Renal safety of newer medications

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Abstract

Over the last 10 years there has been a seismic change in the therapeutic options available to clinicians in managing patients with type 2 diabetes. Three different classes of drugs – the DPP-4 inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors – as well as new insulins such as degludec have added to the repertoire of the diabetologist. However, one concern still remains and limits the management of the patient with diabetes: renal impairment. Many of the options for managing patients with type 2 diabetes, though generally safe in mild to moderate renal impairment, are restricted or ineffective in severe renal impairment.

This article will aim to focus on and discuss the current newer medications, their renal safety and dosing, as well as the implications of use in patients with renal impairment.

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Key words
renal; safety; DPP-4 inhibitors; GLP-1 receptor agonists; SGLT-2 inhibitors

Introduction

Diabetes and renal disease are well known to be related. It has been estimated that 30% of patients with type 1 diabetes and up to 40% of patients with type 2 diabetes will suffer from renal impairment. Both contribute to cardiovascular disease risk and diabetes is also the main cause of end stage renal disease (ESRD) requiring dialysis.

Hyperglycaemia will increase the risk of patients developing renal impairment via both microvascular (diabetic nephropathy) and macrovascular complications (renovascular disease). Both DCCT and UKPDS showed us that tight glycaemic control results in lesser progression to diabetic nephropathy. Intensive glucose control resulted in a 39% reduction in microalbuminuria and a 54% reduction in macroalbuminuria in those with an average HbA1c of 7.9% vs 9.2% in the DCCT study, and a relative risk of 0.76 in patients with HbA1c 7% vs 7.9% in UKPDS. Thus, it becomes important to choose and initiate the appropriate therapeutic agent that reduces the burden of hyperglycaemia at the appropriate time. Hypertension can be either a cause or an effect of renal disease and therefore, in addition to hyperglycaemia management in the diabetic patient, blood pressure is also of paramount importance. Persistent systemic high blood pressure results in pressure on the renal vasculature resulting in barotrauma and hence renal disease.

With the variety of novel therapeutic agents on offer, the prescriber must be clear regarding the efficacy, safety and tolerability of each available option in the setting of renal impairment to make the most informed and beneficial choice for their patients.

DPP-4 Inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors augment insulin uptake and utilisation by inhibiting endogenous DPP-4 to prolong the effects of endogenous incretin hormones. This in turn promotes insulin secretion and glucagon inhibition and reduces gastrectric emptying. The majority of DPP-4 inhibitors are excreted via the kidneys, except for linagliptin which undergoes biliary glucuronidation. DPP-4 inhibitors, though similar in their glucose lowering effect, vary in their pharmacodynamic and pharmacokinetic properties that have implications for prescribing in patients with renal impairment.

In terms of renal safety, these medications have been a useful addition to the management of patients with renal impairment as all of them are safe to use in renal impairment. All except for linagliptin need to be adjusted according to glomerular filtration rate (GFR). (See Table 1.) Renal-specific trials of each DPP-4 inhibitor are discussed below.

Sitagliptin

Sitagliptin was the first DPP-4 inhibitor on the market and is mostly
eliminated (87%) via the renal system, involving tubular secretion; the remainder is via the gastrointestinal (GI) tract.

A 54-week safety and efficacy trial by Chan et al. found a 0.7% reduction in HbA1c with lower hypoglycaemia rate in patients with all stages of chronic kidney disease (CKD) (including ESRD on dialysis) with sitagliptin. These findings were further confirmed by a more recent study which concluded that sitagliptin at a reduced dose (50mg once daily in moderate renal impairment [eGFR 30–50ml/min/1.73m²] and 25mg once daily in severe renal impairment [eGFR <30ml/min/1.73m²]) was safe, well tolerated and weight neutral in patients with all stages of CKD.

**Saxagliptin**

Saxagliptin is eliminated via hepatic and renal pathways with 75% renally excreted and 22% excreted via biliary or GI tract. Renal sub-analysis of the Saxagliptin Assessment of Vascular Outcomes Recorded (SAVOR) study analysed patients with varying degrees of renal impairment (GFR >50, 30–50 and <30ml/min/1.73m²) and found that at a median duration of two years, irrespective of renal function, primary and secondary cardiovascular outcomes were neither increased nor decreased (p=0.19). They also found no difference in reduction of urine microalbumin excretion compared to the general population (p=0.041).

A 52-week randomised controlled trial (RCT) looking at saxagliptin in patients with creatinine clearance <50 or ESRD found that saxagliptin had continued efficacy in terms of HbA1c reduction (mean HbA1c difference -0.73%, p<0.001) and was well tolerated in these groups. Adjusted mean HbA1c reduction in the moderate renal impairment group compared to placebo was -0.94% vs -0.19%, and -0.81% vs -0.49% in severe vs placebo. In those with ESRD, mean change was similar vs placebo (-1.13% vs -0.99%).

Saxagliptin remains well tolerated in all stages of renal impairment; however, dose reduction to 2.5mg once daily is advised at GFR <50ml/min/1.73m² due to the higher accumulation of product at lower levels.

**Vildagliptin**

The majority of vildagliptin is hydrolysed by tissue with a small amount excreted unchanged; 85% is excreted via the kidneys with the remaining excreted via hydrolysis in tissue. Lukashevich et al. assessed the tolerability and efficacy of vildagliptin at half dose (50mg once daily) in moderate to severe renal impairment (GFR <50ml/min/1.73m²) and found that there was efficacious HbA1c reduction with no difference in adverse effects (including severe hypoglycaemia) or tolerability vs placebo.

Safety in ESRD including haemodialysis has also been assessed with notable improvement in HbA1c and good tolerability, and therefore vildagliptin is recommended in patients with all stages of renal impairment, though dosing is reduced to 50mg once daily when GFR is <50ml/min/1.73m². A study looking at 107 patients with diabetic nephropathy (based on albuminuria and GFR) found that, in patients with early nephropathy (presence of microalbuminuria), vildagliptin reduced urinary albumin concentrations; however, the numbers in this study make it difficult to ascertain the relevance in a clinical setting. Another small observation study conducted on 47 patients with type 2 diabetes found a reduction of urine albumin to creatinine ratio (ACR) by 44.6% at eight weeks with 50mg twice daily of vildagliptin.

**Linagliptin**

Linagliptin remains the only DPP-4 inhibitor in clinical use predominantly eliminated via the hepatobiliary system. Only 5% is removed unmetabolised via the kidney. A recent study by McGill et al. assessed the use of linagliptin as add-on vs placebo to patients with severe renal impairment (GFR <30) on pre-existing glycaemic therapy (oral agents or insulin). This RCT found sustained HbA1c improvement at one year (adjusted mean HbA1c reduction 0.71%) with fewer insulin units used, fewer adverse effects and no change to renal function.

Linagliptin has also been found to reduce albuminuria in patients with type 2 diabetes and renal impairment independent of changes in blood pressure (systolic) or HbA1c at 24 weeks. The study found that linagliptin resulted in a 31% and 30% reduction in urinary ACR vs placebo regardless of whether the patients had a systolic blood pressure <137.4mmHg or >137.4mmHg, respectively. However, the implications of whether this is beneficial or not will be addressed by the

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</tr>
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Table 1. Recommendations for DPP-4 inhibitors and renal impairment
MARLINA-T2D trial which is a phase III trial of linitaglutin in patients with type 2 diabetes and albuminuria; it was completed in December 2015 and the results are awaited.21

Alogliptin

Alogliptin is the newest DPP-4 inhibitor to the market and is mostly excreted unchanged in urine (60–71%); the remainder is via the GI tract.22 Data on alogliptin use in renal impairment are not robust due to small numbers; however, plasma concentrations of the medication increase at various stages of renal impairment hence the need to down titrate the dosing based on renal function (see Table 1). A small study by Sakai et al.23 assessed the effects of alogliptin in 36 patients with CKD (defined as eGFR <60ml/min/1.73m² or microalbuminuria >30mg/gCr) at six months and, despite not noticing any improvement in HbA1c, found no change in GFR, with a possible improvement in urinary ACR (not statistically significant).

Thus, in conclusion, DPP-4 inhibitors remain a safe, effective and well-tolerated medication in patients with all stages of CKD provided dose adjustments are made according to GFR (see Table 1). However, long-term data on albuminuria and implications for renal disease/diabetic nephropathy are still awaited.

GLP-1 receptor agonists

The next generation of therapeutic agents, the GLP-1 receptor agonists (GLP-1 RAs), made a significant contribution in the management of diabetes due to both glycaemic and weight improvement. However, one of the main limitations with their unrestricted use are their limitations in severe renal impairment; they are licensed for an eGFR >30ml/min/1.73m².

Exenatide’s safety and tolerability have been assessed in patients with all stages of renal impairment and it was found to be well tolerated in mild (mild 51–80ml/min as per Cockcroft-Gault creatinine clearance [CrCl]) to moderate (CrCl 31–50ml/min) renal failure. However, even at a reduced dose, side effects were intolerable and pharmacokinetics varied, making it ill-advised in patients with severe or end stage kidney disease.25

A number of case reports have noted instances of acute renal impairment in patients taking exenatide. In many cases, patients were noted to have concomitant dehydration and were on medications that could affect renal function, though not always the case.26,27 A case series by Weise et al. noted four patients who presented with acute renal impairment due to exenatide with renal biopsy showing ischaemic glomeruli. They concluded that exenatide itself was not directly nephrotoxic and postulated the causative mechanism was contraction of extracellular fluid which, together with other medication affecting the renin-angiotensin-aldosterone system, contributed to reduction in GFR. They also suggested that there was a natriuretic effect which may contribute to dehydration.28

There are limited data on exenatide use and diabetic nephropathy in human subjects. Zhang et al.29 looked at 31 patients with type 2 diabetes on exenatide vs glimepiride and noted significant improvements in 24-hour urinary albumin excretion in those patients on exenatide. Again, due to small numbers the relevance of these findings remains to be seen.

Liraglutide

The next GLP-1 RA to market was liraglutide, which is degraded in the body via proteolytic mechanisms and differs from exenatide in that it is not predominantly eliminated via the kidneys.

Liraglutide has recently been approved for use above a GFR of 30ml/min/1.73m². The LIRA-RENAL trial30 assessed patients with GFR 30–59 with liraglutide 1.8mg vs placebo as add-on to current therapy at 26 weeks. They found HbA1c reduction (1.05% vs 0.38%) with associated weight loss and fewer hypoglycaemic episodes. There were, however, higher GI side effects and drop outs in the liraglutide group as well as higher amylase levels – though it was not clear whether this was of clinical significance. Overall, liraglutide was tolerated with no change in renal function at the study end. A recent ABCD nationwide audit31 assessed liraglutide 1.2mg use in mild to moderate renal impairment in standard UK-based clinical practice and found that it was safe as well as efficacious; however, it had higher GI side effects in patients with mild or moderate impairment compared to those with normal renal function. Data were insufficient to analyse in moderate renal impairment.

Compared to exenatide, there are fewer cases of liraglutide-induced acute kidney injury, possibly due to its lack of renal excretion; however, the potential for dehydration due to GI side effects is present. The authors could find only one report by Kaakeh et al.32 which noted acute tubular necrosis in keeping with dehydration secondary to liraglutide use.

Lixisenatide

Lixisenatide is a peptide and eliminated via the kidneys through glomerular filtration, tubular resorption and proteolytic degradation.33 It is well tolerated in mild renal impairment (GFR 60–89) to moderate renal impairment (GFR 30–59); however, concentration increases with moderate renal impairment.34 There are limited data in severe renal impairment and ESRD, therefore it is not recommended with a GFR <30.35 A meta-analysis of trials from the GetGoal studies with lixisenatide based on GFR found no difference between clinical endpoints in patients with normal renal function (HbA1c, postprandial and fasting glucose levels) vs impairment, though noted higher side effects in patients with mild renal impairment.34,36

Dulaglutide

Dulaglutide is the most recent GLP-1 RA to market; it is a once-weekly preparation and is degraded in the body by general protein catabolism pathways. It is currently recommended for use in mild to moderate renal impairment (GFR >30); however, pharmacological studies have found pharmacokinetics to be similar.
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GLP-1 receptor agonist | Renal recommendation dosing (eGFR in ml/min/1.73m²) | HbA1c reduction in renal impairment (RI)
---|---|---
Exenatide BD | eGFR >50: 10µg BD  
            eGFR 30–50: use with caution 10µg BD  
            eGFR <30: avoid | Pooled analysis, no clear data
Exenatide modified release | eGFR >50: 2mg QW  
                                      eGFR <50: avoid | Pooled analysis, no clear data
Liraglutide | eGFR >30: 1.2–1.8mg OD  
                   eGFR <30: avoid | -0.66% in moderate RI  
                                      (eGFR 30–59)
Lixisenatide | eGFR >50: 20µg OD  
                     eGFR 30–50: use with caution 20µg OD  
                     eGFR <30: avoid | Pooled analysis, no clear data
Dulaglutide | eGFR >30: 0.75mg or 1.5mg QW  
                      eGFR <30: avoid | Pooled analysis, no clear data

Table 2. Recommendations for GLP-1 receptor agonists and renal impairment

SGLT-2 inhibitor | Renal recommendation dosing (eGFR in ml/min/1.73m²) | HbA1c reduction in renal impairment (RI)
---|---|---
Dapagliflozin | eGFR >60: 10mg OD  
                 eGFR <60: avoid | -0.75% vs 0.67% (placebo) in moderate RI  
                                   (eGFR 30–60)
Canagliflozin | eGFR >60: 100mg or 300mg OD  
                   eGFR 45–60: do not initiate. If already initiated when GFR was >60 reduce dose to 100mg OD  
                    eGFR <45: avoid | -0.33% and -0.44%  
                                   (100mg and 300mg) vs 0.03% (placebo) in moderate RI  
                                   (eGFR 30–50)
Empagliflozin | eGFR >60: 10mg or 25mg OD  
                  eGFR 45–60: reduce dose to 10mg OD  
                   eGFR <45: avoid | -0.37% vs +0.05% (placebo) in moderate RI  
                                   (eGFR >30 to <60)

Table 3. Recommendations for SGLT-2 inhibitors and renal impairment

in patients with mild to severe renal impairment (including dialysis) compared with healthy subjects. The lack of clinical data appears to be the main reason for lack of recommendation with GFR <30; however, there is a phase III study ongoing looking at the use of dulaglutide in patients with type 2 diabetes and moderate to severe renal impairment.

Overall, GLP-1 RAs, despite their clinical efficacy from a glycaemic and weight point of view, have limited use in patients with renal impairment below a GFR of 30, with all contraindicated (Table 2). The tolerance of these medications even in mild renal impairment also may limit their use in patients with CKD.

**SGLT-2 inhibitors**

The most recent class of medications available to clinicians are again limited by renal disease. These medications act on the sodium glucose co-transporter 2 (SGLT-2) receptors found predominantly in the proximal tubule of the kidneys to prevent glucose resorption.

Dapagliflozin

Dapagliflozin is currently licensed for a GFR >60ml/min/1.73m², with both canagliflozin and empagliflozin licensed for a GFR of >45ml/min/1.73m² (though both can only be initiated if GFR is above 60ml/min/1.73m²).

Kohan et al. assessed dapagliflozin 5mg and 10mg doses in moderate renal impairment (eGFR 30–60ml/min/1.73m²) over a 24-week period and, though it was found to be well tolerated, they were unable to show efficacy in terms of HbA1c improvement. They found a non-significant reduction in HbA1c of 0.41% and 0.44% with dapagliflozin 5mg and 10mg vs -0.32% for placebo, though weight loss was significant with dapagliflozin.

Canagliflozin

Canagliflozin was assessed for efficacy and safety in a 26-week trial in patients with GFR 30–50 using 100mg and 300mg doses. The study found HbA1c improvement (-0.33% and -0.44%) as well as a 2–3mmHg improvement in blood pressure in patients taking canagliflozin.

Empagliflozin

Empagliflozin 25mg was assessed in patients with a GFR of 30–60ml/min/1.73m² vs placebo in 374 patients; sustained efficacy (HbA1c -0.37%, -1.17kg weight) and tolerability with empagliflozin were found in such patients. Empagliflozin 50mg, though not available for clinical practice, has also been assessed for all stages of renal impairment with no safety and tolerability concerns; however, being a small study and not looking at clinical efficacy, it is unclear whether this translates into clinical practice suggestions.

One interesting aspect of these medications is the thought that they may be able to reduce albuminuria and hence reduce progression of diabetic nephropathy. This may be in part from the glucose lowering and blood pressure lowering effects; however, other mechanisms, which are still unclear, may also be a reason.

This aspect is being further assessed in Evaluation of the Effects of Canagliflozin on Renal and Cardiovascular Outcomes in Participants with Diabetic Nephropathy (CREDEnCEnE), which is a large RCT assessing the effects of canagliflozin 100mg vs placebo in patients with stage 2 or 3 CKD and macroalbuminuria, with results due in 2019.

SGLT-2 inhibitors therefore provide an interesting medication in...
patients with diabetes. Although their use and efficacy are limited in moderate renal impairment (Table 3), it is their theoretical (and currently investigated) benefit to delay renal disease through their glycaemic, weight, blood pressure and renal filtration effects that make future studies imperative for this class of anti-glycaemic agents.**

**Degludec**

Up until recently, the majority of innovations were occurring in non-insulin therapy. However, this changed with the development of insulin degludec: an ultra-long acting insulin with a flatter baseline than that of other long-acting insulins. It has been assessed in all stages of renal impairment including dialysis dependence, with pharmacokinetic studies showing no need for dose adjustment, similar efficacy to non-renally impaired and good tolerability (only one episode of confirmed hypoglycaemia in a patient with ESRD and no severe hypoglycaemic episodes).**

The recent combination therapy of degludec with liraglutide, iDegLira, has been approved for use in patients with type 2 diabetes; data on use in renal impairment specifically are limited (however, data on its individual components are as mentioned earlier in this article). It is not recommended in patients with moderate to severe renal impairment (GFR <30ml/min/1.73m²) including ESRD.

**Mechanism of medications on albuminuria**

The above-mentioned medications are all beneficial in reducing nephropathy in patients with diabetes via their effect on glycaemic improvement. However, in addition to this effect, there may be other specific benefits. Studies have shown that DPP-4 inhibitors may reduce albuminuria in patients with type 2 diabetes independent of HbA1c reduction. A study on linagliptin has shown a 33% reduction in urinary ACR compared to placebo, and a prospective study with sitagliptin, when added on to sulfonylureas, found a reduction in albuminuria from 76.2±95.6 to 33±41.8mg/g.** Similar effects may or may not be GLP-1 dependent.

GLP-1 RAs have also been shown to reduce albuminuria. Imamura et al. assessed liraglutide in 23 patients with overt diabetic nephropathy on renin-angiotensin blockers and noted a reduction in proteinuria from 2.53±0.48g/g creatinine to 1.47±0.28g/g creatinine (p=0.002). In addition, liraglutide also substantially reduced the rate of decline in eGFR from 6.6±1.5ml/min/1.73m²/year to 0.3±1.9ml/min/1.73m²/year (p=0.003).** Similar improvements have been noted in reducing proteinuria in patients with type 2 diabetes on exenatide. In normoalbuminuric patients, 11.3% developed microalbuminuria or macroalbuminuria vs 20% in those not on exenatide.** The possible mechanisms include reduction in oxidative stress and inflammation with improvement in endothelial function in the kidney (most likely GLP-1 mediated).

SGLT2 inhibitors offer more interest in their effects on the kidneys. Canagliflozin 100mg and 300mg have been found to reduce albuminuria in patients to a greater extent than placebo. A 29.9% and 20.9% reduction in urine ACR was found compared to -7.5% in placebo and it was also noted that the rate of progression of albuminuria was reduced in the canagliflozin group.** Further, dapagliflozin has been found to reduce albuminuria in addition to renin-angiotensin system blockage, and empagliflozin has recently been assessed in 458 patients with pre-existing microalbuminuria 30–300mg/g. Empagliflozin 10mg and 25mg significantly reduced urine ACR by 30% and 25% vs placebo at 24 weeks (p<0.01).**

It is thought the combination of glycaemic improvement, blood pressure reduction and weight loss may offer some added benefits on renal protection; however, specific effects on the renal tubules may have more relevance. Proposed mechanisms include: reduced glomerular hyperfiltration via reduction in proximal tubule sodium resorption leading to reduced sodium delivery thereby reducing intraglomerular pressure; activation of the renin-angiotensin system; reduction in tubular hypertrophy; and reduction in glucose toxicity in the tubules.

The paucity of well-designed clinical trials in this area means that currently there is still a lot to be learned regarding the renal effects of these medications and should hopefully be addressed with upcoming clinical trials (Table 4).

**Conclusion**

Despite the recent advancements in therapeutic options available for the management of diabetes, there are still limited treatment options in patients with severe renal impairment, besides insulin. Of the newer medications only DPP-4 inhibitors have use in all stages of renal impairment though recently liraglutide, lixisenatide, exenatide BD and dulaglutide are now being deemed safe above a GFR of 30. Clinicians must be aware of the restrictions in the setting of renal impairment when using these medications, particularly as the incidence of renal impairment is increasing with the ageing population.

Future medications that are effective in all stages of renal impairment, especially in severe impairment and end stage renal disease/dialysis, would be a valuable addition to the management of patients with type 2 diabetes.
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Key points

- Renal impairment is common in patients with diabetes, and clinicians need to actively review renal function when considering medication choices.
- Newer medications have various restrictions with regard to use in renal impairment. DPP-4 inhibitors are licensed in all stages of renal impairment, GLP-1 receptor agonists are licensed in mild to moderate renal impairment and SGLT-2 inhibitors are licensed for initiation in mild renal impairment, with some further restrictions within each depending on the design.
- Future clinical trials looking specifically at renal outcomes, changes in albuminuria and nephropathy with these newer medications may provide further evidence for their use.

Declaration of interests

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