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Review Article

Renal safety profile of di-peptidyl-peptidase inhibitors: a review of available literature

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ABSTRACT

Diabetic Nephropathy has become the single most import cause of End Stage Renal Disease (ESRD). Various strategies to limit or slow the progress the Diabetic nephropathy are suggested by the guidelines and evidences. By maintaining strict glycemic control the progression of diabetic nephropathy can be altered. Glycemic control in diabetic patients with nephropathy is complex as falling eGFR renders many ant diabetic medications contraindicated while others are needed to be done in low dose. The intent of this review article is to collate the available evidences for renal safety with one such anti diabetic class of medication, dipeptidyl peptidase 4 inhibitor and evaluate the guideline based antidiabetic treatment in Type 2 Diabetes Mellitus patients with renal insufficiency.

Keywords: DPP4 inhibitor, Diabetic Kidney Disease, Linagliptin, Saxagliptin, Sitagliptin, Vildagliptin

INTRODUCTION

Despite better awareness and new developments in treatment of type 1 and Type 2 diabetes and in prevention of type 2 diabetes, there is an unrelenting increase in the number of people with diabetes. One in 15 adults is estimated to have impaired glucose tolerance, and one in seven births is affected by gestational diabetes. Both of these conditions are associated with an increased risk of developing type 2 diabetes in later life.[1]

Diabetic nephropathy has become the single most important cause of end-stage renal disease (ESRD) worldwide. Diabetic nephropathy affects approximately 20-40 % of individuals who have diabetes.[2]

Strategies to slow the rate of loss of renal function in these patients remain area of research interest. Annual screening for micro-albuminuria is critical since it may lead to early identification of nephropathy. Increasing evidence demonstrates that the onset and course of diabetic nephropathy may significantly be altered by several interventions like strict glucose control, use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARBs), all of which, if started early may have significant impact on progression of nephropathy.

Higher risk of macrovascular and microvascular complications is associated with chronically uncontrolled hyperglycemia.[3] Altered renal function is almost always associated with diabetes during the course of the disease.

Therapy of a diabetic patient needs to be re-evaluated if the estimated glomerular filtration rate (eGFR) falls below 60 ml/min rendering some oral anti diabetic drugs contraindicated, while most may need dose adjustment.[4] Rapidly growing population of diabetic nephropathy patients, makes awareness regarding the safe use of oral hypoglycemic agents in such patients, of significant importance.

The Intent of this review article is to collate the available evidences for renal safety with dipeptidyl peptidase 4 inhibitors (DPP4i) and evaluate the guideline- based anti-diabetic treatment in Type 2 diabetes mellitus (T2DM) patients with renal insufficiency.

METHODS

Pubmed database searches were conducted during October- November 2016 to retrieve articles to the safety profile of di-peptidyl peptidase inhibitors in chronic kidney disease. Search words included, "DPP4i in chronic kidney disease", "Sitagliptin/ Linagliptin/ Vildagliptin/ Saxagliptin in Chronic kidney disease/ renal impairment" and "Renal excretion of DPP4i". Journal articles were retrieved from diverse studies of DPP4i in renal impairment/chronic kidney disease. A total of 51 articles were retrieved and 42 were included for this review.

We did not search for literature on alogliptin or other DPP4 inhibitors as only four of the included DPP4 inhibitors are currently available in India while others are unavailable for use to intended readers.

Challenges in management of Diabetic patients with renal insufficiency

Blood glucose control in those with chronic Kidney disease (CKD) adds another level of complexity. Though challenging, glycemic control is essential to delay the onset of complications from diabetes. Detailed knowledge of medications that can be safely used and how renal impairment affects metabolism of these medications, is essential for effective management of T2DM patients with CKD.

Kidney disease outcome quality initiative (KDOQI) guidelines for Diabetes 2012 guidelines recommend an A1c of ~7.0 %.[5] It was shown that intensive treatment did result in a significant decrease in the development of estimated eGFR levels of <60 ml/min/1.73 m^2 in a long-term follow-up study of the original Diabetes Control and Complications Trial (DCCT) treatment groups (long-term effects of intensive vs conventional diabetes treatment on kidney function).[6]

Severity of a patient's kidney dysfunction dictates the management of diabetes in T2DM patients with CKD. This includes the methods that are used to determine the adequacy of diabetes control, such as hemoglobin A1c

(A1C), the potential complications and cautions regarding oral hyperglycemic therapies, and the variable response to insulin therapy as kidney dysfunction progresses.

Additionally, management of comorbid conditions, such as hypertension and hyperlipidemia, and evaluation for the development of conditions associated with CKD, such as anemia, hyperphosphatemia, and hyperparathyroidism, must also be considered in the care of patients with diabetes and CKD.

ANTI-DIABETIC THERAPIES IN RENAL IMPAIRMENT

Although all available insulin preparations can be used in patients with CKD, and there is no specified advised reduction in dosing for patients on insulin, about 30 to 80% of insulin removal is through kidneys. Prolonged insulin half-life is associated with reduced kidney function and decrease in insulin requirements as GFR declines.[7]

Though metformin is the initial choice in the treatment of Type 2 DM owing to its pleiotropic effects and excellent safety profile, widespread use in patients with impaired kidney function is not very desirable at least in advanced chronic kidney disease (CKD) stages due to an increased risk of lactic acidosis.[8,9] FDA does not recommend metformin to be used with serum creatinine ≥1.5mg/dl and ≥1.4mg/dl in males and females respective.

Since metformin is cleared by the kidney, to reduce the risk of lactic acidosis in individuals with even modest renal impairment, metformin should be used judiciously.[10] Similarly excretion of sulphonylurea metabolites are through renal clearance, leading to an increased risk of hypoglycemia as glomerular filtration rate (GFR) declines. Risk of hypoglycemia is significant with glimepiride and glyburide as eGFR falls below 60 ml/min/1.73 m^2.[11] A cohort of 33,243 sulfonylurea users chosen from 719 clinical practices in the United Kingdom showed that the rate of diagnosis of hypoglycemia made by physicians is higher for glibenclamide than for other sulfonylureas.[12]

Nateglinide can be used in those undergoing dialysis as active metabolite is cleared by hemodialysis but in patients not on hemodialysis the active metabolite of nateglinide accumulates with low GFR, hence nateglinide should not be used with an eGFR <60 ml/min/1.73 m^2.[13] Repaglinide appears safe to use in individuals with CKD.[14] However, it is reasonable to exercise caution in those with more severe renal dysfunction, such as an eGFR <30 ml/min/1.73 m^2.

SGLT2 inhibitors increase glucose excretion in urine which results in reduction in A1c of about 0.9-1.0%.[15] Canagliflozin should not be used in excess of 100mg/day in patients with an eGFR of 45 to <60 ml/min/1.73m^2 as it

causes intravascular volume contraction. Its use should be avoided if the eGFR is <45 ml/min/1.73 m^2 because of an increase in adverse events as well as reduced efficacy. Dapagliflozin is not approved for use if the eGFR is <60 ml/min/1.73 m^2. Empagliflozin may be used down to an eGFR of 45 ml/min/1.73 m^2. Cost, however remains a major drawback for the SGLT2 inhibitor therapy.

DPP4I IN MANAGEMENT OF DIABETIC PATIENTS WITH RENAL INSUFFICIENCY

All available DPP-4 inhibitors are highly selective, oral formulations approved as treatment for Type 2 Diabetes mellitus (T2DM) either as mono-therapy, add-on or initial combinatorial therapy with other glucose-lowering agents.

Unlike peroxisome proliferator-activated receptor (PPAR) alpha/gamma agonists, DPP-4 inhibitors do not display the water and salt retention.[16]

Table 1: Nice guidelines recommendation on metformin use in patients with impaired renal function.

Nice Guidelines state that:
Start metformin treatment in a person who is overweight or obese (tailoring the assessment of body-weight-associated risk according to ethnic group) and whose blood glucose is inadequately controlled by lifestyle interventions (nutrition and exercise) alone
Metformin should be considered as an option for first-line glucose-lowering therapy for a person who is not overweight
Metformin should be continued if blood glucose control remains or becomes inadequate and another oral glucose-lowering medication is added
The dose of metformin should be stepped up gradually over weeks to minimize risk of gastro-intestinal (GI) side effects. Consider a trial of extended-absorption metformin tablets where GI tolerability prevents continuation of metformin therapy
In adults with type 2 diabetes, review the dose of metformin if the estimated glomerular filtration rate (eGFR) is below 45 ml/minute/1.73m^2:
Stop metformin if the eGFR is below 30 ml/minute/1.73m^2
Prescribe metformin with caution for those at risk of a sudden deterioration in kidney function and those at risk of eGFR falling below 45ml/minute/1.73m^2
Benefits of metformin therapy should be discussed with a person with mild to moderate liver dysfunction or cardiac impairment so that:
Due consideration can be given to the cardiovascular-protective effects of the drug
An informed decision can be made on whether to continue or stop the metformin

Table 2: Pk/Pd parameters of the available DPP4i.

	Sitagliptin	Saxagliptin	Vildagliptin	Linagliptin
Dose	100mg OD	5mg OD	50 mg BD	5mg OD
Half-life ($t_{1/2}$) h	12.4	2.2-3.8	1.3-2.4	12.5-21.1
Elimination	Kidneys (Mostly Unchanged)	Liver and Kidneys	Kidneys >> Liver Inactive Metabolite	Bile (Mostly unchanged)
Dose adjustment in renal Impairment	Yes	Yes	Not for mild impairment	No
Selectivity for DPP4	>2600 fold than DPP8	>400 fold than DPP8	>90 folds than DPP8	>10000 fold than DPP8
Potential for drug-drug Interaction*	Low	High (Cyp3A4/5 inducers/ inhibitors)	Low	Low
Food effect	No	No	No	No

Table 3: Dose adjustment according to chronic kidney disease stages (CKD stages as described by National Kidney foundation).

DPP4i	CKD Stage				
	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Sitagliptin	No Change		If eGFR >50 ml/min No change, If GFR< 50 ml/min 50 mg OD	25mg OD	
Vildagliptin	No Change		50mg OD		
Saxagliptin	No change		2.5mg OD	Contraindicated	
Linagliptin	No change				
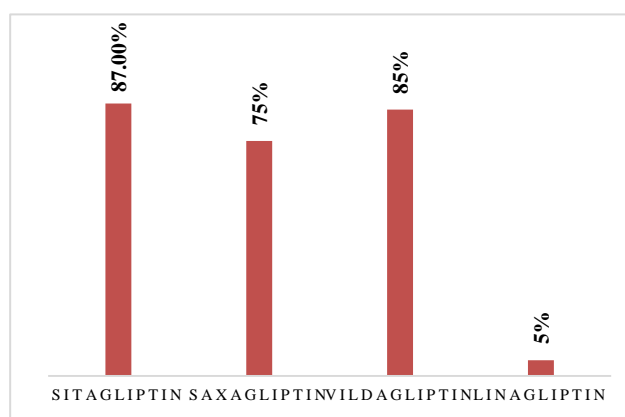
Figure 1: Renal excretion of DPP4i.

Table 4: Data for stage 5 from USRDS include approximately 230,000 patients treated by dialysis, and assume 70,000 additional patients not on dialysis.

Stages and prevalence of chronic kidney disease				
Stage	Description	GFR (mL/min/1.73m2)	Prevalence*	
	At increased risk	≥ 90 (with CKD risk factors)	N(1000s)	%
1	Kidney damage with normal or ↑GFR	≥ 90	5,900	3.3
2	Kidney damage with mild ↓ GFR	60-89	5,300	3
3	Moderate ↓ GFR	30-59	7,600	4.3
4	Severe ↓ GFR	15-29	400	0.2
5	Kidney Failure	<15 (or dialysis)	300	0.1

GFR estimated from serum creatinine using MDRD Study equation based on age, gender, race and calibration for serum creatinine. For stages 1 and 2, kidney damage estimated by spot albumin-to-creatinine ratio >17mg/g in men or >25mg/g in women on two measurements

A potential nephron-protective effect of DPP-4 inhibitors has been revealed by the studies assessing the attenuation of renal dysfunction in an ischemia-reperfusion injury model and remnant kidneys.[17] Same mechanism may well be associated with inhibition of apoptosis and inflammation and increased antioxidant production.

Although a large number of trials have assessed the proteinuria-lowering effect of DPP-4 inhibitors, only a few have investigated the effect of these agents on renal function, particularly in individuals at an early stage of renal impairment.[18]

SITAGLIPTIN

Sitagliptin is an oral, once-daily, dipeptidyl peptidase-4 inhibitor indicated for the treatment of type 2 diabetes. Sitagliptin is cleared primarily by the kidney, with 80% of an oral dose excreted unchanged in the urine.[19,20] Renal clearance was found to be around 350 ml/min in an open label study pharmacokinetic profile of sitagliptin in 30 patients categorized according to creatinine clearance, suggesting active secretion as well as filtration is responsible for the its renal excretion.

The same analysis found that increases in sitagliptin $AUC_{0-\infty}$ were 2.3- fold higher for moderate RI (renal impairment) patients, 3.8-fold higher for severe RI and 4.5-fold higher for patients with ESRD. C_{max} was moderately increased, and C_{24} increased as renal function decreased. Patients with ESRD showed significantly increased T_{max}, and the terminal $t_{1/2}$ increased in relation with declining kidney function. Renal clearance of sitagliptin was found to be in proportion with creatinine clearance.[21]

Results from various trials suggest the safety of sitagliptin use in CKD with appropriate dose adjustments and that hypoglycemia rates were significantly less when compared with sulfonylureas.[22]

SAXAGLIPTIN

SAVOR-TIMI 53, a double blind placebo controlled trial to assess the cardiovascular safety and efficacy of saxagliptin, did not include patients with a history of end-stage renal disease (ESRD), on long-term dialysis, renal transplantation, or a serum creatinine level of >6.0 mg/dL.[23]

Boulton et al showed that compared with healthy subjects, the geometric mean area under the plasma concentration-time curve (AUC_∞) for saxagliptin was 16% higher for mild, 41% higher for moderate and 108% (2.1-fold) higher for severe renal impairment, respectively.[24] Similarly the AUC_∞ values for 5-hydroxy saxagliptin ranged from 67% to 347% (4.5-fold) higher in subjects with mild, to severe renal impairment, respectively. With decrease in creatinine clearance (CL_{CR}) values, saxagliptin and 5-hydroxy saxagliptin (active metabolite) AUC_∞ increased or became more variable. A little less than quarter of saxagliptin dose (sum of saxagliptin and 5-hydroxy saxagliptin) was cleared by haemodialysis over 4-hour dialysis session.

VILDAGLIPTIN

Vildagliptin is approved for the maximum daily dose of 100 mg (as 50 mg twice-daily) either as a monotherapy or in a fixed dose combination with metformin for the treatment of T2DM.[25-28] Unlike competitive and dose dependent DPP-4 inhibition as seen with sitagliptin,

vildagliptin demonstrates different enzyme kinetics termed as 'substrate blocker'.[29]

Oral absorption of vildagliptin occurs within 3 hours and the drug is rapidly and extensively metabolized, most likely in the liver. Although the excretion of Vildagliptin is through liver, cytochrome enzymes do not appear to be involved in drug metabolism.[30] Approximately 25% of the oral dose is excreted unchanged in the urine.[30,31]

In a double-blind, randomized, parallel-group, 52-week clinical trial with 369 patient of T2DM and moderate or severe Renal impairment for comparing safety and efficacy of vildagliptin (50mg qd, n=216) and placebo (n=153) when added to ongoing stable antihyperglycaemic treatment, Kothny et al demonstrated that vildagliptin in addition to on going anti-hyperglycemic therapy had a safety profile similar to placebo during 1-year observation with a clinically significant and consistent decrease in A1C throughout 1-year with vildagliptin treatment.[32]

In a 12 week retrospective analysis, GALvus In Addition to metformin versus thiazolidinediones (TZD)/ metformin in T2DM (GALIANT) the overall incidence of AEs in patients with mild renal impairment were comparable to those reported in subjects with normal renal function (37.8% vs 40.1%). Discontinuation due to AEs was comparable for patients with normal renal function and those with mild renal impairment.[33]

Lukashevich et al. large, multicenter, randomized, double-blind, placebo-controlled study undertaken to assess safety, tolerability, and efficacy of vildagliptin added to current anti-diabetic therapy in 515 T2DM patients (Most patients on insulin treatment) with moderate (CrCl 30 to 50 mL/min/1.73 m^2) or severe (CrCl 30 mL/min/1.73 m^2) renal impairment.[34]

The study population consisted 294 patients with moderate renal failure (vildagliptin n=165; Placebo= 129) and 221 patients with severe renal failure (vildagliptin n=124; Placebo n=97). After 24 weeks of treatment, the between-treatment difference in adjusted change in HbA1c was -0.5%±0.1% (P, 0.0001) in subjects with moderately impaired (baseline HbA1c 7.9%) and-0.6%±0.1% (P, 0.0001) in patients with severely impaired renal function (baseline HbA1c 7.7%).

Compared to placebo, vildagliptin, when added to ongoing anti-diabetic drugs, elicited a significant decrease in HbA1c in patients with moderate or severe renal impairment, and a safety profile comparable to placebo in both subgroups.[34]

Presented evidences suggests that in T2DM patients, with moderate or severe renal failure, vildagliptin, by increasing availability of incretin hormones (GLP-1 and GIP), maintains a non-inferior efficacy to the one observed in subjects with normal renal function and long term HbA1c reduction of 0.6%-0.8% along with a favourable safety profile in term of bodyweight neutrality and low risk of hypoglycemic events.[35,38,40]

LINAGLIPTIN

The majority (~80%) of Linagliptin dose is excreted via the entero-hepatic system with only ~5% of its overall elimination dependent on kidneys.[36]

In a pooled analysis, Groop et al showed that the presence of mild/ moderate renal impairment had no clinically significant impact on the efficacy and safety of linagliptin in subjects with T2DM. In subjects with T2DM and severe renal impairment, 5 mg dose was tolerated with an acceptable safety profile and, when added to existing background therapy, achieved a placebo-corrected reduction in HbA1c of 0.72% during 52 weeks of treatment.[37]

A double-blind, placebo-controlled designed to investigate the long-term safety, tolerability, and efficacy of linagliptin exclusively in patients with type 2 diabetes and severe renal impairment showed that the addition 5mg of linagliptin once daily to ongoing glucose-lowering therapy provides a clinically significant HbA1c reduction after 12 weeks and maintained over 52 weeks with a safety and tolerability profile similar to placebo in this patient population.

Also Linagliptin was associated with low risk of severe hypoglycemia, stable body weight.[38]

Owing to the fact that only a small fraction of the drug is excreted by urine, current evidences point to little or no dose change in mild to moderate renal impairment.[39]

DISCUSSION

Kidneys are commonly involved as part of the end organ damage in type 2 diabetes mellitus (T2DM) patients as hyperglycemia and hypertension in these patients contribute significantly towards the renal failure and End Stage Renal Disease (ESRD). Attenuation of disease or slowing of progression is possible by intensive management blood pressure and blood glucose. However, many patients will still develop diabetic nephropathy. The combination of diabetes and CKD is particularly significant in regards to CVD risk, necessitating aggressive control of risk factors.[40]

Attentions to several aspects are mandated while managing the patients of T2DM with CKD. Glycemic control is of high importance in these patients and should be optimized in a safe and monitored manner, to reduce complications. Regular screening for development of nephropathy should be performed to identify micro-albuminuria or reductions in GFR, if identified; management shall include individualized anti-diabetic treatment.

Considering the common association between T2DM and impaired renal function new alternative to existent treatment are needed urgently. Achieving glycemic and overall metabolic control pharmacologically becomes difficult once renal function begins to deteriorate as many anti diabetic drugs are rendered contraindicated.

Since actions of Dipeptidyl peptidase 4 inhibitors (DPP4i) are glucose dependent they do not increase the risk of hypoglycemia and are weight neutral. Incretin hormones, released from the small gut after meals stimulates insulin secretion from the pancreas. DPP4i inhibits the inactivation of incretin hormones such as GLP-1. DPP 4 inhibitors do not display the water and salt retention as seen with peroxisome proliferator activated receptor (PPAR) gamma agonists.

The action of DPP 4 inhibitors is based on inhibition of type 1 glucagon like peptide (GLP-1), which has beneficial renal and cardiac actions beyond those on glucose homeostasis. But, there are other peptide hormones that themselves are substrates of DPP 4, with direct cardio-renal effects. Pancreas GLP-1, mainly via the GLP1-R, has direct effects on the heart, vessels and kidney. In fact there are substrates of DPP-4 other than incretins with proven renal and cardiovascular implications like BNP/ANP, NPY, PYY or SDF-1a. Preclinical evidence shows that DPP-4 inhibitors may not only be beneficial in settings of acute renal failure and chronic kidney diseases such as diabetic nephropathy, but also in cardiac diseases such as myocardial infarction and heart failure.

The only DPP-4 inhibitor that is not excreted by the kidney and may not need dose adjustment at any degree of declining kidney function is Linagliptin. Apparent normalization in markers of oxidative stress and inflammation seen in animal studies during 12 weeks of treatment with vildagliptin, no or minimal influence on blood pressure and proven cardiac safety may list Vildagliptin as an effective alternate choice amongst other renal excreted DPP4i for T2DM patients with mild to moderate renal failure.[41,42]

To explore the potential of DPP-4 inhibitors for treatment of T2DM patients with acute kidney failure, chronic kidney failure and acute myocardial infarction as well as heart failure, further adequately powered clinical phase 3 and 4 trials aiming to demonstrate clinically meaningful benefits - and safety - are warranted.

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