Introduction

Just over one million people, or 5.4% of Australian adults, have type 2 diabetes. This equates to one in every eighteen adults. We need to be familiar with the management of diabetes and impact of renal impairment, as almost 30% of patients with diabetes have this complication. The combination of type 2 diabetes and renal impairment poses a significant challenge. These patients are at very high risk of macrovascular complications as they are more prone to hypoglycaemia (an independent risk factor for cardiovascular disease), in addition to obesity, hypertension, dyslipidaemia and obstructive sleep apnoea. Moreover, when patients with diabetes develop renal impairment, they are also likely to have other microvascular complications, such as retinopathy and diabetic neuropathy, and these all complicate their management.

Early, tight glycaemic control at the time of diagnosis is the key to preventing diabetes-related complications. The HbA1c should be less than 6% (42mmol/mol). Good glycaemic control (HbA1c less than 7%, or 53mmol/mol) can delay the progression of renal impairment. The use of angiotensin-converting enzyme inhibitors (ACE-inhibitors), angiotensin II receptor blockers (ARBs), and

Take Home Messages

- Metformin should always remain the first-line hypoglycaemic agent, followed ideally by an SGLT2i and then a DPP4i.
- Sulphonylureas increase the risk of hypoglycaemia, especially if the patient has renal impairment. Use a shorter-acting sulphonylurea, such as gliclazide.
- A dose reduction is required for most DPP4i when the eGFR is <45mL/min/1.73m². Linagliptin is mostly cleared by the liver and so the same dose is used across all levels of renal function.
- SGLT2i prevent sodium and glucose reabsorption in the renal tubules, reducing blood glucose, blood pressure and the glomerular hyper-filtration that can worsen diabetic nephropathy. They also reduce cardiovascular events and cause weight loss, but have reduced efficacy in renal impairment.
- Typically, a basal insulin is used in patients with high fasting glucose levels. Premixed and basal-bolus insulin regimens are suitable for those with high fasting and post-prandial glucose levels.
Hypoglycaemic Agents and Renal Impairment

Almost all hypoglycaemic agents (new and old) are affected by renal function. Some of these medications can have a beneficial effect on the risk of cardiovascular disease and the progression of nephropathy. Therefore, the estimated glomerular filtration rate (eGFR) is most important to consider when a clinician decides the most suitable hypoglycaemic agent for a patient.

Metformin

Metformin, a biguanide, has been used since the 1950s. Its sister drug, phenformin, carried a significant risk of fatal lactic acidosis in the 1970s and similar concerns were raised with metformin, especially if it were to be used in patients with renal impairment.

It is important to note that the Therapeutic Goods Administration (TGA) states that patients who have an eGFR below 60mL/min/1.73m² should not take metformin because of the risk of lactic acidosis. However, most doctors follow Australian guidelines that advise metformin can be taken, at a reduced dose, by patients with an eGFR between 30-60mL/min/1.73m².

There are still myths that metformin can damage the kidneys. In a 2010 Cochrane meta-analysis of 347 trials with over 70,000 patients-years, not a single case of lactic acidosis was found in those taking metformin.

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The current recommendation for metformin dosing is a maximum of 2g/day in patients with an eGFR over 60mL/min/1.73m², and while the product information lists it as contraindicated with an eGFR less than 60mL/min/1.73m², most professional societies, including the RACGP, recommend metformin up to 1g/day for an eGFR between 30mL/min/1.73m² and 60mL/min/1.73m², and contraindicated when the eGFR is less than 30mL/min/1.73m².

Patients on metformin need assessment before receiving intravenous iodinated contrast media. While the Product Information states patients with renal impairment should stop their metformin at least 48 hours prior to the test, the Royal Australian and New Zealand College of Radiologists (RANZCR) recommends patients who have an eGFR above 30mL/min/1.73m² should continue taking metformin. RANZCR recommends patients with an unknown recent eGFR or an eGFR less than 30mL/min/1.73m², or who are unwell or have deteriorating renal function, should cease metformin for at least 48 hours from the time of the examination and have an eGFR performed prior to restarting metformin.

There are studies suggesting metformin is beneficial in patients with renal impairment and that there is a 22% lower mortality risk compared to those using other hypoglycaemic agents. Furthermore, given that renal impairment increases the risk of hypoglycaemia, and this in turn increases cardiovascular risk, the use of metformin may have additional benefits (as it does not cause hypoglycaemia).

The use of a purely glucocentric approach in the management of diabetes would produce a poor outcome.

Sulphonylureas

Like metformin, sulphonylureas have also been in use since the 1950s. They bind to the potassium channels in the pancreatic β-cells and cause the release of insulin. Most sulphonylureas have active metabolites that rely on renal excretion. As sulphonylureas cause insulin secretion even in the presence of low blood glucose levels, the risk of hypoglycaemia is increased, especially if the patient has renal impairment.

However, sulphonylureas can be used in patients with renal impairment. Care should be taken to use only the minimum effective dose, and when possible, use a shorter-acting sulphonylurea, such as gliclazide. A dose reduction of the sulphonylurea may be necessary to avoid hypoglycaemia if additional hypoglycaemic agents are added, or if renal function declines.

Thiazolidinediones

The use of glitazones has reduced significantly since concerns were raised regarding cardiovascular safety of rosiglitazone. Dose adjustment is not necessary as the serum drug level does not rise in renal impairment. However, glitazones can stimulate sodium reabsorption, leading to fluid retention, oedema and heart failure. There is also an increased fracture risk, especially in post-menopausal women with chronic kidney disease, so the use of this class of medication in patients with renal impairment is not ideal.
**α-Glucosidase Inhibitors**

Acarbose mostly acts on the gastrointestinal tract. It slows carbohydrate absorption and so reduces the post-prandial rise in blood glucose. It does not cause hypoglycaemia and is minimally affected by renal impairment. The use of acarbose is limited due to the significant gastrointestinal side-effects, including flatulence, bloating and diarrhoea.

**Dipeptidyl Peptidase-4 Inhibitors**

Dipeptidyl peptidase-4 (DPP-4) is an enzyme found on most cell surfaces that degrades incretin hormones, including glucagon-like peptide-1 (GLP-1) and gastric inhibitory polypeptide (GIP). Incretins are hormones produced after eating. They stimulate insulin release, reduce glucagon release, slow gastric emptying and increase satiety. Their function is glucose dependent, making the risk of hypoglycaemia minimal. Patients with type 2 diabetes have reduced incretin levels,19 thus the inhibition of the degradation of DPP-4 enhances its function.

A dose reduction is required for most DPP-4 inhibitors when the eGFR decreases in order to stay within the therapeutic window. In most cases, when the eGFR is less than 45 mL/min/1.73 m², the dosage needs to be adjusted. The exception is linagliptin, as this is mostly cleared by the liver and so the same dose is used across all levels of renal function. DPP-4 inhibitors generally are extremely well tolerated.

DPP-4 inhibitors are very useful in patients with renal impairment. As long as the correct dose is prescribed, they can even be used in dialysis patients and there is little to no hypoglycaemia risk.20 No other hypoglycaemic agents have the same safety profile and tolerability in patients with severe renal impairment.

**GLP-1 Receptor Agonists**

Another way to increase incretin function is by providing an incretin analogue, such as an GLP-1 receptor agonist (GLP-1), that is not degraded by the DPP-4 enzyme. GLP-1 receptor agonist molecules are difficult to absorb through the gastrointestinal tract and may be degraded by digestive enzymes. Currently, they are only available in a subcutaneous injectable form (daily, twice daily or weekly). Oral forms are currently being developed and the research looks promising.22 GLP-1 analogues increase satiety and cause weight loss of approximately five to ten kilograms. They have a low risk of hypoglycaemia.

Exenatide bd and weekly preparations are currently contraindicated in patients when eGFR is less than 30mL/min/1.73m² as there is reduced renal clearance. This may increase gastrointestinal intolerance, including nausea, vomiting and diarrhoea. These symptoms already occur in up to 30% of patients with normal renal function who are taking these medications.

Liraglutide and Dulaglutide can be used in those with renal impairment without dose adjustment. Dulaglutide and Liraglutide have also been shown to reduce urinary albumin excretion, slow the progression of diabetic nephropathy24 and reduce cardiovascular events.25,26

**Sodium Glucose Linked Transporter-2 Inhibitors**

Sodium glucose linked transporter-2 (SGLT-2) inhibitors are the latest addition to diabetes management. They function by blocking the SGLT-2 channels (found exclusively in the renal tubules), to prevent sodium and glucose reabsorption. This has the direct effect of reducing blood glucose, blood pressure and an indirect effect of reducing the glomerular hyper-filtration that can worsen diabetic nephropathy.27 Apart from preventing deteriorating renal impairment, SGLT-2 inhibitors also reduce cardiovascular events in those with pre-existing cardiovascular disease.28 They are also one of the few hypoglycaemic agents that causes weight loss (approximately three to four kilograms).

The problem with the use of SGLT-2 inhibitors in patients who have renal impairment is that these medications have reduced efficacy. SGLT-2 inhibitors work by reducing glucose reabsorption, and this ability is lessened as glomerular filtration declines. All SGLT-2 inhibitors may be used with an eGFR over 45 mL/min/1.73 m². Please also be aware that current recommendation from the Australian Diabetes Society requires SGLT-2 inhibitors be ceased 2 days before and the day of surgery to prevent euglycaemic ketoacidosis.

**Insulin**

Until DPP-4 inhibitors were available, insulin was the only agent indicated for use in patients with severe renal impairment. Insulin excretion is reduced in the presence of renal impairment, and in many cases a dose reduction is required to prevent hypoglycaemia. It is therefore important to review insulin doses regularly. There is no consensus or guidelines on the choice of insulin type in renal impairment, and so this choice should be based on the patient’s blood glucose profile. Typically, a basal insulin would be used in patients with high fasting glucose levels, whilst premixed and basal-bolus insulin regimens would be suitable for those with high fasting and high post-prandial glucose levels.

**Renal dialysis**

Dialysis can affect glycaemic control through the clearance of insulin, glucagon and hypoglycaemic agents and the alteration of glucose metabolism. Dialysates directly affect the blood glucose, insulin, glucagon and hypoglycaemic agents and the alteration of glucose metabolism. Dialysates directly affect the blood glucose, blood pressure and an indirect effect of reducing the glomerular hyper-filtration that can worsen diabetic nephropathy.27 Apart from preventing deteriorating renal impairment, SGLT-2 inhibitors also reduce cardiovascular events in those with pre-existing cardiovascular disease.28 They are also one of the few hypoglycaemic agents that causes weight loss (approximately three to four kilograms).

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Table 1: Characteristics of hypoglycaemic agents and implications in renal impairment (Intellectual property of the author).

<table>
<thead>
<tr>
<th>eGFR (mL/min)</th>
<th>&lt;30</th>
<th>30-45</th>
<th>45-60</th>
<th>&gt;60</th>
<th>Hypoglycaemia</th>
<th>Weight</th>
<th>CV benefit</th>
<th>Renal benefit</th>
</tr>
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<tbody>
<tr>
<td>Metformin</td>
<td>Contraindicated</td>
<td>1g daily</td>
<td>2g daily</td>
<td>No</td>
<td>Loss</td>
<td>Yes</td>
<td>Yes</td>
<td></td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>OK</td>
<td>Yes</td>
<td>Gain</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Acarbose</td>
<td>Contraindicated</td>
<td>OK</td>
<td>No</td>
<td>Neutral</td>
<td>Yes</td>
<td>No</td>
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<tr>
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<td>OK</td>
<td>No</td>
<td>Gain</td>
<td>No</td>
<td>No</td>
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<tr>
<td>DPP-4 inhibitor</td>
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<tr>
<td>Alogliptin</td>
<td>6.25mg daily</td>
<td>12.5mg daily</td>
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<td>No</td>
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<tr>
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<td>100mg daily</td>
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<td>50mg bd</td>
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<td>Loss</td>
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<tr>
<td>GLP-1 agonist</td>
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<tr>
<td>Exanatide</td>
<td>Contraindicated</td>
<td>5mcg or 10mcg bd or 2mg weekly</td>
<td>No</td>
<td>Loss</td>
<td>No</td>
<td>Yes</td>
<td></td>
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<tr>
<td>Dulaglutide</td>
<td>Not Recommended</td>
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<td>Liraglutide</td>
<td>1.8mg daily</td>
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<td></td>
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<tr>
<td>SGLT-2 inhibitors</td>
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<tr>
<td>Dapagliflozin</td>
<td>Ineffective</td>
<td>10mg daily</td>
<td>No</td>
<td>Loss</td>
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<td>Empagliflozin</td>
<td>10mg or 25mg daily</td>
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<td>Yes</td>
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<tr>
<td>Ertugliflozin</td>
<td>5mg or 15mg daily</td>
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<td>Yes</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Insulin</td>
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<td>Yes</td>
<td>Gain</td>
<td>No</td>
<td>No</td>
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</tbody>
</table>

In the recent past, some glucometers had been found to give falsely elevated glucose readings in dialysis patients. Fortunately, most of these problems have been resolved.

**Optimising Management in Presence of Renal Impairment**

There is an increased risk of hypoglycaemia and cardiovascular events in patients with renal impairment. The optimal hypoglycaemic agents would have a minimal risk of hypoglycaemia, preferably induce weight loss, prevent or slow progression of nephropathy and reduce cardiovascular risk to a greater extent than can already be achieved through blood pressure and lipid control. Metformin, SGLT-2 inhibitors and some GLP-1 agonists fit into this category. Unfortunately, an SGLT-2 inhibitor plus GLP-1 agonist combination is currently not approved by the Therapeutic Goods Administration (TGA) nor is this combination subsidised via the Pharmaceutical Benefits Scheme (PBS).

Metformin should always remain the first-line hypoglycaemic agent, but the dose should be limited to 2g daily to minimise gastrointestinal side-effects. Again, it is contraindicated according to the product information when eGFR is less than 60mL/min/1.73m², but Guidelines recommend the dose may be reduced to 1g daily when the eGFR is between 30mL/min/1.73m² and 60mL/min/1.73m². It is contraindicated when the eGFR is under 30mL/min/1.73m².

The second-line agent should ideally be an SGLT-2 inhibitor (given the renal, cardiovascular and weight loss benefits), as long as reasonable renal function still exists (an eGFR greater than 45 mL/min/1.73m²). Tolerability of the SGLT-2 inhibitors can be problematical, as some patients develop significant polyuria and recurrent thrush.

If SGLT-2 inhibitors are not suitable or not tolerated, a DPP-4
inhibitor, dose adjusted to the renal function could be used next. Whilst this type of hypoglycaemic medication does not provide renal, cardiovascular or weight-loss benefits, it is at least effective, well-tolerated and does not cause hypoglycaemia. Sulphonylureas also work well as second line agents and had been used in this manner for decades. The slight weight gain and hypoglycaemic risk makes them less ideal given the various alternatives available today.

Acarbose could also be considered, but the significant gastrointestinal side-effects makes it intolerable for most patients. GLP-1 agonist is currently approved for second line therapy only in patients with intolerance or contraindication to metformin or sulphonylurea, so is not commonly used for second line therapy.

There is an increased risk of hypoglycaemia and cardiovascular events in patients with renal impairment.

Choices of third line therapy are somewhat dependent on which second line therapy has been used.

For patients on metformin and an SGLT-2 inhibitor, adding a DPP-4 inhibitor or a sulphonylurea works well. The addition of a GLP-1 agonist is currently approved by the TGA or PBS.

For patients on metformin and DPP-4 inhibitor, adding a SGLT-2 inhibitor or a sulphonylurea also works well. Again, adding a GLP-1 agonist is not approved.

For patients on sulphonylurea, adding a SGLT-2 inhibitor, a DPP-4 inhibitor or a GLP-1 agonist as third line therapy all work well. SGLT-2 inhibitor and GLP-1 agonist both reduce body weight but are less well tolerated generally, whereas a DPP-4 inhibitor is usually well tolerated.

Insulin could be used at any stage, whether it be first line or fourth line. It is most effective in terms of glycaemic control, making it the best agent for patients with very high glucose levels. Insulin, however, has the highest risk of hypoglycaemia and weight gain, so it is often used later in the course of diabetes after other agents have been tried, given the additional benefits other agents can provide (weight, hypoglycaemia, cardiovascular and renal). Choice of insulin depends on the glycaemic profile at the time of initiation. Basal insulin should be used if there is a raised fasting blood glucose. Pre-mixed or basal-bolus insulins are indicated if both the fasting and post-prandial blood glucose levels are raised. Insulin can be used with metformin and sulphonylurea, plus a SGLT-2 inhibitor, DPP-4 inhibitor or GLP-1 agonist (ie. any one of these three newer agents). PBS subsidy criteria currently does not allow insulin to be used with the SGLT-2 inhibitor/DPP-4 inhibitor combination, SGLT-2 inhibitor/GLP-1 agonist combination or DPP-4 inhibitor/GLP-1 agonist combination.

Conclusion

Choosing the right medication and using the correct dose is important to optimise the management of type 2 diabetes in patients with renal impairment. However, equally important is the control of hypertension. The aim should be under 140/90mmHg if there is no microalbuminuria and under 130/80mmHg if microalbuminuria is present. Antihypertensive medications commonly used in patients who have renal failure include ACE inhibitors, ARBs and calcium channel blockers.

Diabetes itself is a major cardiovascular risk factor. The control of other cardiovascular risk factors, such as dyslipidaemia, hypoglycaemia, obesity, alcohol excess, smoking and obstructive sleep apnoea is also vital. The use of a purely glucocentric approach in the management of diabetes would produce a poor outcome, especially in those patients who also have renal impairment.

Declaration

Dr Ivan Kuo was commissioned by Healthed for this article. The ideas, opinions and information presented are solely those of the author. The author declares no significant competing financial, professional or personal interests that might influence this article.

Further Reading


References

Optimising Management of Type 2 Diabetes in Presence of Renal Impairment

Figure 1: Current treatment algorithm for patients with renal impairment under the Pharmaceutical Benefits Scheme (Intellectual property of the author).

### eGFR >60
- **Metformin up to 2g daily**
- **SGLT-2 inhibitor**
  - Dapagliflozin 10mg daily
  - Empagliflozin 10mg or 25mg daily
  - Ertugliflozin 5mg or 15mg daily
- **DPP-IV inhibitor**
  - Alogliptin 25mg daily
  - Linagliptin 5mg daily
  - Saxagliptin 5mg daily
  - Sitagliptin 100mg daily
  - Vildagliptin 50mg bd
- **GLP-1 agonist**
  - Exenatide 5mcg or 10mcg bd
  - Exenatide 2mg weekly
  - Dulaglutide 1.5mg weekly

### eGFR 45-60
- **Metformin up to 1g daily**
- **SGLT-2 inhibitor**
  - Dapagliflozin 10mg daily
  - Empagliflozin 10mg or 25mg daily
  - Ertugliflozin 5mg or 15mg daily
- **DPP-IV inhibitor**
  - Alogliptin 12.5mg daily
  - Linagliptin 5mg daily
  - Saxagliptin 5mg daily
  - Sitagliptin 100mg daily
  - Vildagliptin 50mg daily
- **GLP-1 agonist**
  - Exenatide 5mcg or 10mcg bd
  - Exenatide 2mg weekly
  - Dulaglutide 1.5mg weekly

### eGFR 30-45
- **Metformin up to 1g daily**
- **DPP-IV inhibitor**
  - Alogliptin 12.5mg daily
  - Linagliptin 5mg daily
  - Saxagliptin 2.5mg daily
  - Sitagliptin 50mg daily
  - Vildagliptin 50mg daily
- **GLP-1 agonist**
  - Exenatide 5mcg or 10mcg bd
  - Exenatide 2mg weekly
  - Dulaglutide 1.5mg weekly

### eGFR <30
- **Metformin contraindicated**
- **DPP-IV inhibitor**
  - Alogliptin 6.25mg daily
  - Linagliptin 2.5mg daily
  - Saxagliptin 2.5mg daily
  - Sitagliptin 25mg daily
  - Vildagliptin 50mg daily
Optimising Management of Type 2 Diabetes in Presence of Renal Impairment


