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Research Article

An Observational Retrospective Real-World Study to Evaluate the Effect of Teneligliptin on Parameters of Renal Function, Glycemic Control, and Safety in Indian T2DM Patients with Chronic Kidney Disease (TOP RENAL)

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Abstract

Background: Teneligliptin has shown better efficacy, tolerability and reduced associated complications in patients with type 2 diabetes mellitus (T2DM) and chronic kidney disease (CKD). The aim of this study was to evaluate the effect of Teneligliptin on renal function and glycemic control in Indian T2DM patients with CKD in a real-world setting.

Methodology: This was a retrospective, observational study that included 377 patients from 4 study sites across India. Details from prescriptions and laboratory investigations of individual patient were recorded. Primary and secondary outcomes measured were changes in the renal parameters, [eGFR, serum creatinine, and blood urea nitrogen] and glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and body weight at 3 months and 6 months (±2week) as compared to baseline.

Results: 377 patient's data collected during August'22-October'22 and grouped according to baseline eGFR (ml/min/1.73m2): G3a: 45-59 (n=102); G3b: 30-44 (n=124); G4: 15-29 (n=151). The mean age was 59.86±9.58 years and 47% were females. Renal parameters: eGFR, Sr creatinine and BUN were assessed at baseline, 3 months and 6 months. Results showed non-significant changes in eGFR, Sr. creatinine and BUN at 3 and 6 months in all three groups. No safety concerns or hypoglycemia were reported during the study.

Conclusion: Teneligliptin use in Indian T2DM patients with mild to severe renal impairment was well tolerated with no safety concerns and showed significant improvement in glycemic control.

Keywords: Diabetes Mellitus; Glycemic Control; Renal Impairment; Teneligliptin

Abbreviations

T2DM	:	Type 2 Diabetes Mellitus
CKD	:	Chronic Kidney Disease
eGFR	:	estimated Glomerular Filtration Rate
HbA1c	:	Glycated Hemoglobin
FPG	:	Fasting Plasma Glucose
PPG	:	Postprandial Plasma Glucose
BUN	:	Blood Urea Nitrogen
ACR	:	Albumin-To-Creatinine Ratio
TZD	:	Thiazolidinediones
DPP-4i	:	Dipeptidyl-peptidase IV inhibitors

Introduction

Diabetes Mellitus (DM) is recognized as a global health concern, imposing a considerable impact on human life and a burden on socio-economic development [1]. International Diabetes Federation (IDF, 2021) estimated that nearly 537 million adults have diabetes at present and this number is expected to increase to 783 million (12%) by 2045 [2]. Diabetes, together with its host of micro- and macro-vascular complications, is the 10th leading cause of death [3]. Chronic kidney disease (CKD) or diabetic kidney disease (DKD), is characterized by persistently low estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2 and/or elevated urinary albumin (albumin-to-creatinine ratio [ACR] ≥ 30 mg/g), and is one of the major macro-vascular complications of DM. According to the previous studies, T2DM was the second leading cause of CKD and CKD-related deaths and the third leading cause of CKD-related disability-adjusted life years (DALYs) [4,5].

According to the American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) 2022 executive summary, the choice of therapy for T2DM depends on the patient's cardiac, cerebrovascular, and renal status [6]. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) guideline, only a few of several oral hypoglycemic agents can be administered in CKD patients, including sulfonylurea (Glipizide and Gliclazide), Meglitinide (Repaglinide), Thiazolidinediones (TZD), and Dipeptidyl-peptidase IV (DPP-4) inhibitors [7,8].

Teneligliptin, a novel 3rd generation DPP4 inhibitor, is a competitive reversible inhibitor of the enzyme DPP4. DPP4 inhibitors exert antihyperglycemic effects by inhibiting the DPP4 enzyme and thereby enhancing levels of endogenous glucagon-like peptide 1 (GLP1) and other incretin hormones. This action stimulates glucose-dependent insulin synthesis and secretion and suppresses glucagon secretion. Teneligliptin has a unique structure exhibiting five consecutive rings (J-shaped) and has an exceptional potency and long-lasting effect [9,10]. Studies on the pharmacokinetics of Teneligliptin suggest no dose adjustment is required, irrespective of renal impairment [11]. Approximately 34% of the administered dose of Teneligliptin is excreted unchanged via the renal route, while 66% is metabolized and eliminated via the hepatic and renal routes [12].

Several evidence of the efficacy and safety of Teneligliptin in Indian T2DM patients are available but there is no robust data available on the safety and effectiveness of Teneligliptin in Indian T2DM patients with CKD. Hence, this real- world, multicenter, retrospective, observational study that aimed to evaluate the effect of Teneligliptin on renal parameters in T2DM patients with CKD was conducted.

Methodology

TOP RENAL study was six months real- world, retrospective, observational, multicenter study on Indian T2DM patients with CKD treated with Teneligliptin orally once daily. The study data collection were done between August 2022 to October 2022.The protocol of TOP RENAL was approved by the Excel endocrine center Institutional Ethics committee and was in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP).

The TOP RENAL study enrolled adult (>18 years of age) T2DM patients with eGFR ≥ 15 ml/min/1.73 m^2 to ≤ 60 ml/min/1.73 m^2 at the time of treatment initiation with Teneligliptin; patients who were initiated on Teneligliptin and had no change in their prescription of anti-diabetic medication or other concomitant

medications for the consecutive six months; and patients for whom complete data of the six months were available according to the study endpoints. Type 1 diabetes patients, pregnant or breast-feeding females; those with known liver or kidney dysfunction (eGFR < 15 ml/min/1.73m^2) or with any Cardiovascular Disease (CVD) event at the time of initiation of treatment with Teneligliptin; patients with renal impairment requiring dialysis; and patients who were diagnosed with or suffering from COVID-19 infection were excluded from the study.

The study investigators and site personnel identified the patient data as per the enrollment criteria from the available patient medical records at the study site. Prescriptions and laboratory investigations of individual patients were uploaded from each site into a web-based database by study investigators. Qualified data entry personnel entered data from prescriptions into electronic data collection form.

The primary endpoint of the study was change in eGFR, serum creatinine (Sr. Creatinine) and blood urea nitrogen (BUN) from baseline to 3 and 6 months. Secondary endpoints were changes in glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), postprandial glucose (PPG), and body weight at 3 and 6 months as compared to baseline, and percentage of patients achieving HbA1c ≤7 % at 6 month. Safety of Teneligliptin was assessed throughout the study.

Statistical Analysis

Demographic characteristics, continuous data like age, weight etc. were summarized with n, mean, Standard Deviation (SD), range and Confidence Intervals (CI). Effectiveness parameters such as HbA1c, FPG, and PPG were presented using descriptive statistics and changes from baseline were evaluated. Number of patients achieving the HbA1c level of <7% were summarized with count (%). Paired t-test was applied to assess the statistical significance and p value<0.05 was considered statistically significant. Incidences of adverse events were summarized with count (%).

Results

Data of 377 patients were collected across 4 centers from India during August 2022 to October 2022 and were analyzed. Of the 377 subjects, 179 (47.5 %) were females. The mean age (±SD) of the study population was 59.9 (±9.58) years. The baseline demographic and clinical characteristics such as duration of the diabetes were presented in Table 1. Concomitant anti-diabetic medications of the study population are presented in Table 2.The dose of Teneligliptin used was 20 mg once daily in the study population (n=271), there were a few patients (n=106) who were either initiated or up-titrated to Teneligliptin 40 mg once daily.

PARAMETER	Overall (N=377)
Age (Years)	
Mean (SD)	59.9±9.58
Gender	
Male	198 (52.52 %)
Female	179 (47.5 %)
Weight (kg)	
Mean ±SD	68.4± 9.52
BMI (Kg/m^2)	
Mean±SD	27.6±4.62
Systolic Blood Pressure (mmHg)	
Mean±SD	133.5 ±11.84
Diastolic Blood Pressure (mmHg)	
Mean±SD	80.5± 7.11
Duration of Diabetes (N=256)	
1 to 5 years	129 (50.4%)
6 to 10 years	104 (40.6%)
>10 years	23 (9 %)
Data Not Available	121
Abbreviations: BMI (Body Mass Index); SD= Standard Deviation	

Table 1: Demographics and clinical characteristics of the study population.

Effect of Teneligliptin on Renal Parameters:

Patients were classified based on the captured eGFR values. Of the 377 patients, 102 patients had eGFR between 45-59 mL/min/1.73m^2 (G3a), 124 patients had eGFR 30-44 mL/min/1.73m^2 (G3b) and 151 had eGFR 15-29 mL/min/1.73m^2 (G4). Overall, the mean eGFR (mL/min/1.73m^2) at baseline, 3 months and 6 months were 36.4±12.3, 36.4±12.4, and36.8±12.5, respectively. The overall differences in eGFR in the follow up visits were not statistically significant (P> 0.05) (Figure 1). In the G3a, G3b, and G4 groups, the baseline eGFR values were 51.7±3.6, 40±3.6 and 23.2±3.4, respectively. After 6 months, these values were 52.1±4.5, 40.5±4.5 and 23.4±3.2 respectively. There was no significant change in serum creatinine and BUN levels from baseline (1.86±0.53 and 21.42±9.69, respectively) to six months (1.85±0.54 and 21.08±10.82, respectively) (Table 2).

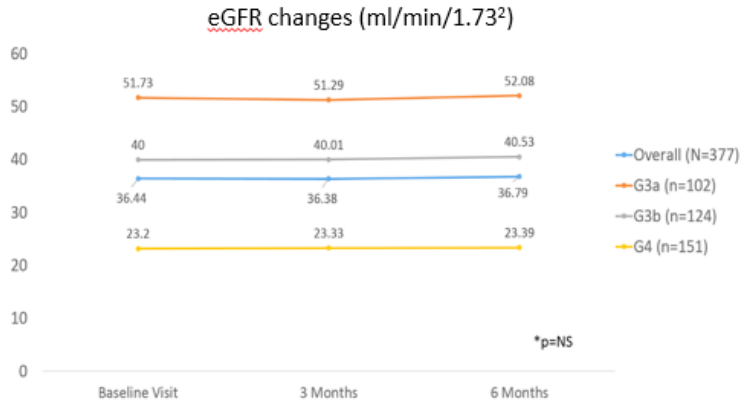

Figure 1: Change in eGFR (ml/min/1.73m²).

Concomitant Medications	G3a (n %)	G3b (n %)	G4 (n %)
METFORMIN	33 (8.75%)	10 (2.65%)	105 (27.85%)
METFORMIN+ ALPHA- GLUCOSIDASE INHIBITOR	2 (0.53%)	9 (2.39%)	2 (0.53%)
METFORMIN+ SGLT2 INHIBITORS	0.00%	0.00%	1 (0.27%)
METFORMIN + SULFONYLUREA	51 (13.53%)	27 (7.16%)	8 (2.12%)
METFORMIN + SULFONYLUREA + THIAZOLIDINEDIONE	1 (0.27%)	2 (0.53%)	1 (0.27%)
METFORMIN+ SULFONYLUREA + ALPHA- GLUCOSISADE INHIBITOR	2 (0.53%)	16 (4.24%)	1 (0.27%)
METFORMIN + SULFONYLUREA + SGLT2 INHIBITORS	0.00%	3 (0.80%)	1 (0.27%)
ALPHA- GLUCOSISADE INHIBITOR	2 (0.53%)	8 (2.12%)	5 (1.33%)
ALPHA- GLUCOSISADE INHIBITOR+SGLT2 INHIBITORS	0.00%	2 (0.53%)	0.00%
MEGLITINIDE	1 (0.27%)	10 (2.65%)	1 (0.27%)
MEGLITINIDE+ALPHA- GLUCOSISADE INHIBITOR	2 (0.53%)	25 (6.63%)	12 (3.18%)
MEGLITINIDE+SGLT2 INHIBITORS	0.00%	5 (1.33%)	4 (1.06%)
MEGLITINIDE+SULFONYLUREA+METFORMIN	0.00%	0.00%	1 (0.27%)
SGLT2 INHIBITORS	0.00%	0.00%	1 (0.27%)
SULFONYLUREA	6 (1.59%)	5 (1.33%)	7 (1.86%)
SULFONYLUREA+ SGLT2 INHIBITOR	0.00%	1 (0.27%)	0.00%
SULFONYLUREA+ALPHA-GLUCOSIDASE INHIBITOR	1 (0.27%)	0.00%	0.00%
SULFONYLUREA + THIAZOLIDINEDIONE	1 (0.27%)	0.00%	1 (0.27%)
SULFONYLUREA + THIAZOLIDINEDIONE + ALPHA- GLUCOSIDASE INHIBITOR	0.00%	1 (0.27%)	0.00%
	102 (27.06%)	**124 (32.89%)**	**151 (40.05%)**

Table 2: Concomitant Anti-Diabetic Medications (eGFR Class wise) of the study population.

Effect of Teneligliptin on Glycemic Parameters

The mean HbA1C (% ± SD) at baseline, 3 months and 6 months were 8.05±0.67, 7.62 ±0.81 and7.23±0.79, respectively. The mean change in HbA1c from baseline across both time intervals was found to be statistically significant (P < 0.001). In the G3a, G3b, and G4 groups, the mean reductions in HbA1c values were 0.73, 1.08, and 0.67, respectively.

The proportion of patients that achieved HbA1c levels ≤ 7 % at 6 months was 48.81% (Figure 2). The overall mean baseline FPG significantly decreased from baseline 142.9± 32.9to 128.1±35.4at 6 months (P <0.0001). Similarly, significant (P <0.0001) reduction was seen in overall PPG from baseline200.75±32.29to174.9±35.94at 6 months (Table 3).There was no significant change in body weight was observed throughout the study duration.

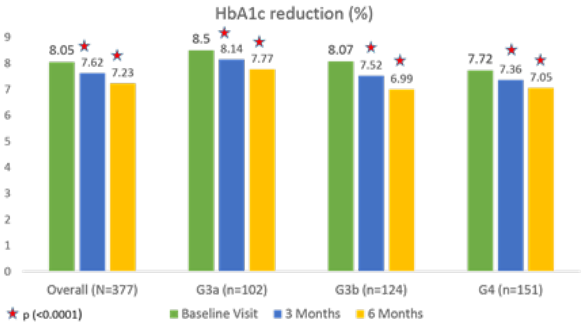

Figure 2: Change in HbA1c (%).

Class	Baseline Visit	Follow-up Visit (3 Months)	Follow-up Visit (6 Months)	Intragroup p-value (Paired t-test) Baseline to 3 months	Intragroup p-value (Paired t-test) Baseline to 6 months
Serum Creatinine (Mean ± SD)					
Overall	1.86±0.53	1.85±0.53	1.85±0.54	-0.22003	-0.1401
eGFR (G3a) (45-59)	1.31±0.14	1.32±0.13	1.3±0.12	-0.1032	-0.31846
eGFR (G3b) (30-44)	1.61±0.25	1.57±0.24	1.59±0.27	-0.04656	-0.2959
eGFR (G4) (15-29)	2.45±0.19	2.44±0.21	2.44±0.22	-0.52736	-0.48774
Blood Urea Nitrogen (BUN) (Mean ± SD)					
Overall	21.42±9.69	21.21±10.9	21.08±10.8	0.21289	0.09129
eGFR (G3a) (45-59)	17.41±10.31	16.84±9.97	16.65±9.76	0.14071	0.08522
eGFR (G3b) (30-44)	17.64±7.54	17.29±10.6	17.02±11.3	0.3275	0.16112
eGFR (G4) (15-29)	27.24±7.75	27.37±8.73	27.39±7.52	0.50115	0.47885
PPG (mg/dl) (Mean ± SD)					
Overall	200.75±32.29	186±34.97	174.9±35.9	<0.0001	<0.0001
eGFR (G3a) (45-59)	187.2±36.9	170.18±25.99	159.14±23.87	<0.0001	<0.0001

Class	Baseline Visit	Follow-up Visit (3 Months)	Follow-up Visit (6 Months)	Intragroup p-value (Paired t-test) Baseline to 3 months	Intragroup p-value (Paired t-test) Baseline to 6 months
eGFR (G3b) (30-44)	198.52±24.81	177.15±30.4	159.14±21.76	<0.0001	<0.0001
eGFR (G4) (15-29)	211.7±30.71	203.98±35.91	198.49±39.13	<0.0001	<0.0001
FPG (mg/dl) (Mean ± SD)					
Overall	142.99±32.91	135.44±32.84	128.03±35.37	<0.0001	<0.0001
eGFR (G3a) (45-59)	144.89±30.04	136.43±21.57	125.82±18.45	-0.00015	<0.0001
eGFR (G3b) (30-44)	121.38±27.96	110.47±25.23	99.7±25	<0.0001	<0.0001
eGFR (G4) (15-29)	159.44±28.36	155.28±30.91	152.79±33.32	<0.0001	<0.0001

Abbreviations: eGFR= estimated Glomerular Filtration Rate; HbA1c= Glycated Hemoglobin; FPG= Fasting Plasma Glucose; PPG= Postprandial Plasma Glucose; BUN= Blood Urea Nitrogen; SD= Standard Deviation.

Table 3: Changes in Renal Parameters (Sr. Creatinine and BUN) and Glycemic Parameters (FPG and PPG).

Safety Profile

There were no adverse events reported data in any of the patients.

Discussion

This study aimed to assess the effect of Teneligliptin on renal parameters in Indian T2DM patients with CKD in real world setting as it is widely used in India. Primarily liver eliminates Teneligliptin, hence dose modification is not required when using in mild to moderate renal impairment patients [13]. Findings from our 'TOP RENAL' real-world study illustrated the effectiveness of Teneligliptin in reducing HbA1c levels (mean reduction from baseline: 0.82 %, P < 0.001) in T2DMpatients with CKD. It was observed that the eGFR of patients was maintained, suggesting no adverse effects of Teneligliptin on renal functions. Similar results were obtained in RUBY study that reported the least squares mean change in HbA1c adjusted to the baseline was - 0.68 to - 0.85% and - 0.71 to - 0.85% across the eGFR groups, respectively [14]. RUBY study observed that long-term treatment with Teneligliptin was generally well- tolerated in patients with any stage of renal impairment from normal to end-stage renal disease [14]. Tanaka K, et al. (2016) conducted a study in T2DM patients with CKD who were treated with Teneligliptin at 20 mg/day or Linagliptin at 5 mg/day for 6 days and then switched to the other agent for another 6 days and reported that Linagliptin and Teneligliptin have comparable effects on the mean amplitude of glucose excursions in T2DM patients with CKD and are potentially useful and safer for treatment of such patients [15].

Agrawal P et al. (2021) treated patients with suboptimal control of T2DM (HbA1c >7.5%) with Teneligliptin monotherapy and observed a persistent reduction in HbA1C (p< 0.001) [16]. It also reported that the difference in eGFR across different time intervals was not statistically significant (p = 0.958), indicating that administration of Teneligliptin did not have any impact on eGFR [16]. These studies indicated adequate glycemic control with Teneligliptin in T2DM patients with no adverse impact on renal function.

The two large-scale RWE studies in the Indian population, TREAT-India 1 (N=4305 patients) and 2 (N= 10,623 patients), reflected the effectiveness of Teneligliptin in improving glycemic control in patients with T2DM when prescribed as monotherapy or as add-on to one or more antidiabetic drugs [17,18]. Teneligliptin also significantly reduced HbA1c (1.13% p < 0.0001) in patients with impaired renal function without worsening the eGFR [18]. Insight into differences in chemical structure, the binding mode to DPP4, and the lipophilicity of each DPP4 inhibitor suggests differences in their renoprotective effects as well.

Kitada M et al (2019) reported that shifting from other DPP4 inhibitors to Teneligliptin for 24 weeks reduces plasma DPP4 activity, which was associated with a reduction in albuminuria [19]. Han E, et al (2020) observed that switching from Linagliptin to Teneligliptin reduced FBG (148.1 ± 47.1 to 139.6 ± 43.4 mg/dL), HbA1c (7.9 ± 1.3 to 7.5 ± 1.2%), and PBG (224.8 ± 77.4 to 205.8 ± 70.8 mg/dL) levels (all P < 0.05) [20]. Dange S et al (2020) also reported Teneligliptin to be equally effective in comparison

to Sitagliptin and can be considered a good cost-effective option as an add-on for patients with T2DM uncontrolled on metformin monotherapy [21].

The emerging clinical evidence suggests that Teneligliptin has strong antioxidative and Reno-protective effects that might be independent of its blood glucose-lowering effects [22]. Sagar M, et al. (2016) elucidated improvement in endothelial function and reduction in renal and vascular oxidative stress in patients with T2DM and CKD with the use of Teneligliptin [23]. Mitra A and Ray S (2020) demonstrated that marginal improvement of kidney function as expressed through a borderline change in the ACR ($P = 0.052$) from baseline to three months [24].

In a systematic review and meta-analysis, no significant risk of any hypoglycemia with Teneligliptin as compared to placebo (OR 0.84; 95% CI 0.44–1.60; $I^2 = 0\%$; $P = 0.60$) was found, but the risk was 1.84 times higher when combined with other hypoglycemic agents [25]. A post-marketing surveillance of more than 10,000 patients on Teneligliptin reported the occurrence of adverse effects in 3.85% of patients. The most frequent adverse effects included gastrointestinal disorders (0.8%), most commonly constipation [26].

Limitations

With retrospective design of the study some inherent limitation are applicable to study. Randomized controlled trial with larger sample size should be conducted to get further insights.

Conclusion

Teneligliptin use in Indian T2DM patients with mild to severe renal impairment did not adversely affect the renal function. It was well tolerated with no safety concerns and showed significant improvement in glycemic control.

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Competing interest- None

Declaration of Interest: Nil

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