Utility of antidiabetes medications in chronic kidney disease: A review

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Article points

1. Many antidiabetes agents are contraindicated or require dose reductions in people with chronic kidney disease.
2. Selecting the most appropriate agents reduces the risk of microvascular complications and may prevent further kidney impairment and improve quality of life.
3. Frequent monitoring of kidney function will help in adjusting therapy as needed to provide the best regimen.

Key words

- Antidiabetes agents
- Chronic kidney disease

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There is a large body of evidence describing the utility of antidiabetes agents in people with chronic kidney disease (CKD). Clinical decisions should take into account the pharmacokinetic variability and potential adverse events seen when these agents are used in renally impaired patients. In this article, the authors review the literature and summarise which antidiabetes agents are safe, with dose reductions if necessary, in people with CKD.

Careful selection of antidiabetes agents in people with varying degrees of chronic kidney disease (CKD) is a necessity. Owing to the high incidence of renal impairment in people with diabetes, it is crucial to continually monitor kidney function and adjust medication doses in accordance with the degree of renal impairment. Along with careful selection of medications, monitoring of blood glucose as well as kidney function should be ongoing.

This literature review was conducted to explore the utility of antidiabetes agents in people with varying degrees of renal impairment. A number of trials of individual antidiabetes agents have been published. In each of these, the impact of impaired renal function was considered. The results of these trials have been analysed and used to determine which agents can be used in people with decreased renal function, and at what dose.

Literature review

DPP-4 inhibitors

Dipeptidyl peptidase-4 (DPP-4) inhibitors increase endogenous exposure to native glucagon-like peptide-1 (GLP-1) through inhibition of the enzyme responsible for its degradation, DPP-4. They have a low risk of hypoglycaemia and other side effects, and they have a neutral effect on weight. Owing to their extensive renal clearance, dose adjustments may be required.

Sitagliptin is cleared significantly more slowly as renal impairment increases. Compared with people with no renal impairment, the area under the curve (AUC) for plasma concentrations was almost two times higher in people with mild renal impairment, and 3.8 times higher in those with severe impairment (Bergman et al, 2007). Sitagliptin's Summary of Product Characteristics (SPC) recommends decreasing the dose from 100 mg daily to 50 mg daily if creatinine clearance (CrCl) rates are <50 mL/min, and to 25 mg daily if rates are <30 mL/min.

Saxagliptin is metabolised via cytochrome P450 enzymes to an active metabolite that is, in turn, eliminated renally. The effect of this additional active metabolite was noted in a phase 3 study (Nowicki et al, 2011). A significant reduction in HbA_{1c} compared with placebo was seen in all patient groups, with a greater reduction in participants with moderate and severe renal impairment compared to those with normal function. Minimal accumulation of the parent drug was seen compared to the metabolite, which had increased trough levels with increased severity of baseline renal impairment. Owing to these findings and the presence of an active metabolite that is excreted primarily by the kidneys,

the SPC recommends a reduction in the daily dose from 5.0 mg to 2.5 mg in people with CrCl rates ≤50 mL/min.

Alogliptin was found to have similar drug accumulation to sitagliptin in people with renal impairment (Davis, 2014). It maintains its efficacy in terms of reducing HbA_{1c} (Sakai et al, 2014), but the SPC recommends reducing the daily dose to 12.5 mg in people with CrCl rates of 30–50 mL/min, and to 6.25 mg in those with CrCl rates <30 mL/min.

Vildagliptin also maintains its efficacy in people with renal impairment (Lukashevich et al, 2011); however, owing to the drug's renal clearance, the SPC recommends reducing the dosage to 50 mg once daily (down from 50 mg twice daily) in people with CrCl rates <50 mL/min.

Linagliptin is the exception to the rule of the high degree of renal clearance with DPP-4 inhibitors; only 5% of the oral dose is eliminated renally. Graefe-Mody et al (2011) confirmed that renal impairment does not have clinically meaningful effects on linagliptin's clearance and long-term exposure; therefore, no dose adjustment is required in people with CKD. Beyond the convenience of not needing a dose adjustment with linagliptin, there are data suggesting a possible benefit in terms of reducing albuminuria, although the mechanism is not fully understood. A pooled analysis of four randomised, double-blind, placebo-controlled studies with a total of 217 people suggested that linagliptin reduced urinary albumin-to-creatinine ratio by 28% compared with baseline (Groop et al, 2013). This reduction in albuminuria is associated with a decreased risk of progression of renal impairment, including end-stage renal disease (ESRD).

GLP-1 receptor agonists

The GLP-1 receptor agonists have several mechanisms of action, including stimulation of glucose-dependent insulin secretion; suppression of glucagon secretion, resulting in decreased hepatic production of glucose; slowing of gastric emptying; and promotion of satiety (Triplitt et al, 2014).

Exenatide and **extended-release exenatide** are stated to confer an increased risk of acute kidney injury in their SPCs. While the risk has been identified, the frequency is small. In the US, the Food and Drug Administration (2009) reported 78 cases of altered kidney function over a span of 33 months. A pooled analysis of 19 randomised controlled trials involving exenatide 5 µg or 10 µg twice daily over 12–52 weeks demonstrated a low rate of renal impairment-related events – 1.6 per 100 person-years, with no significant difference versus the comparator groups (Macconell et al, 2012). While the risk of acute kidney injury may be low, it should be noted that exenatide is eliminated by renal mechanisms, with an increased half-life observed in people with reduced renal function. Thus, exenatide should not be given to people with severe renal impairment or ESRD (CrCl rate <30 mL/min).

Liraglutide is not eliminated renally or hepatically; however, some caution needs to be taken as there are limited data on its use in people with renal impairment. A meta-analysis of the six LEAD (Liraglutide Effect and Action in Diabetes) studies showed that liraglutide was fairly well tolerated in people with renal impairment, aside from increased rates of nausea that were observed in those with moderate or severe renal impairment (CrCl rate <60 mL/min; Davidson et al, 2011). Overall, there was no significant change in efficacy or safety in patients with mild renal impairment (CrCl rate 60–89 mL/min).

A significant study supporting the use of liraglutide as a means of preventing renal dysfunction was recently presented at the 2016 European Association for the Study of Diabetes (EASD) Annual Meeting. Secondary analysis of the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation) trial demonstrated a 26% reduction in the risk of new and persistent macroalbuminuria and a 22% reduction in incident or worsening nephropathy compared with placebo (Marso et al, 2016). There were no significant differences in need for renal replacement therapy, doubling of serum creatinine levels or death from renal causes.

Liraglutide has also been studied in patients with dialysis-dependent ESRD and was found to be efficacious in this population; however, the patients studied required much lower doses with slower titration to avoid excessive gastrointestinal adverse effects (Idorn et al, 2016). Within the EU, however, liraglutide's SPC does not recommend use in people with severe renal disease, including people with ESRD.

Page points

1. Of the dipeptidyl peptidase-4 inhibitors, sitagliptin, saxagliptin, vildagliptin and alogliptin all require dose reductions people with renal impairment; however, linagliptin does not.
2. Of the glucagon-like peptide-1 receptor agonists, exenatide should not be used in people with severe renal impairment. Dulaglutide, albiglutide and lixisenatide do not require dose adjustment in mild to moderate renal impairment; however, they are not recommended in people with severe impairment owing to a lack of clinical data.
3. Liraglutide does not require dose adjustment in people with kidney disease, and recent data suggest it may even have a renoprotective effect.

Page points

1. Insulin is partially metabolised in the kidney; therefore, dose adjustments are needed with all insulin types. This adjustment should be made on an case-by-case basis.
2. Of the meglitinides, nateglinide needs no dose reduction, while repaglinide has a lower maximum tolerated dose in renally impaired people.
3. Metformin has dosing limitations for men and women with serum creatinine levels of ≥132 µmol/L and ≥123 µmol/L, respectively, and is contraindicated in people with moderate to severe renal impairment.
4. Of the sodium–glucose cotransporter 2 inhibitors, dapagliflozin is contraindicated in moderate to severe renal impairment. Canagliflozin and empagliflozin should not be started in people with stage 3 kidney disease but can be continued at reduced doses if the estimated glomerular filtration rate remains above 45 mL/min/1.73 m^2.

Neither **dulaglitide** nor **albiglutide** require dose adjustment in people with mild or moderate renal impairment, according to their SPCs. However, owing to limited data in people with severe renal impairment or ESRD, these agents are not recommended for use in these populations.

Lixisenatide, similarly, does not require dose adjustment in people with mild or moderate renal impairment. However, there is no therapeutic experience in people with severe renal impairment or ESRD; therefore, the SPC does not recommend using it in these populations.

Insulin

Exogenous insulin contains only the active form of insulin and is degraded via the muscle, liver and kidney. About 15–20% of insulin metabolism occurs in the kidney (Triplitt et al, 2014). Therefore, it is recommended that reduced doses of insulin, no matter the form, should be given to people with renal impairment. This dose adjustment should be individualised on a case-by-case basis (Berns and Glickman, 2016). As always, in people with CKD, monitoring of blood glucose should be maintained while on insulin therapy. With declining kidney function, there is an increased risk of hypoglycaemia, emphasising the importance of blood glucose monitoring in this population.

Meglitinides

The two meglitinides, repaglinide and nateglinide, stimulate insulin secretion from the pancreas. While repaglinide does not rely heavily on kidney function for excretion, **nateglinide** is hepatically metabolised, with renal excretion of active metabolites (Berns and Glickman, 2016). However, nateglinide's short half-life and duration of action contribute to the conclusion that accumulation should not be seen and that dose adjustment is probably unnecessary in people with CKD, as well as those undergoing dialysis (Devineni et al, 2003).

Repaglinide has been shown to be tolerable across the spectrum of renal impairment, up to a maximum dose of 4 mg three times daily (Hasslacher, 2003). However, the maximum tolerated dose tended to be lower in people with more severe renal impairment; therefore, dose reduction may be needed but should be tailored to the individual.

Metformin

Metformin, which suppresses glucagon production, is one of the most efficacious antidiabetes agents. It is eliminated by the kidneys unchanged, with little plasma protein binding (Lipska et al, 2011). Owing to the rare but serious complication of lactic acidosis, metformin has dosing limitations for men and women with serum creatinine levels of ≥132 µmol/L and ≥123 µmol/L, respectively. However, there is some debate as to how stringently these recommendations should be followed. The American Diabetes Association (ADA) and the EASD both report that metformin is safe if the estimated glomerular filtration rate (eGFR) exceeds 30 mL/min/1.73 m^2, and if kidney function is monitored frequently (Inzucchi et al, 2015).

SGLT2 inhibitors

Sodium–glucose cotransporter 2 (SGLT2) inhibitors act by lowering the renal threshold for glucose reabsorption while also increasing glucose excretion. This results in reduced plasma glucose levels, osmotic diuresis and a caloric loss that promotes weight loss (Yale et al, 2013).

Canaglifozin has been shown to be effective in people with mild to moderate CKD; however, it is also associated with a temporary fall in eGFR at treatment initiation (Yale et al, 2013; Yamout et al, 2014). Therefore, the SPC recommends that it should not be initiated if eGFR is <60 mL/min/1.73 m^2. It can be continued, with a dose reduction from 300 mg to 100 mg, if eGFR falls below 60 but remains above 45 mL/min/1.73 m^2, but it should be stopped if eGFR falls any lower.

Dapagliflozin does not maintain its effects in people with reduced eGFR. It forms an inactive metabolite, increased amounts of which occur in individuals with declining kidney function (Kasichayanula et al, 2013). In addition, steady-state renal glucose clearance reduces by 42%, 83% and 84% in mild, moderate, and severe impairment, respectively, rendering the drug less effective. Therefore, there are more stringent guidelines on who can receive dapagliflozin. The manufacturer recommends avoiding use in people with an eGFR <60 mL/min/1.73 m^2.

Empagliflozin appears to be effective and well tolerated at all levels of renal dysfunction

(Barnett et al, 2014). In June 2016, at the ADA Scientific Sessions, the renal outcomes of empagliflozin's cardiovascular safety study, EMPA-REG OUTCOME, were presented. The data suggested that empagliflozin was responsible for a 39% reduction in incident or worsening nephropathy and a 38% reduction in new-onset macroalbuminuria (Wanner et al, 2016).

As with canagliflozin, the manufacturer recommends not starting empagliflozin in people with an eGFR <60 mL/min/1.73 m^2, reducing the dose to 10 mg in people whose eGFR falls to 45–59 mL/min/1.73 m^2 and discontinuing if eGFR falls below 45 ml/min/1.73 m^2.

Sulfonylureas

Sulfonylureas promote insulin secretion by the pancreas. The newer-generation sulfonylureas – glipizide, gliclazide, glimepiride and glibenclamide – are metabolised by the liver, and glibenclamide is the only one to produce clinically active metabolites. Glipizide has no active metabolites and glimepiride produces one inactive metabolite and another that has 33% of the activity of the parent drug. Gliclazide's significant hepatic metabolism results in metabolites with minimal hypoglycaemic activity.

Glipizide is the second-generation sulfonylurea of choice in people with CKD according to National Kidney Foundation (2012) guidelines. Its lack of active metabolites and shorter half-life (2–4 hours) compared to glimepiride (5–9 hours) and glibenclamide (10 hours) also contribute to it having a reduced risk of hypoglycaemia in people with CKD. The manufacturer recommends conservative initial and maintenance glipizide doses in people with renal impairment.

Due to the minor effect the kidneys have on its metabolism, **gliclazide** would also be a good option for treatment in renally impaired patients. The half-life, although slightly longer, should not be majorly impacted by the presence of renal impairment. However, the SPC recommends caution and monitoring for hypoglycaemia when using gliclazide in people with renal disease.

Glimepiride can be used in renally impaired patients; however, lower levels of the active drug and increased levels of its metabolites have been observed in people with moderate to severe renal impairment. The SPC recommends switching to insulin in people with severe renal impairment.

Due to the active metabolites and long half-life of **glibenclamide**, caution in patients with renal impairment is warranted. The potential accumulation of the drug and its active metabolites increases the risk of hypoglycaemia; therefore, the other sulfonylureas are considered a better alternative (Triplitt et al, 2014).

Pioglitazone

Pioglitazone works by enhancing tissue sensitivity to insulin as well as decreasing glucose production from the liver (Berns et al, 2016). It does not accumulate in people with renal impairment and, therefore, does not need dose adjustment (Budde et al (2003). However, it has been shown to increase the risk of developing CKD compared to placebo, as well as decreasing eGFR in those who already have CKD (Schneider et al, 2008). This places some limitation on the use of pioglitazone in people with CKD. Interestingly, however, in this same study, pioglitazone reduced the risk of a composite endpoint of all-cause mortality, myocardial infarction and stroke in people with CKD, but not those without it.

Clinical applications

Renal function plays a major role in the decision of which antidiabetes agent to utilise. Preferably, agents that rely minimally on the kidneys for metabolism and elimination should be selected. Dose reductions are often recommended in people with renal dysfunction, as summarised in *Table 1*.

Among the DPP-4 inhibitors, linagliptin is one agent that does not require dose adjustments and may even improve albuminuria (Graefe-Mody et al, 2011).

Sulfonylureas show substantial efficacy, and glipizide or gliclazide would be the sulfonylureas of choice in people with CKD, owing to the former's short half-life and lack of metabolites, and the latter's hepatic metabolism. It is important to note, however, that conservative dosing is recommended to maintain efficacy and safety.

If using an SGLT2 inhibitor, despite the class's heavy reliance on renal glucose elimination, canagliflozin or empagliflozin would probably be the best options, but neither should be initiated in patients with a CrCl rate <45 mL/min. With

Page points

1. Of the sulfonylureas, glipizide and gliclazide would be the agents of choice. Glipizide and glimepiride require dose reductions, and glibenclamide is not recommended below a creatinine clearance rate of 50 mL/min.
2. Pioglitazone does not require dose adjustment in people with renal impairment; however, it has been associated with an increased risk of chronic kidney disease, which places some limitation on its use in this population.

Table 1. Indications and dose adjustment recommendations of antidiabetes medications at varying creatinine clearance levels.

Medication	Creatinine clearance rate (mL/min)			
	≥60	45–59	30–44	<30
Linagliptin	◆	◆	◆	◆
Sitagliptin	◆	◆ ≥50 ◇ <50 *	◇ *	◇ †
Saxagliptin	◆	◆ >50 ◇ ≤50 ‡	◇ ‡	◇ ‡
Alogliptin	◆	◆ >50 ◇ ≤50 §	◇ §	◇ ‖
Vildagliptin	◆	◆ ≥50 ◇ <50 *	◇ *	◇ *
Exenatide	◆	◆	◆	◆
Liraglutide	◆	◆	◆	◆ ¶
Dulaglutide	◆	◆	◆	◆ ¶
Albiglutide	◆	◆	◆	◆ ¶
Lixisenatide	◆	◆	◆	◆ ¶
Insulin	◇	◇	◇	◇
Repaglinide	◆	◆	◆ >40 ◇ 20–39	◇ 20–39 ◆ <20
Nateglinide	◆	◆	◆	◆
Metformin	◆	◇	◇	◆
Glipizide	◇	◇	◇	◇
Gliclazide	◇	◇	◇	◇
Glimepiride	◇	◇	◇	◇
Glibenclamide	◇	◇ ≥50 ◆ <50	◆	◆
Canagliflozin**	◆	◇ ‡‡	◆	◆
Dapagliflozin**	◆	◆	◆	◆
Empagliflozin**	◆	◇ §§	◆	◆
Pioglitazone	◆	◆	◆	◆

◆=The drug can be given at this creatinine clearance rate; ◇=Dose reductions are recommended at this creatinine clearance rate; ◆=The drug is not recommended with this creatinine clearance rate, or no data are available.

* 50 mg once daily.

† 25 mg once daily.

‡ 2.5 mg once daily.

§ 12.5 mg once daily.

‖ 6.25 mg once daily.

¶ Limited or no clinical experience in patients with severe renal impairment or end-stage renal disease; therefore, not recommended.

** These agents are assessed according to estimated glomerular filtration rate (not creatinine clearance rate).

‡‡ Do not exceed 100 mg/day. Agent can be continued, but should not be started, at estimated glomerular filtration rates <60 mL/min/1.73 m^2.

§§ Do not exceed 10 mg/day. Agent can be continued, but should not be started, at estimated glomerular filtration rates <60 mL/min/1.73 m^2.

the recent positive evidence of its effects on renal outcomes, empagliflozin may currently be the agent of choice in those with moderate renal impairment.

Within the GLP-1 receptor agonist class, although liraglutide is not eliminated renally and has demonstrated efficacy, there are limited data available in people with severe renal impairment; therefore, cautious use is recommended. With the recently released data suggesting a renoprotective effect (Marso et al, 2016), those with mild to moderate impairment may benefit from use of liraglutide in preventing progression of albuminuria; however, it is not conclusive whether it will prevent renal outcomes from occurring.

Insulin can be used at all levels of CKD, but strict monitoring of blood glucose should be employed as well as an individualised dosing regimen; often, lower doses are required to achieve glycaemic goals.

As there is a significantly increased risk of cardiovascular outcomes in people with CKD, there is concern over the use of pioglitazone in people with this comorbidity. If pioglitazone is chosen, its dose does not need to be adjusted; however, eGFR should be monitored carefully to ensure it does not decline.

Of the meglitinides, nateglinide does not require dose adjustment and so would be preferred over repaglinide. However, these agents are less commonly used because of the inconvenience of frequent dosing and the risk of weight gain and hypoglycaemia.

Patients undergoing haemodialysis are recommended to use insulin rather than oral agents. This is partly due to the lack of data on oral agents during dialysis. *Table 2* outlines which agents have been studied and may be used in such patients. The preferred oral agents in this population are glipizide and repaglinide, as their hepatic metabolism results in lower risk of hypoglycaemia (Berns et al, 2016).

Ongoing glycaemic monitoring is also a crucial aspect in people with CKD who are taking diabetes medications. HbA_{1c} checks are recommended at baseline and every 3–6 months, with a goal of <53 mmol/mol (7.0%; Cavanaugh, 2007; McCulloch, 2016). Annual tests of urinary albumin-to-creatinine ratio and baseline and periodic serum creatinine checks are also recommended (McCulloch, 2016). The National Kidney Foundation (2012) guidelines use eGFR to stage the level of CKD;

therefore, this should be monitored periodically to determine the current stage of the patient and adjust medication doses appropriately.

Owing to the potential for increased risk of hypoglycaemia with some agents, self-monitoring of blood glucose should be maintained, to aid in prevention of further kidney injury and microvascular complications.

Estimating renal function

The majority of antidiabetes medications are recommended to have their doses adjusted according to calculated CrCl rate. Given the difficulty in using a consistent method to calculate CrCl, as well as the fact that most healthcare providers use eGFR to monitor kidney function, the manufacturers of newly approved medications, including the SGLT2 inhibitors, seem to be using eGFR to determine dosing. Although eGFR and CrCl rate are not directly interchangeable, they do provide similar estimates of renal function.

Summary

The high incidence of CKD in people with diabetes reaffirms the necessity of ensuring that people with this comorbidity are on the correct antidiabetes agents. Selecting the most appropriate agents may reduce the risk of microvascular complications, prevent further kidney impairment and improve quality of life. Frequent monitoring will help in adjusting therapy as needed to provide the best regimen. Through careful selection and continual monitoring, an individualised care plan that maintains safety and efficacy can be created for these patients. ■

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Table 2. Indications of antidiabetes agents in people undergoing haemodialysis.

Medication	Use acceptable in dialysis recipients
Linagliptin	◆
Saxagliptin	◇ *
Sitagliptin	◇ †
Alogliptin	◇ ‡
Vildagliptin	◇ ‖
Exenatide	◆ §
Liraglutide	◆ ‖
Dulaglutide	◆ ‖
Albiglutide	◆ ‖
Lixisenatide	◆ ‖
Insulin	◆
Nateglinide	◆
Repaglinide	◆
Metformin	◆
Glipizide	◆
Gliclazide	◆
Glimepiride	◆
Glibenclamide	◆
Canagliflozin	◆
Dapagliflozin	◆
Empagliflozin	◆
Pioglitazone	◆

◆=The drug can be used in people on dialysis; ◇=The drug can be used, with caveats; ◆=The drug is not recommended in people on dialysis.
* Administer 2.5 mg once daily after dialysis.
† Administer 25 mg once daily without regard to timing of dialysis.
‡ 6.25 mg once daily.
§ Use is not recommended in people with creatinine clearance <30 mL/min; intermittent and continuous haemodialysis will reduce clearance to 0.9 L/hour compared to the normal 9.1 L/hour.
‖ Limited clinical experience in people with severe renal impairment or end-stage renal disease.