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Research Article

A Real-World Observational Study on Diabetes Mellitus Patients Administering Dual Combination Therapy of Teneligliptin and Metformin to Evaluate Renal Function

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Abstract

Introduction: Despite the improvements in our knowledge of the pathophysiology of Type 2 Diabetes Mellitus (T2DM) and the development of new therapeutic approaches, the management of T2DM patients is still suboptimum. **Objective:** The aim of the ADMIRE study was to evaluate the renal function (serum creatinine and estimated Glomerular Filtration Rate (eGFR)) of the patients who were receiving teneligliptin and metformin combination therapy for T2DM in a real-world setting. **Design/Settings/Participants:** This was a multicenter, real-world, observational, cohort study; conducted across 600 centers in India from July 2021 to September 2022. Patients aged ≥ 18 to ≤ 85 years with uncontrolled T2DM (HbA1c ≥7.0 %) and eGFR of 60 mL/min/1.73m^2 receiving combination therapy of teneligliptin and metformin as part of routine clinical practice were included in the trial. **Results:** Of the total 15,321 subjects enrolled in the study renal parameters were available for 1019 patients which were analyzed for the study objective (N=1019). At the end of six months, the mean eGFR improved by 13.54 mL/min/1.73m^2 (p - 0.0013). A significant reduction was observed in (mean) serum creatinine (by 0.6 mg/dl), FPG (by 36.77 mg/dL), PPG (by 66.79 mg/dL), HbA1c (by 1.07%). A total of 27.70% of the patients achieved an HbA1c value that was less than 7%. **Conclusion:** ADMIRE study showed that the introduction of combination therapy with metformin and teneligliptin significantly improves the renal profile and glycemic control in the Indian population with uncontrolled DM in real-world settings; demonstrating that it is safe and effective.

Keywords: Type 2 Diabetes Mellitus; Teneligliptin; Metformin; Renal; ADMIRE; Dual therapy

List of Abbreviations

ADA	:	American Diabetes Association	e-GFR	:	Estimates of Glomerular Filtration Rate
ADRs	:	Adverse Drug Reactions	FPG	:	Fasting Plasma Glucose
DM	:	Diabetes Mellitus	HbA1c	:	Glycated Hemoglobin
DPP-4	:	Dipeptidyl Peptidase-4 Inhibitor	OAD	:	Oral Antidiabetic Drug
			PPG	:	Postprandial Glucose
			SD	:	Standard Deviation
			T2DM	:	Type 2 Diabetes Mellitus

Introduction

India ranks second after China in the global diabetes epidemic with 77 million people with diabetes [1]. The "Asian Indian Phenotype" which refers to certain unique clinical and biochemical abnormalities in Indians including increased insulin resistance, makes Asian Indians more prone to diabetes and premature complications [2,3]. The VERIFY trial investigated the long-term clinical benefits of early combination treatment vs. the standard-of-care metformin monotherapy in newly diagnosed type 2 diabetes (T2DM) and reported that the early intervention with a combination therapy of vildagliptin plus metformin provided greater and durable long-term benefits compared with the current standard-of-care initial metformin monotherapy [4]. Also, per the latest guidelines for 'Standard of Cares in Diabetes-2023' by the American Diabetes Association® (ADA), for diabetes management 'pharmacologic approaches that provide the efficacy to achieve treatment goals should be considered, including combination therapy, that provide adequate efficacy to achieve and maintain treatment goals [5]. It recommends that 'early combination therapy can be considered in some individuals at treatment initiation to extend the time to treatment failure [5]. Diabetes is the most common cause of kidney failure, accounting for nearly 44 percent of new cases [6,2]. The natural history of diabetic kidney disease includes glomerular hyperfiltration, progressive albuminuria, declining Glomerular Filtration Rate (GFR), and ultimately, end-stage renal disease [7]. Per the 'Standard of Cares in Diabetes-2023' guidelines, in adults with T2DM and established/high risk of atherosclerotic cardiovascular disease, heart failure, and/or chronic kidney disease, the treatment regimen should include agents that reduce cardio-renal risk [5].

Teneligliptin is a novel DPP-4 inhibitor developed in Japan. 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 [8,9]. Hence, it is viewed as an important agent for controlling hyperglycemia in T2DM patients with renal impairment [8]. A post-marketing surveillance of more than 10,000 patients with T2DM receiving long-term teneligliptin in Japan reported, that the safety and efficacy of teneligliptin were maintained in patients with renal impairment and patients on dialysis [10]. A retrospective analysis by Chudasama DB, et al. showed a clinically significant decrease in HbA1c on combination therapy with teneligliptin and metformin [11].

However, there were no large-scale community-based studies conducted in the Indian population to examine the effects of combination therapy of teneligliptin and metformin on renal function in T2DM patients. The objective of our study was to evaluate the renal function of the patients who were receiving teneligliptin and metformin combination therapy for T2DM in a real-world setting.

Methods

This was a multicenter, real-world, observational, cohort study to evaluate the effect of teneligliptin and metformin therapy on eGFR and glycemic parameters. This study was conducted across 600 centers in India after receiving approval from Suraksha Ethics Committee. The study was conducted from July 2021 to September 2022. The participants were recruited after voluntary written informed consent.

Patients' data were included in the study based on the following selection criteria:

Inclusion criteria:

- Male or female patients, age ≥ 18 to ≤ 85 years.
- Uncontrolled T2DM with HbA1c ≥7.0 %
- eGFR (MDRD) at screening > 60 mL/min/1.73m^2
- Patients receiving Teneligliptin and Metformin combination therapy as part of routine clinical practice.

Exclusion criteria:

- Female patients who were pregnant or breastfeeding
- Patients with known liver or kidney dysfunction
- Patients suspected of or known to have an intolerance to Teneligliptin or Metformin.
- Presence of any other clinically significant disease or laboratory findings that in the Investigator's opinion could have affected the study outcomes or continued participation of the patient in the study.
- Participation in another study concurrently or within four weeks before the Screening Visit.

The study sites and study investigators were selected based on the site feasibility assessment. A total of 15,321 patients were enrolled in the study from 600 different sites across India. The diagnosis was based on a detailed history and clinical examination. As part of routine clinical practice patient follow-up was conducted at 3 months and 6 months. Prescriptions for individual patients were uploaded from each site into a web-based database by study investigators or site personnel and data from prescriptions were entered into electronic data collection form by qualified data entry personnel.

As part of the study procedures, the following data were collected from the prescriptions of the qualified patients by the study investigator and designated study site personnel.

1. Patient demographics such as age, weight, height, and comorbid health conditions

2. Patient vital signs such as blood pressure, pulse rate, body temperature, and respiratory rate

3. Laboratory investigation results which included renal function test (estimated glomerular filtration rate (eGFR)), glycated hemoglobin (HbA1c), fasting plasma glucose (FPG), and postprandial plasma glucose (PPG) Concomitant medication information.

4. Adverse event information.

Statistical Analysis

The continuous data like age, weight, etc., were summarized with n, mean, Standard Deviation (SD), range, and confidence intervals. The categorical data like sex etc., were depicted with count (%). The efficacy parameters such as a change in eGFR, HbA1c, FPG, and PPG were presented using descriptive statistics, and changes from baseline were evaluated. The number of patients achieving the HbA1c level of < 7% was summarized with count (%). The incidences of adverse events were also summarized with count (%). Other safety measures such as physical examination and vital signs were summarized using descriptive statistics and change from baseline.

Results

Of the total 15,321 subjects enrolled in the ADMIRE study, the renal parameters such as serum creatinine (Sr. Creatinine) and eGFR for the three-time points i.e., baseline, 1st follow-up (three months), 2nd follow-up (six months) were available for 1019 patients in this real-world study. Data for these 1019 subjects were analyzed further for the study objective, (N = 1019).

Of these 1019 patients, 380 (37.3%) were females. The mean age of the patient population was 52.91 ± 11.1 years. Demographics of the study population are presented in Table 1.

Parameter	Count (N=1019)
Gender	
Male	639 (62.7 %)
Female	380 (37.3 %)
Height (cm)	
Mean	164.93 ± 9.35
Weight (Kg)	
Mean	70.96 ± 12.17

Table 1: Demographics of the study population.

Renal Parameter (Sr. Creatinine and eGFR) Analysis:

For the analyzed 1019 study subjects, at baseline, the mean Sr.Creatinine (mg/dL) value was 0.92. It remained constant at 1st follow-up (3 months) but reduced to 0.86 at 2nd follow-up (6 months) [reduced by 0.6 mg/dL from the baseline, p-value - 0.0001]. Changes in the Sr.Creatinine levels are presented in Figure 1.

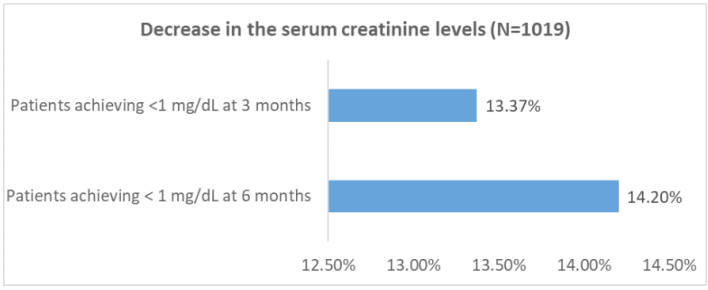

Figure 1: Changes in serum creatinine levels.

For the 1019 study subjects, the mean eGFR (mL/min/1.73m$^{2)}$ value at baseline was 88.34. It was 92.14 at 1st follow-up. The mean eGFR value improved to 101.88 at 2nd follow-up [improved by 13.54 from the baseline, p-value - 0.0013]. A comparison of the changes in renal parameters at each time point (Sr.Creatinine and eGFR) is presented in Figure 2.

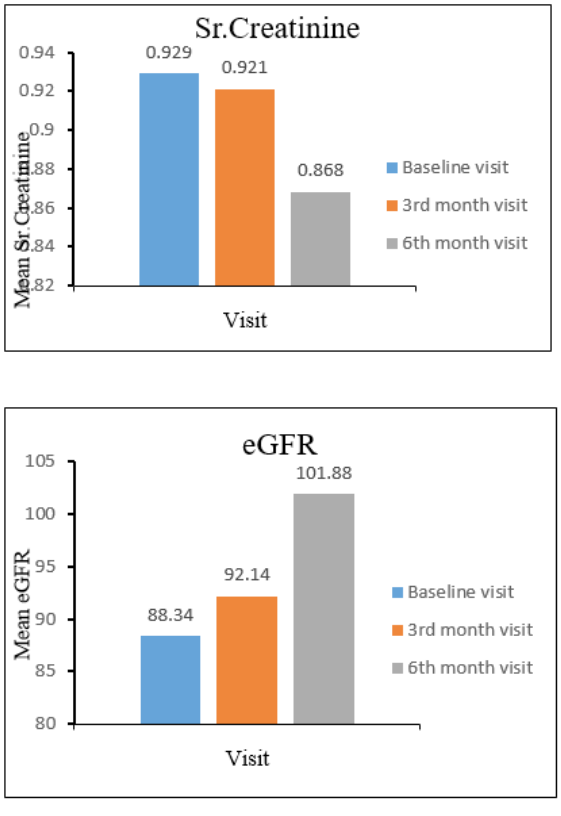

Figure 2: Changes in renal parameters (Sr. Creatinine and eGFR).

Glycemic parameter (FPG, PPG, HbA1C) Analysis:

For the 1019 study subjects, the mean FPG (mg/dL) value at baseline was 163.65. It reduced to 142.22 and 126.88, at 1st and 2nd follow-ups, respectively. At 2nd follow-up reduction in the mean FPG from the baseline was 36.77 [p-value - 0.0001].

The baseline mean PPG (mg/dL) value for the 1019 study subjects was 242.79. The mean PPG value reduced to 200.18 at 1st follow-up. At 2nd follow-up, the mean PPG value was reduced by 66.70 from the baseline to 176 [p-value - 0.0001].

The baseline mean HbA1c (%) value was 8.431 for the analyzed 1019 subjects. At 1st follow-up mean HbA1c value for this sub-set reduced to 7.78. At 2nd follow-up, it reduced to 7.36, the mean reduction from the baseline was by 1.07 [p-value - 0.0001].

Of the 1019 subjects, 130 (12.77%) achieved an HbA1c value of < 7% at 1st follow-up (3 months), and a total of 282 (27.7%) subjects achieved an HbA1c value of < 7% at 2nd follow-up.

A summary of changes in glycemic parameters (FBG, PPG, and HbA1c) at each time point are presented in Figure 3.

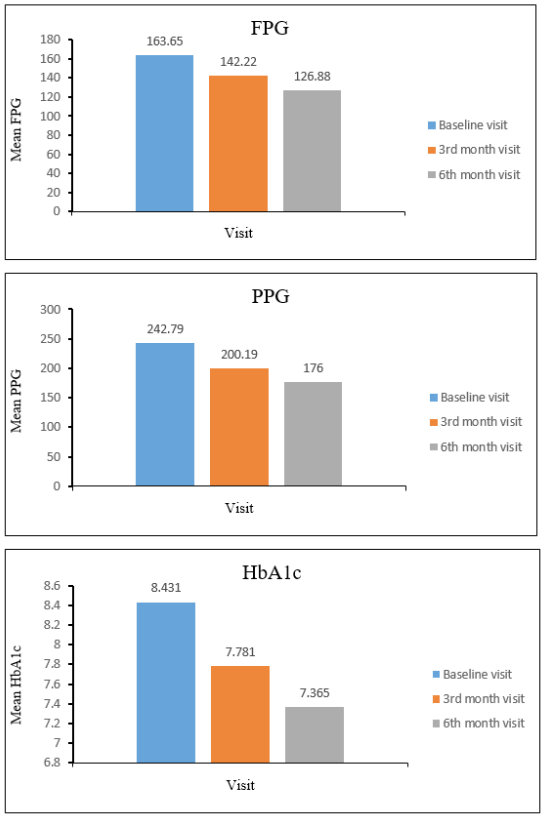

Figure 3: Changes in Glycemic parameters (FBG, PPG, HbA1c).

A summary of HbA1c distribution at baseline and changes at 2nd follow-up (6 months) are presented in Table 2.

HbA1c (%) Distribution	Baseline Visit (N= 1019)	At 2nd Follow-up Visit (N= 1019)
<7	0	282 (27.7%)
07-Sep	817 (80.17%)	712 (69.83%)
<9-10	122 (11.95%)	15 (1.43%)
>10	80 (7.88%)	10 (1.02%)

Table 2: A Summary of HbA1c distribution and changes at 2nd follow-up.

Discussion

The effectiveness of teneligliptin in the Indian population was first highlighted in the RWE study TREAT-INDIA (n=4305) conducted by Ghosh et al., in which teneligliptin as a monotherapy and add-on therapy was shown to significantly reduce HbA1c (overall reduction by 1.37±1.15%), FPG (overall reduction by 51.29±35.41mg/dl) and PPG (overall reduction by 80.89±54.27mg/dl).[12] Similar findings in the Indian population were reported by another real-world efficacy study conducted by Nashikkar et al [13].

A study by Ji L, et al. to evaluate the efficacy and safety of teneligliptin added to metformin in Chinese patients with T2DM mellitus inadequately controlled with metformin reported, that teneligliptin added to ongoing metformin treatment significantly decreased HbA1c and FPG levels compared with placebo, and the combination was safe and tolerable [14]. A study by Kim MK et al. similarly evaluated the efficacy and safety of combination therapy of teneligliptin with metformin in Korean T2DM with a 16-week, randomized, double-blind, placebo-controlled phase III trial [15]. It observed that the study arm on combination therapy of teneligliptin with metformin showed a decrease in HbA1C by 0.85%, and in FPG by 0.93mmol/L. It concluded that the combination therapy was well tolerated and effective [15].

Study findings by Ji L, et al. [14] and Kim MK et al. [14] concur with our study analysis, which reported a significant reduction in the mean values at six months from baseline, in HbA1C by 1.07% [p-value - 0.0001], FPG by 36.77 mg/dL [p-value - 0.0001], and PPG by 66.70 mg/dl [p-value - 0.0001] along with improvement in renal parameters (eGFR, Serum creatinine). At the end of our study, 282 (27.7%) subjects achieved HbA1c value of less than 7%.

A study by Lee M, et al. evaluated the effectiveness and safety of teneligliptin added to patients with T2DM inadequately controlled by oral antidiabetic drug(OAD) triple combination

therapy of metformin, sulphonylurea, and sodium-glucose co-transporter-2 inhibitor, and reported that teneligliptin could be a valid option as a fourth OAD for the treatment of patients with T2D inadequately controlled with a triple combination of OADs [16].

Recent guidelines for DM management by ADA recommend the use of early combination therapy to provide adequate efficacy to achieve and maintain treatment goals and extend the time to treatment failure [5]. In the 'ADMIRE' study, we observed significant improvement in renal profile with an increase in Sr. Creatinine and eGFR values and also a statistically significant reduction in the glycemic parameters (FPG, PPG, and HbA1c) of the patients receiving combination therapy of Teneligliptin and Metformin for T2DM.

Conclusion

ADMIRE study showed that the introduction of combination therapy with metformin and teneligliptin significantly improves both renal and glycemic profiles in the Indian population with uncontrolled T2DM in real-world settings. This demonstrates that combination therapy with metformin and teneligliptin is safe and effective in the Indian population.

Trial Registration number: CTRI/2021/07/034834

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