ± 59.67 | 135.02 ± 43.27 | 26.10%                 | Significant (<0.001) |
| SGPT (ALT) (U/l)          | 38.36 ± 12.57  | 33.29 ± 9.34   | 13.20%                 | Significant (<0.001) |
| SGOT (AST) (U/l)          | 34.73 ± 11.05  | 30.01 ± 7.75   | 13.50%                 | Significant (<0.001) |

the inhibitors exert anti-oxidant, anti-inflammatory, and anti-fibrotic effects [23,24]. DPP-4 is expressed in most organs and cell types, but the activity levels are tissue-dependent. DPP-4 is expressed at relatively high concentrations in the kidney, especially in the brush borders of proximal tubular cells [23]. Some studies have found that DPP4 expression increased in pathological conditions such as diabetic nephropathy [25-27]. Numerous preclinical and clinical studies now support the notion that DPP-4 exerts a reno-protective effect [28-32].

In this study B.P. was significantly decreased at 6 months when compared to baseline. The ADVANCE study found that a 5.6 mmHg fall in systolic BP reduced the risk of major macro- or microvascular events; in particular, the development of microalbuminuria was significantly reduced [33]. Therefore, to prevent the development and progression of DKD, the ADA recommends that treatment should aim to reduce the BP below 140/90 mmHg [34].

In the present study, gemigliptin reported significant reduction in FPG and PPG by 32.6% and 31.4% respectively. At 6 months, clinically significant and meaningful 1.5% reduction in HbA1c was noted. Effects on renal parameters were also found significantly positive in this study, with an increase in eGFR by 12%, reduction of Sr. creatinine by 8.8% and reduction in the proportion of patients with proteinuria by 34.2 % and

also reduction in UACR by 25%. In one study by Hattori et al., in 37 non-CKD diabetic patients in which sitagliptin was administered at a dose of 50-mg, UACR was reduced compared to placebo [19]. Similarly, in one another study by Mori et al. reduction in albuminuria in T2DM patients after six months of treatment with sitagliptin compared with other antidiabetic agents [19].

Gemigliptin also improved the lipid parameters with LDL reduction being as much as 25.03% and with TG reduction of about 26.1%. Weight neutrality was observed with Gemigliptin. These results are very relevant and important in daily clinical practice since renal disease alters the pharmacokinetics of most DPP4 inhibitors.

Gemigliptin also improved liver profile by reducing SGOT and SGPT by about 13.2% and 13.5% respectively. Considering the fact that post-prandial hypertriglyceridemia is one of the characteristic feature of T2DM patients and is caused by increased production of ApoB48 and ApoB100. In one study by Chang et al. it was found that gemigliptin reduces ApoB48 levels after a high-fat diet in T2DM patients [19].

No episode of hypoglycemia was reported in this study. There was no worsening of retinopathy or neuropathy with the use of gemigliptin, which indicates that gemigliptin is safe for use in patients of diabetes with multiple comorbidities. Additionally, the proportion

of gemigliptin eliminated via urine is roughly equal to the proportion eliminated via faeces. Therefore, the drug can be used without dose adjustment in patients with T2DM and renal impairment.

## Conclusion

In the present GEM study, gemigliptin reduced albuminuria independent of age, gender, duration of diabetes, HbA1c and SBP. Gemigliptin could ameliorate diabetic nephropathy by reducing urine albumin excretion and mitigating the reduction of eGFR in diabetic patients. Gemigliptin may be considered a safe and effective treatment modality in type 2 diabetic patients with moderate renal impairment.

## Limitations

The study has some obvious limitation such as retrospective, open-labelled design, small sample size, variation in concomitant antidiabetic therapy, and lack of comparative drug and placebo groups. Considering these limitations results of this study must be interpreted with caution and cannot be generalized. A well designed, large sampled RCT is required to estimate the place of gemigliptin in Asian Indian patients with moderate DKD.

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## Conflict of interests

None

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