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Review Article

Internal Medicine Section

Teneligliptin in Management of Diabetic Kidney Disease: A Review of Place in Therapy

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ABSTRACT

Diabetes is a global health emergency of this century. Diabetic nephropathy is the most common microvascular complication associated with Type 2 Diabetes Mellitus (T2DM). T2DM has been reported as a major etiological factor in almost 45% of patients undergoing dialysis due to kidney failure. Lifestyle modifications; cessation of smoking, optimum control of blood glucose, blood pressure and lipids are required to reduce the progression of Diabetic Kidney Disease (DKD). Presently, Dipeptidyl peptidase-4 (DPP-4) inhibitors are preferred in the management of T2DM due to their established efficacy; favorable tolerability including, low risk of hypoglycaemia; weight neutrality and convenient once-a-day dosage. Present evidence suggests that linagliptin and teneligliptin can be used safely without dose adjustments in patients with T2DM with renal impairment, including End Stage Renal Disease (ESRD). There is a limited data about teneligliptin particularly in T2DM patients with renal impairment. The objective of this review is to evaluate efficacy and safety of teneligliptin in T2DM patients with renal impairment, in order to assess the current place in therapy and future prospects of teneligliptin. Reported evidence suggests that teneligliptin has consistent pharmacokinetic in mild, moderate, severe or ESRD, without any need for dose adjustments. Limited data from small sample studies of teneligliptin in DKD patients reported significant improvements in glycaemic parameters. Additionally, there is an improvement in kidney parameters like glycated albumin, urinary albumin and eGFR. There is an evidence of reduction in biomarkers of kidney impairment like P-selectin (sP-selectin), Platelet-Derived Microparticles (PDMPs) and Plasminogen Activator Inhibitor 1 (PAI-1). Clinical significance of these will be known in near future. Thus, teneligliptin has an important place of therapy in the management of T2DM with renal impairment.

Keywords: Diabetes mellitus, Dipeptidyl peptidase-4 inhibitor, Renal impairment

INTRODUCTION

Diabetes Mellitus (DM)

Epidemiology

One of the largest global health emergencies of the 21st century, diabetes, inflicts more and more people every year. The prevalence of diabetes mellitus in India has soared alarmingly high over the past four decades. Evidently, International Diabetes Federation (IDF) in 2015 reported India as the territory with second highest number of adults with diabetes, 69.2 million, behind China [1]. The number of people with diabetes in India has been estimated to reach 123.5 million by 2040 [1]. In addition to the high number of adults who are currently estimated to have diabetes, 36.5 million adults in India have been reported to be suffering from Impaired Glucose Tolerance (IGT) [1]. IGT subjects the individuals to a high risk of developing the diabetes mellitus in the near future. In its recent report, IDF projected 63.6 million Indians with IGT by 2040. Surprisingly, India spent less than 3% of the global total (Int'l $ 23 billion) expenditure on diabetes [1].

Complications

In 2015, globally, around five million people aged between 20 years and 79 years died due to diabetes; accounting for one death every six seconds [2]. The microvasculature complications include nephropathy, neuropathy, retinopathy, while macrovascular complications including Myocardial Infarction (MI), stroke and Peripheral Vascular Disease (PVD). The underlying mechanisms proposed in the pathogenesis of diabetic complications include oxidative stress created by the overproduction of Reactive Oxygen Species (ROS) and defects in the insulin signal transduction pathway [3]. The UK Prospective Diabetes Study (UKPDS) found a 37% decrease in microvascular disease and a 14% reduction in MI by every 1% reduction in glycated haemoglobin (HbA1c) [4]. In people with T2DM, a 10-year follow up study reported lower rates of MI (relative reduction- 33%, p=0.005) and diabetes related death (relative reduction- 21%, p=0.01) with maintenance of good glycaemic control [5].

Diabetic Kidney Disease (DKD)

Epidemiology

Diabetic nephropathy is one of the most common microvascular complications of T2DM. It has been the major aetiological factor of kidney failure in nearly 45% of patients undergoing dialysis [6,7]. Published data from the US population reported nearly 15–23% of diabetic patients with moderate to severe CKD having a potential to progress to ESRD [8]. Results from a recent multicenter observational study in Indian T2DM patients reported presence of CKD in about 46% of the patients (eGFR<60 ml/min/1.73 m^2) [9].

Diagnostic and Intensive Treatment Strategies for DKD

Screening of patients with T2DM for DKD should begin at initial diagnosis and should be performed regularly. At least once a year, assessment of urinary albumin, serum creatinine and eGFR in all patients with or without comorbid hypertension should be exercised [10]. There may be absence of elevations in urine albumin initially in some CKD patients, hence, both blood and urine screening tests are necessary [11].

The emergence of CKD in patients with T2DM complicates the life-long management of diabetes with increased risk of morbidity and mortality. Reduction in GFR with the progression of nephropathy limits the pharmacological options available for achieving optimal glycaemic control. This may further result into higher probabilities of initiation of insulin therapy [9]. A number of interventions have been demonstrated to reduce the risk and slow the progression of DKD.

A meta-analysis of seven trials (UKPDS 33, UKPDS 34, VA Diabetes Feasibility Trial, ACCORD, ADVANCE, VADT, Kumamoto study) in T2DM patients reported reduced risk of developing microalbuminuria and macroalbuminuria with intensive glucose control [12]. Landmark trials like ACCORD, ADVANCE and VADT showed that lower HbA1c levels were associated with reduced onset or progression of microvascular complications [13]. However, the effect of lowering mean HbA1c is much less with regards to macrovascular disease. Thus, lowering HbA1c leads to benefit with regards to nephropathy [11]. [Table/Fig-1] shows HbA1c targets recommended by major guidelines for T2DM patients with CKD [11,13,14].

An Overview of Challenges with Available Oral Anti-Diabetic Agents

Selection of glucose lowering agents should be based on patient's glycaemic goal, age, hepatic function, nephropathy, postprandial excursion, etc., that impose limitations on treatment, as well as the attributes and adverse effects of each regimen. Limitations of different available oral anti-diabetic agents have been enlisted in [Table/Fig-2].

DPP-4 INHIBITORS IN MANAGEMENT OF DKD

A major consideration is whether newer therapies, including, DPP-4-inhibitors, Glucagon-like peptide-1 receptor agonists (GLP-1 RA), and Sodium-glucose co-transporter 2 (SGLT2) inhibitors can also be used safely and effectively across the spectrum of renal impairment. DPP-4 inhibitors are novel oral treatment agents for T2DM that provide important reduction in glycated haemoglobin, possessing a low risk for hypoglycaemia and without weight gain [2]. The glucose lowering effect of DPP-4 inhibitors in T2DM patients with CKD is similar to that seen in patients without CKD. Also, DPP-4 inhibitors have been reported to reduce the levels of glycated albumin, which is a better indicator of glycaemic control than glycated haemoglobin, without hypoglycaemia in patients with ESRD undergoing dialysis [2]. Furthermore, literature suggests protective action of DPP-4 inhibitors on kidneys due to reduction in the incidence of albuminuria [15]. The possible nephroprotective properties of DPP-4 inhibitors may be postulated to be due to reduction of oxidative stress and inflammation and improvement of endothelial dysfunction. Effects of DPP-4 inhibitors may be both Glucagon-like peptide-1 (GLP-1) dependent and independent [16].

Guideline	Target HbA1c for T2DM with CKD
Kidney Disease Outcomes Quality Initiative (KDOQI), 2012 [11]	7%
American Diabetes Association (ADA), 2017 [13]	< 8%
American Association Of Clinical Endocrinologists and American College of Endocrinology (AACE/ACE), 2016 [14]	7 to 8%

[Table/Fig-1]: HbA1c targets recommended by major guidelines for T2DM patients with CKD.

Teneligliptin: Newer Addition in the Management of DKD

Teneligliptin: Favourable Pharmacokinetics in DKD

Teneligliptin, a novel DPP-4 inhibitor developed in Japan and recently available in some countries, has a unique structure and binds to S1, S2, and S2 extensive subsite of DPP-4 enzyme leading to enhanced potency and selectivity. It is a Class 3 DPP-4 inhibitor, along with sitagliptin. Additional binding to S2 extensive site apart from S1 and S2 sites imparts stronger inhibitory action on DPP-4 enzyme with teneligliptin. Moreover, teneligliptin has been reported to have fivefold higher activity than sitagliptin due to J-shaped anchor-lock domain, strong covalent bonds with DPP-4 and more extensive S2 extensive binding than sitagliptin [2]. In humans, teneligliptin is primarily metabolized by Cytochrome P450 (CYP) 3A4 and Flavin Mono Oxygenases (FMO) [17]. Approximately, 34% of administered dose of teneligliptin is excreted unchanged via the renal route, while 66% is metabolized and eliminated via., the hepatic and renal routes [2].

Halabi A et al., evaluated the pharmacokinetics of teneligliptin in renally impaired and healthy subjects. The grades of renal impairment ranged from mild to end stage. The study reported that maximum plasma concentration (C_{max}) following a single oral dose of 20 mg teneligliptin was unaffected by mild, moderate and severe renal impairment. An increase in Area under curve ($AUC_{0-\infty}$) was observed in all groups relative to the reference group, without any relation to the magnitude of renal impairment. In subjects with ESRD (post-dialysis), both C_{max} and AUC_{0-43} of teneligliptin were higher than that in matched healthy subjects. An important outcome of the study was <80% plasma protein binding in subjects with renal impairment and ESRD. This observation matched the FDA guidelines that states-for drugs with a relatively low extent of plasma protein binding (<80%) alterations in protein binding due to impaired renal functions are likely to be small in relative terms [18]. The results of the study confirmed that no dose adjustment may be needed with teneligliptin, irrespective of renal impairment, ESRD or dialysis [19].

Teneligliptin: Efficacy and Tolerability in DKD

A prospective study assessed the utility of teneligliptin in patients undergoing Haemodialysis (HD). In the group which had patients newly started/switched from other medications to teneligliptin, a reduction of 36.7 mg/dL in blood glucose level was noted at four weeks. Also, a significant difference existed between teneligliptin treated patients and those who continued with other anti-diabetic therapies, with respect to glycated albumin (-3.1%, p<0.05, 28 weeks) and HbA1c (-0.57%, p= 0.057, 24 weeks). The perception of glycated albumin level, as a reliable marker for monitoring glycaemic control in ESRD patients with diabetes, strengthened the results of this study even more. Also, C-peptide level was reported to have increased significantly post teneligliptin treatment. Thus, teneligliptin may be regarded as an agent that promotes insulin secretion from pancreas and contributes to better glycaemic control

Category	Limitation in DKD
Metformin	Cannot be used if eGFR<30 ml/min/1.73 m^2
Sulfonylureas	Increased risk of hypoglycaemia, if eGFR<60 ml/min/1.73 m^2
Meglitinide and D-phenylalanine derivative	The active metabolite of nateglinide accumulates in CKD; should not be used with an eGFR<60 ml/min/1.73 m^2. Exercise caution with repaglinide in those with more severe renal dysfunction (eGFR<30 ml/min/1.73 m^2), start at the lowest dose (0.5 mg)
Thiazolidinediones	Fluid retention is a major limiting side effect, limiting their use in CKD, particularly patients on dialysis
Alpha-glucosidase inhibitors	Serum levels of acarbose and metabolites increase significantly, with compromised renal functioning Miglitol not recommended if eGFR<25 ml/min/1.73 m^2
Dipeptidyl peptidase-4 inhibitors (DPP4-i)	Dose adjustment needed with a reduced eGFR
Sodium-glucose co-transporter 2 (SGLT2) inhibitors	Canagliflozin should be avoided if, eGFR<45 ml/min/1.73 m^2 Dapagliflozin is not approved for use if eGFR is <60 ml/min/1.73 m^2

[Table/Fig-2]: Limitations of oral anti-diabetic agents in DKD [11].

in diabetic patients with ESRD. No incidences of hypoglycaemia were reported [20].

An open label, single arm trial in diabetic patients (n=10) undergoing HD assessed the variation in efficacy of teneligliptin relative to HD. Teneligliptin was reported to cause an improvement in blood glucose AUC in patients during HD as well as non HD days (p=0.004). Significant reduction in glycated albumin, HbA1c and fasting plasma glucose was reported. No cases of severe hypoglycaemia were observed [21].

Teneligliptin: In Comparison to other DPP4 inhibitors

Teneligliptin was studied against linagliptin in a randomized crossover trial to measure the efficacy of glycaemic control in T2DM patients with CKD (n=13). Baseline HbA1c was <9 % with eGFRs<60 ml/min 1.73 m^2. After exposure to either of the DPP4 inhibitors for a period of six days, patients were switched to the other agent for the next six days. Continuous glucose monitoring revealed no significant difference between linagliptin (83.8±34.0 mg/dL) and teneligliptin (82.6±32.6 mg/dL), for the changes in Mean Amplitude of Glucose Excursions (MAGE). Thus, the researchers of the study concluded, linagliptin and teneligliptin have comparable effects on MAGE in T2DM patients with CKD and are potentially useful and safe for treatment of such patients [22].

Sagara M et al., compared the efficacy of teneligliptin and sitagliptin on oxidative stress and endothelial function in T2DM patients with CKD. Reactive hyperaemia peripheral arterial tonometry was used to assess peripheral endothelial function. Endothelial dysfunction was defined as Reactive Hyperaemia Index (RHI) <0.670. T2DM patients with CKD (n=45) receiving sitagliptin for at least 12 months were randomized to receive either teneligliptin (n=22) or ongoing therapy of sitagliptin (n = 23) for 24 weeks. Results of the study concluded teneligliptin to be equivalent, if not superior, to sitagliptin for reported changes in HbA1c, eGFR, or urinary albumin excretion levels. Only teneligliptin, of the two interventions, significantly improved reactive hyperaemia index values (1.49±0.32 to 1.55±0.29, p<0.01), reduced levels of 8-hydroxy-2'-deoxyguanosine, an oxidative stress marker (7.1±4.9 to 5.4±2.9 ng/m Cre, p<0.05) and reduced urinary liver type fatty acid binding protein (L-FABP) (p<0.05). Improvements in urinary L-FABP levels have been associated with positive outcomes for patients at high risk for renal disease and Atherosclerotic Cardiovascular Disease (ASCVD), in published literature [23].

Teneligliptin: Effect on Useful Biomarkers of DKD

PDMPs plays a role in the pathogenesis of vascular complications in patients with T2DM. Diabetes is also characterized by increased expression of Cell Adhesion Molecules (CAM), elevation of PAI-1,

Study design/ Number of patients/ Duration of study	Study groups	Effect on HbA1c/ blood glucose level	Remarks
Open label, parallel group, six-armed study; n=48; 3 days [19]	• Mild impairment (estimated creatinine clearance- ≥50 to ≤80 ml/min) (n=8) • Moderate impairment (estimated creatinine clearance- ≥30 to ≤50 ml/min) (n=8) • Severe renal impairment (estimated creatinine clearance- <30 ml/min) (n=8) • ESRD (Receiving dialysis for >3 months before dosing) (n=8) • 2 healthy control groups (estimated creatinine clearance- >80 ml/min) (n=16)	• NA (Pharmacokinetic study)	• Dose adjustment may not be needed with teneligliptin in renally impaired or ESRD subjects
Bi-center, prospective, non-randomized study; n=43; 28 weeks [20]	• Teneligliptin group (Teneligliptin 20 mg OD; n= 14) • Control group (Continued ongoing antidiabetic therapy; n = 29)	• The difference in HbA1c between the teneligliptin group and the control group was -0.57 % (p = 0.057) • Blood glucose level showed a 36.7 mg/dl decrease from four weeks in the teneligliptin group (p<0.05). • The difference in GA (at 28 w) between the teneligliptin group and the control group was -3.1 % (p<0.05)	• Teneligliptin is a significantly effective and well tolerated therapy in T2DM patients with ESRD
Open label, single arm, intervention trial; n= 10; 4 weeks [21]	• Teneligliptin 20 mg/day	• Significant reduction in GA (p=0.001), HbA1c (p=0.001) and FPG (0.001) without severe hypoglycaemia.	• Improvement was reported in blood glucose AUC on both HD days (p=0.004), and NHD days (p=0.004)
Randomized crossover study; n=13; 17 days [22]	• Group A- Teneligliptin 20 mg/day for six days from hospital day 5 and then switched to linagliptin 5 mg/day on hospital day 11 for six days. • Group B- Linagliptin 5 mg/day for six days from hospital day 5 and then switched to teneligliptin 20 mg/day on hospital day 11 for six days	Changes in MAGE: • Linagliptin- 83.8 ± 34.0 • Teneligliptin- 82.6 + 32.6, p=0.807	• Teneligliptin and linagliptin have comparable effects on MAGE in T2DM patients with CKD
Open label, prospective, randomized study; n=45; 24 weeks [23]	• Sitagliptin (50-100 mg/day, n=23) • Teneligliptin (20 mg/day, n=22)	• No significant differences in changes of HbA1c, eGFR, or urinary albumin excretion levels between the two groups (p=non significant)	• Only teneligliptin significantly improved RHI values, percent changes in RHI and d-ROMs. • Teneligliptin may reduce renal and vascular oxidative stress in T2DM patients with CKD
Open label, single arm, intervention trial; n=103; 6 months [24]	• Teneligliptin 20 mg/day	• Significant reduction in plasma levels of sP-selectin, PDMPs, and PAI-1 (p<0.05 after 3 months and p<0.01 after 6 months, for all three parameters) compared with baseline levels. • Plasma levels of adiponectin were significantly increased (p<0.05 after 3 months and p<0.01 after 6 months)	• Results for sP-selectin, PDMPs, and PAI-1 were more significant in HD patients than in NHD patients
Randomized, double blind, placebo controlled, parallel group study; n=324; 12 weeks [25]	• Teneligliptin 10 mg/day (n=84) • Teneligliptin 20 mg/day (n=79) • Teneligliptin 40 mg/day (n=81) • Placebo (n=80)	• Significantly greater reductions in HbA1c (p<0.001) and FPG (p<0.001) with teneligliptin	• Lower incidences of proteinuria in teneligliptin 20 mg (2.5%, n= 2/79) and 40 mg group (2.5%, n=2/81) as compared to the placebo group (5%, n= 4/80)

[Table/Fig-3]: Summary of clinical studies with teneligliptin in study population with renal impairment.

increased serum levels of sP-selectin, sE-selectin, and soluble Vascular Adhesion Molecule 1 (sVCAM-1). A research with an objective to study the effect of teneligliptin on these CVD-related biomarkers was undertaken by Okuda Y et al. HD and non-HD patients with T2DM (n=103) received either teneligliptin monotherapy or combination therapy (e.g., teneligliptin plus a sulfonylurea) for six months. Treatment with teneligliptin significantly reduced plasma levels of sP-selectin, PDMPs, and PAI-1 compared with baseline levels. Plasma levels of adiponectin were significantly increased. Teneligliptin demonstrated significant reduction in sE-selectin and sVCAM-1 levels, after six months of treatment. Importantly, the results for sP-selectin, PDMPs, and PAI-1 were more significant in HD patients than in non HD patients. Teneligliptin induced increase in adiponectin may also have an antiplatelet effect by enhancing NO production. It was concluded that teneligliptin has anti-atherothrombotic effect, a beneficial characteristic in the primary prevention of CVD in patients with T2DM on HD [24].

In a randomized placebo controlled study, T2DM patients (n=324) were randomized to receive teneligliptin 10, 20 or 40 mg, or placebo, once daily before breakfast for 12 weeks. Teneligliptin at a dose of 20 mg and 40 mg was found to be associated with fewer incidences of proteinuria (2.5%, n= 2/79 and 2.5%, n=2/81, respectively) as compared to the placebo group (5%, n= 4/80). However, the study did not establish any significance [25]. [Table/Fig-3] summarizes the clinical studies available with teneligliptin in T2DM patients with renal impairment and healthy volunteers.

SUMMARY

The rapid rise of diabetes in India has been reported in published literature. Diabetes has emerged as a major aetiological factor of kidney failure in nearly 45% of patients undergoing dialysis. This makes it necessary to individualize glycaemic control, to reduce complications, in a safe and effective manner. We intended to review all the published clinical data to evaluate the usage of teneligliptin in T2DM patients with renal impairment.

Teneligliptin, due to dual mode of excretion, offers a notable advantage of clinical use in renally impaired T2DM patients without dose adjustment. Clinical studies have reported results in favour of teneligliptin, as a monotherapy and in combination with other oral antihyperglycaemics, for T2DM with DKD.

In reported literature, teneligliptin has shown to exhibit stable pharmacokinetic parameters irrespective of grades of renal impairment. This gives teneligliptin an advantage over other DPP4 that; mean plasma concentrations of teneligliptin for healthy volunteers and those with varying degree of renal impairment were almost identical. Teneligliptin was shown to cause significant reduction in glycated albumin, HbA1c and fasting plasma glucose, however, small sample size of all studies is a limiting factor. On a scale of superiority, teneligliptin proved to be a non inferior anti-hyperglycaemic as compared to other DPP4 inhibitors like sitagliptin and linagliptin in DKD in terms of reduction in HbA1c, fasting blood glucose level, glycated albumin levels and biomarkers.

Though, the results of reported studies yield positive remarks for the usage of teneligliptin in T2DM patients with renal impairment, large clinical data is needed.

CONCLUSION

By the virtue of, DPP4 receptor occupation at S2 extensive subsite, dual mode of excretion and positive results in all the clinical data reported so far, teneligliptin is being viewed as an important agent for controlling hyperglycaemia in T2DM patients with renal impairment. More studies in this area may bring forward stronger implications for teneligliptin.

ABBREVIATIONS

n- number of patients; NA- Not applicable; ESRD- End stage renal disease; HbA1c- glycated haemoglobin level; OD- once daily; GA- glycated albumin; FPG- fasting plasma glucose; HD- haemodialysis; NHD- non-haemodialysis; MAGE- mean amplitude of glucose excursions; eGFR- estimated glomerular filtration rate; RHI- reactive hyperaemia index; dROMS- reactive oxygen metabolites test; T2DM- type 2 diabetes mellitus; CKD- chronic kidney disease; PDMP- platelet-derived microparticles; PAI-1- plasminogen activator inhibitor 1.

Conflict of Interest: Mr. Preetesh A. Mishra and Dr. Onkar C Swami are full time employees of Unichem Laboratories Limited, which actively markets teneligliptin. The other authors report no conflicts of interest in this work.

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