Chronic kidney disease

Doing simple things well for those most at risk

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The incidence of chronic kidney disease (CKD) is increasing worldwide. A holistic approach to management that includes nonpharmacological and pharmacological strategies to manage risk factors, as well as advocating for patients, particularly those most at risk, can significantly slow the progression of CKD. Input from multidisciplinary team members, including a nephrologist, CKD nurse and allied health professionals, can further reduce the progression of CKD, delay kidney failure and avoid CKD-related mortality.

Chronic kidney disease (CKD) is a global public health emergency, with its incidence increasing in parallel with growing rates of obesity, diabetes, hypertension and cardiovascular disease (CVD).[1] Over 2 million adults in Australia, representing 11% of the adult population, are estimated to have biomedical signs of CKD, and the number of people progressing to kidney failure requiring dialysis (kidney replacement

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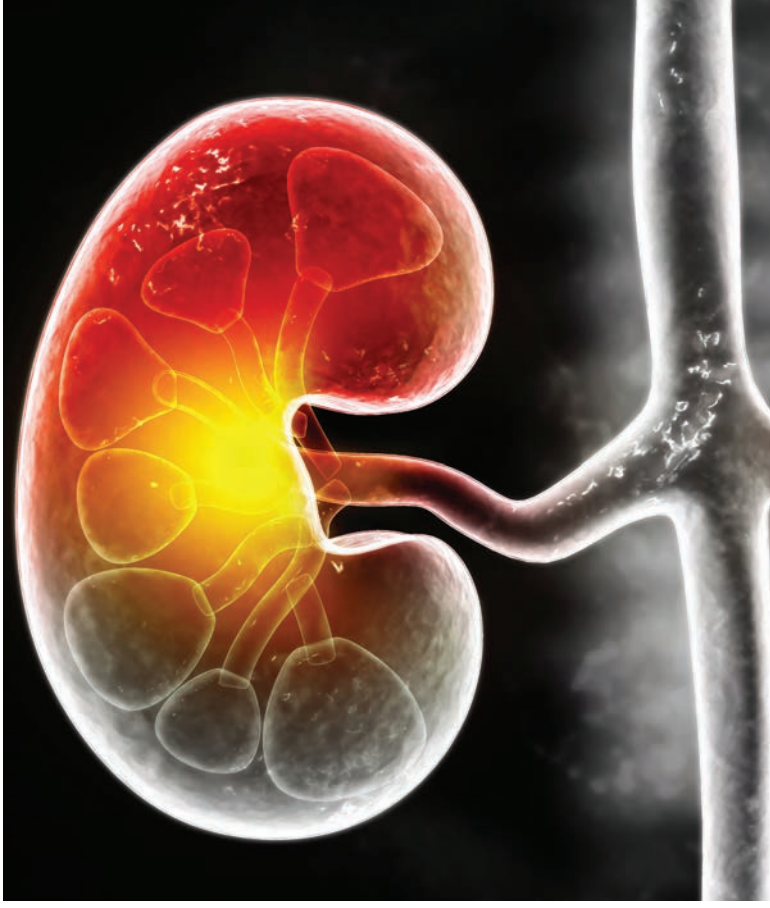

KEY POINTS

- The incidence of chronic kidney disease (CKD) is increasing in Australia and worldwide, placing a significant burden on the healthcare system and economy.
- A thorough weight history, assessment of volume status and use of three essential tests (blood pressure, estimated glomerular filtration rate and spot urine albumin to creatinine ratio) are imperative to the diagnosis of CKD.
- Aboriginal and Torres Straits Islander people are twice as likely to develop CKD and five times more likely to develop kidney failure requiring dialysis compared with non-Indigenous Australians.
- Nonpharmacological measures, including optimising diet and nutrition, regular exercise and managing mental health, and a culturally responsible approach to care contribute to a patient's overall wellbeing and improved health.
- Risk factors for developing CKD, including diabetes, hypertension, obesity and cardiovascular disease, should be managed aggressively with pharmacotherapy.
- The four pillars of medical management for patients with CKD are renin-angiotensin system inhibitors, sodium-glucose cotransporter-2 inhibitors, glucagon-like peptide-1 receptor agonists and nonsteroidal mineralocorticoid receptor antagonists.

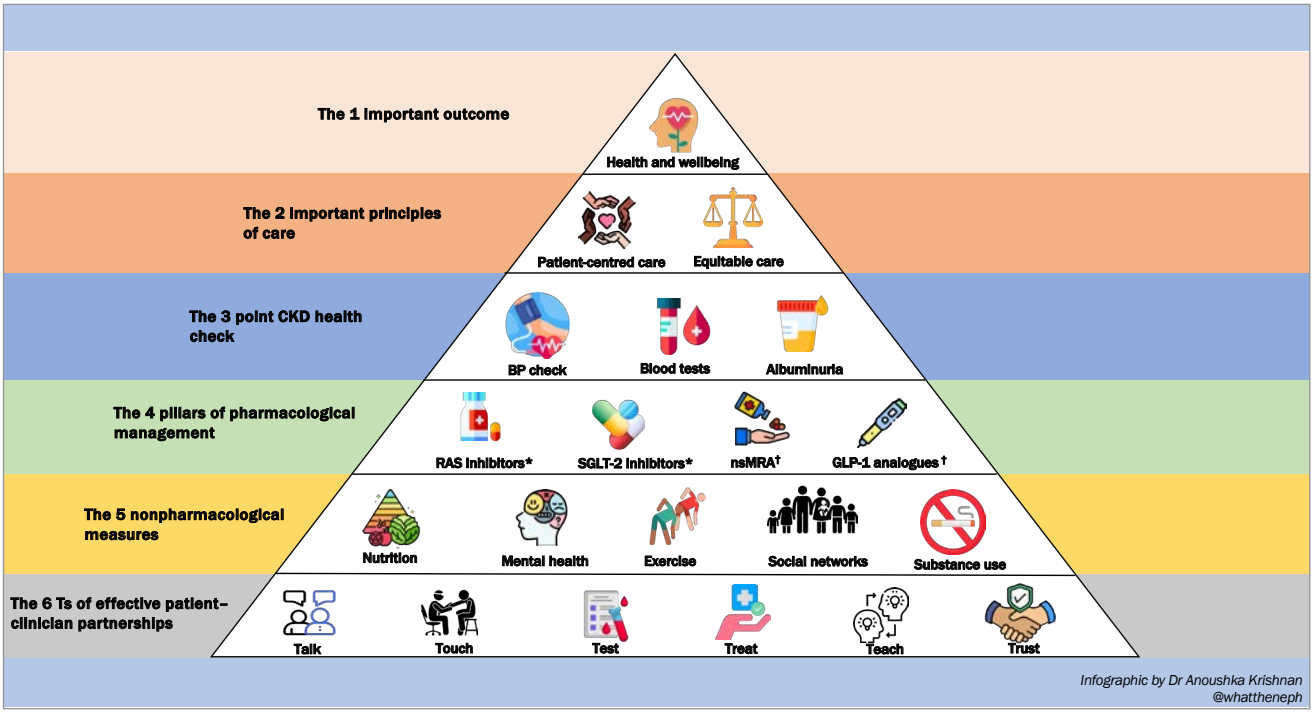

Figure. The chronic kidney disease management pyramid.

Abbreviations: BP = blood pressure; CKD = chronic kidney disease; DKD = diabetic kidney disease; GLP-1 = glucagon-like peptide-1; RAS = renin-angiotensin system; nsMRA = nonsteroidal mineralocorticoid receptor antagonist; SGLT-2 = sodium-glucose cotransporter-2.
* Use to manage CKD. † Use to manage DKD.

therapy) more than doubled between 2000 and 2021.[2,3] This also comes at a burgeoning cost to public health systems. In 2021, CKD and kidney failure cost the Australian healthcare system $2.38 billion and, internationally, care of people with CKD has threatened to overwhelm the UK's NHS.[2,4,5] Diabetic kidney disease consistently contributes to about 40% of cases of kidney failure, followed by glomerulonephritis and hypertensive kidney disease.[6] Aboriginal and Torres Strait Islander people are five times more likely to develop kidney failure requiring dialysis (per population size) than non-Indigenous Australians.[2]

CKD screening programs in Australia have been simplified to include three essential tests: blood pressure (BP), estimated glomerular filtration rate (eGFR) and spot urine albumin to creatinine ratio (uACR). Screening is widely promoted through Kidney Health Australia via many medical avenues, but is implemented with only partial success.[7] Home-based screening methods are being developed to improve population screening for CKD;[8] however, translating screening data and a CKD diagnosis into effective CKD therapy poses a further challenge. A recent study showed that pharmacotherapy for CKD management was underprescribed in primary care, with only 4.1% of eligible patients with CKD in Australia prescribed a sodium-glucose cotransporter-2 (SGLT-2) inhibitor.[9] Achieving implementation closer to 75% has been estimated to prevent over 3600 cardiorenal events and 1300 kidney failure episodes a year.[10]

At a population level, effective public health policy and resourced strategies can promote kidney health among communities with high CKD risk.[11] The core of public health strategy includes facilitating access to quality nutrition, adequate fitness and physical activity, and providing support to people seeking smoking and alcohol cessation. Effective public health strategies also facilitate access to affordable pharmacological approaches. Recently, several drugs have been developed that show a significant impact on reducing the progression of CKD, both in people with and without diabetes. This article discusses how clinicians can promote conceptually simple actions into highly effective health benefits for patients who are most at risk of kidney disease. The cornerstones of CKD management are summarised in the Figure.

First principles of best care

First principles of best care aim to improve the overall health of people with CKD, particularly at-risk populations. Key aspects of management include providing culturally responsible delivery of kidney care, promoting effective patient–clinician partnerships and delivering targeted care to optimise outcomes. These principles are outlined in Box 1.[12]

Optimise holistic care

Mindset (mental wellness)

Patients' regular practices of healthful living are fundamental to kidney health and preventing related conditions associated with

CKD. Over-riding social, financial, pain or mental health issues can be temporary or permanent barriers to healthful practices. These factors may cause elevated cortisol levels (hypercortisolism), resulting in insulin resistance, insomnia, hunger, hypertension, central adiposity and proximal muscle weakness, which contributes to accelerating diabetes, CVD and CKD progression.[13] Online cognitive behavioural therapy modules, such as those provided by This Way Up (https://thiswayup.org.au), may help patients manage poor sleep and anxiety associated with hypercortisolism, and are best prescribed for couples or households rather than isolated individuals, provided they have the technological access and determination to complete the programs.[14]

In the authors' experience, mnemonics can help patient's focus attention systematically on their chosen problem area, starting with 'looking after your-SELFF', an acronym for Sleep, Exercise, Love, Foods and Fluids. Improving the quality of caloric intake takes priority over quantity, and includes prioritising a plant-based diet, avoiding ultra-processed foods and optimising water intake.[15] Referral for formal dietetic assessment and individualised advice is a standard of care but, in the authors' experience, broad direction can be quickly given as positive suggestions, for example, 'just eat real food', 'keep foods crunchy and colourful', 'swap salt flavouring to pepper, garlic, lemon and ginger' and 'make your drink a fashion statement traffic light: add mint, strawberry, lemon and orange to plain water for DIY potassium citrate'. Patients keen to avoid similar metabolic issues in their children or grandchildren should be encouraged to avoid smoking and make sure that special treats do not become daily habits.

Metabolic and psychological challenges

Supportive weight management

Avoid introducing assumptions or shame in collaborative health planning around weight management. Appreciating the metabolic and psychological challenges faced by many patients with CKD can sometimes be quickly gleaned by taking a five-point weight history of birth, teen post-puberty, maximum adult, minimum adult and current weight – then asking when and why the extreme values occurred, and with what functional impact. Episodes of extreme weight loss and volume depletion (e.g. teenage anorexia nervosa) can leave lasting kidney damage with osteoporosis. Conversely, for patients who are overweight, the dates of onset of painful arthritis, sleep apnoea, high BP, diabetes and stress incontinence are often precipitated by preceding weight gains.

Routine patient assessment

Routine examination of patients with CKD should include a five-point volume assessment, based on height, weight, postural change in BP and pulse rates, determining the extent of oedema and peripheral perfusion by capillary refill (and where possible, visualisation of jugular venous pressure). Total body weight measurement can be an understandably emotive issue and should be explained to patients as comprising the sum total of fluid, fat, muscle and bone weights, with each component having an individualised optimum range that is mostly genetically determined. Most people understand their weight in kg rather than body mass index (BMI). Therefore, using the rule of thumb that an individual's normal body weight (in kg) should roughly corresponds to their height (in cm) minus 100 (i.e. a BMI of 25 kg/m^2) allows patients to better estimate their target body weight. Investigations for target organ damage from high BP and diabetes is routine and reimbursed by Medicare.

Glycaemic control

Food accessibility, security, affordability and preparation, nutrition quality, eating frequency and culturally-based eating rituals are important considerations in understanding and supporting a patient's glycaemic control, and a referral to an accredited practicing dietitian may be considered where indicated.[16] Along with self-monitoring of blood glucose levels, made easier with the recent availability of continuous glucose monitoring devices (PBS subsidised for people with type 1 diabetes), the Kidney Disease Improving Global Outcomes (KDIGO) guidelines endorse measuring glycated haemoglobin (HbA_{1c}) to monitor glycaemic control, even in individuals with CKD despite limitations associated with concurrent anaemia.[17] HbA_{1c} targets are now individualised, and range from below 6.5% to below 8% in patients with diabetes and CKD.[17] Higher targets are usually reserved for patients with several comorbidities or at increased risk of hypoglycaemia.

Metformin has been a long-standing high-value, low-cost agent for metabolic improvement without weight gain but needs progressive dose reduction as GFR falls to avoid nausea or diarrhoea, and should be ceased immediately if a patient is unwell. Dipeptidyl peptidase-4

1. FIRST PRINCIPLES OF BEST CARE FOR IMPROVING THE HEALTH OF PEOPLE WITH CKD

Provide culturally responsible delivery of kidney care for people who need it the most

- Aboriginal and Torres Strait Islander people
- Patients who are vulnerable to accelerated kidney disease

Promote effective patient–clinician partnerships

- Use concepts such as the '6Ts' (talk, touch, test, treat, teach, trust; Figure)[12]

Deliver care to target optimal outcomes

- Improve the global survival of Aboriginal and Torres Strait Islander people
- Close the age gap for the onset of dialysis-requiring kidney failure
- Manage risk factors such as diabetes and hypertension
- Promote the use of new effective medications such as SGLT-2 inhibitors
- Address behaviour modification with regard to diet, exercise and consumption of addictive substances such as cigarettes, e-cigarettes or alcohol

Abbreviations: CKD = chronic kidney disease; SGLT-2 = sodium-glucose cotransporter-2.

2. PRESCRIBING AND MONITORING TIPS FOR RAS INHIBITORS

- Manage the expected increase in SCr level:
  - reduce or withdraw diuretics
  - choose calcium channel blockers as preferred second-line agents for blood pressure management
  - patients with an acute rise in SCr of >25% should be evaluated for volume depletion (from aggressive diuretic use), concomitant use of NSAIDs and bilateral renal artery stenosis, with the aim to try and continue the RAS blockade after these risk factors have been managed
- Manage hyperkalaemia:
  - limit dietary potassium intake
  - avoid drugs that can impair potassium excretion
  - avoid constipation (ensure adequate fluid intake, exercise, laxatives) and allow for concomitant use of diuretics
  - reduce metabolic acidosis with the use of sodium bicarbonate and concurrent use of potassium binders such as patiromer
- Counsel patients on the value of preparing a sick-day management plan:
  - include temporary cessation of drugs such as RAS inhibitors, diuretics, metformin, sulfonylureas, SGLT-2 inhibitors and NSAIDs
  - Kidney Health Australia provide a patient friendly sick day action plan template (https://www.kidney.org.au/uploads/resources/KHA-How-To-Sick-Day-Action-Plan-single.pdf)
- Combination ACE inhibitors and angiotensin receptor blockers are not recommended

Abbreviations: RAS = renin-angiotensin system; SCr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2.

inhibitors are similarly weight-neutral and have few side effects as eGFR falls. Conversely, sulfonylureas and insulin may cause weight gain and increase the risk of hypoglycaemia, especially in patients with CKD stages 4 and 5. A detailed approach to glycaemic management in the context of CKD has been recently published.[18] Use of SGLT-2 inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists is discussed below.

Management of hypertension

Optimising BP control is crucial to reducing CKD risk. Nonpharmacological measures include dietary salt reduction (<2 g sodium intake or <5 g sodium chloride per day) and regular exercise (at least 150 minutes per week of moderately intense physical activity as tolerated).[19] Weight loss, smoking cessation and reducing alcohol consumption are useful adjunct measures.[8] Current target BP is individualised, with a recommended target of at least 130/80 mmHg or lower if tolerated, with the safety caveat to avoid symptomatic hypotension.[7] Target BP can be safely maintained by home BP monitoring and taking measurements on sitting and standing, taking medications at night rather than morning, ensuring good hydration during hot weather or physical exertion and providing patients the authority to reduce the dose of medications if low BP is consistently symptomatic.

Cardioprotection

Low kidney function and albuminuria are independently additive major cardiac risk factors, with cardiovascular (CV) events the cause of 95% of deaths in people with CKD before reaching kidney failure. Therefore, aggressive cardioprotection is crucial.[20] CKD causes dyslipidaemia (i.e. low HDL-cholesterol and high triglyceride levels) and nephrotic syndrome causes hyperlipidaemia (i.e. raised LDL-cholesterol); therefore, optimising kidney function (by monitoring eGFR) and pursuing antiproteinuric therapies are crucial. Statins do not retard CKD progression or reduce cardiac events in patients who have developed kidney failure; however, they are recommended to reduce CV events in patients with CKD aged under 50 years with just one additional CV risk factor, regardless of lipid level.[21,22] Aspirin is no longer recommended for the primary prevention of CVD in people with CKD because of the increased bleeding risk associated with its use and a lack of proven benefit.[23,24]

Screening

Individuals at risk of developing CKD should undergo a kidney health check every one to two years, incorporating the three essential BP, eGFR and uACR tests promoted by Kidney Health Australia.[7] Aboriginal and Torres Strait Islander peoples are twice as likely to develop CKD than non-Indigenous Australians. Therefore an annual health check from 18 years of age that includes measuring BP, uACR and eGFR is recommended to encourage regular surveillance and promote early detection and management, and is reimbursed under MBS item 715.[25] Recommendations for culturally safe kidney care in First Nations Australians is a nationally recognised and inaugural guideline carefully informed and endorsed by First Nation people, clinicians and peak health organisations, and is useful resource for clinicians and consumers.[26]

Targeted therapeutics

RAS inhibitors

Renin-angiotensin system (RAS) blockade has stood the test of time in CKD management. Several studies over the past three decades have demonstrated the kidney and cardioprotective benefits and albuminurialowering effects of RAS inhibitors.[27-31] They are used as first-line agents in the management of proteinuria and hypertension (with or without diabetes). Typically, changes in BP and serum creatinine (SCr) and serum potassium levels are monitored two weeks after initiation of these agents.[7] A temporary increase in SCr level less than 25% due to the vasodilatory effects on the glomerular outflow is a predictable effect in the first few days, and the agent should be continued. A decline in kidney function of more than 25% is an indication to cease the drug and consider other factors and

referral of the patient to a nephrologist. Additionally, RAS blockade inhibits the action of aldosterone, predisposing patients to hyperkalaemia, particularly in patients with advanced CKD. Tips for prescribing and monitoring RAS inhibitors are highlighted in Box 2.

SGLT-2 inhibitors

SGLT-2 inhibitors were initially used to treat malaria, and later developed as hypoglycaemic agents. Although their impact on glycaemic control is modest, their efficacy in reducing the progression of CKD and heart failure, irrespective of diabetes status, has been a game changer for patients. SGLT-2 inhibitors are now the second-line agent of choice for managing diabetes (after metformin).[17] More recently, dapagliflozin and empagliflozin showed a 39% and 28% risk reduction in kidney-related outcomes, respectively.[32,33]

Dapagliflozin is PBS listed for patients with CKD independent of diabetes status (eGFR 25 to 75 mL/min/1.73 m^2 and uACR 22.6 to 565 mg/mmol); empagliflozin is TGA indicated for adults with CKD stages 2 and 3a and a uACR 30 mg/g (3 mg/mmol) or higher, or CKD stages 3b to 5 regardless of uACR. SGLT-2 inhibitors are not approved for use in patients on kidney replacement therapy (dialysis or transplant); however, the RENAL LIFECYCLE trial is currently underway to address the efficacy of dapagliflozin in patients with severe CKD (Clinical Trials Identifier: NCT05374291). SGLT-2 inhibitors are also not indicated for those with polycystic kidney disease or acute glomerulonephritis requiring immunosuppression.

SGLT-2 inhibitors are simple to use and have a low side-effect profile. However, as with RAS inhibitors, SGLT-2 inhibitor use can lead to an acute increase in SCr level in the first four weeks of initiation due to glomerular haemodynamic changes. This dip in kidney function is not associated with a greater long-term decline and is, in fact, associated with a rebound and, ultimately, slower progression of CKD.[7] The risk of genital mycotic infections is increased and should be managed with patient education on maintaining meticulous groin hygiene and close monitoring for signs of infection. Euglycaemic diabetic ketoacidosis is also a concerning adverse effect of SGLT-2 inhibitor use, particularly in people with diabetes, and withdrawal of insulin should be considered in those experiencing starvation and acute sickness. Tips for prescribing and monitoring SGLT-2 inhibitors are highlighted in Box 3.

3. PRESCRIBING AND MONITORING TIPS FOR SGLT-2 INHIBITORS

- Perform an accurate volume assessment before prescribing an SGLT-2 inhibitor:
  - estimate jugular venous pressure
  - assess for peripheral oedema and lung auscultation
- Manage the expected rise in SCr level:
  - reduce or withdraw diuretics
  - choose calcium channel blockers as preferred second-line agents for blood pressure management
- Avoid hypovolaemia in euvolaemic patients:
  - consider adding a diuretic or antihypertensive agent
  - do not start these agents until hypovolaemia is corrected
- Manage increased risk of genital mycotic (including Candida) infections:
  - educate patients on maintaining meticulous groin hygiene
  - monitor closely for signs of infection
  - consider providing patients with a home mid-stream urine collection pot, a pathology request form and antifungals for prompt presumptive therapy at the time of initial SGLT-2 inhibitor prescription
  - the risk of severe urinary tract infections is not significant compared with other hypoglycaemic agents
- Manage the risk of hypoglycaemia in people with diabetes:
  - consider reducing the dose of medications, such as insulin or sulfonylureas, to reduce the risk of hypoglycaemia
  - the risk is low, especially in individuals without diabetes
- Manage the risk of euglycaemic diabetic ketoacidosis in people with diabetes:
  - consider withdrawal of insulin in those who experience starvation and acute sickness, which are risk factors
- Counsel patients on the value of preparing a sick-day management plan (see Box 2)
- Dapagliflozin is PBS listed for CKD independent of diabetes status

Abbreviations: CKD = chronic kidney disease; SCr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2.

Nonsteroidal MRAs

Mineralocorticoid receptor antagonists (MRAs) such as spironolactone have an established role in the management of heart failure and refractory hypertension (especially in patients with low to normal potassium levels), and also reduce albuminuria.[34-36] However, the side-effect profile, which includes increased risk of hyperkalaemia, acute kidney injury and gynecomastia, can often limit their use. Finerenone is a nonsteroidal MRA that is more selective for mineralocorticoid receptors. It has a lower risk of hyperkalaemia (similar to that of lower-dose spironolactone). Recent placebo-controlled trials have shown a synergistic effect of finerenone with RAS blockade in reducing the risk of kidney function decline and CV events in patients with type 2 diabetes and albuminuria, but there is a need for electrolyte monitoring as CKD advances.[37,38] Finerenone is listed on the PBS for patients with CKD (eGFR of 25 mL/min/1.73 m^2 or higher and uACR of 22.6 mg/mmol or higher) with type 2 diabetes in combination with RAS blockers and SGLT-2 inhibitors, unless medically contraindicated or intolerant. Tips for prescribing and monitoring nonsteroidal MRAs are highlighted in Box 4.

4. PRESCRIBING AND MONITORING TIPS FOR NONSTEROIDAL MRAs

- The nonsteroidal MRA finerenone can be added to RAS blockers and SGLT-2 inhibitors for treatment of CKD and type 2 diabetes as per current PBS criteria:
  - eGFR ≥25 mL/min/1.73 m^2 and uACR ≥22.6 mg/mmol
- Monitor serum potassium levels:
  - withhold finerenone if potassium level >5.5 mmol/L
- Manage hyperkalaemia (see Box 2):
  - restart finerenone if potassium level ≤5 mmol/L; but caution is advised in more advanced CKD
- Finerenone is PBS listed for CKD with type 2 diabetes*

Abbreviations: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; MRA = mineralocorticoid receptor antagonists; RAS = renin-angiotensin system; SCr = serum creatinine; SGLT-2 = sodium-glucose cotransporter-2; uACR = urine albumin-creatinine ratio.

*See full PBS schedule for details (www.pbs.gov.au/pbs/).

GLP-1 receptor agonists

GLP-1 receptor agonists (such as dulaglutide and semaglutide) stimulate glucose-dependent insulin release from pancreatic beta cells and suppress glucagon release from alpha cells. They are now a well-established third-line treatment for type 2 diabetes (after metformin and SGLT-2 inhibitors).[16] GLP-1 receptor agonists slow gastric emptying, suppress appetite and inhibit unnecessary hepatic gluconeogenesis, thus aiding weight loss, which further improves insulin sensitivity. They have gastrointestinal side effects and increase the risk of hypoglycaemia, although this risk is low.

Even more effective analogues, such as tirzepatide, the first glucose-dependent insulinotropic polypeptide/GLP-1 receptor agonist (or twincretin), and combination semaglutide-cagrilintide, show promise in achieving improved glycaemic control and weight loss.[39,40] Tirzepatide is currently only TGA approved for type 2 diabetes, and semaglutide-cagrilintide is undergoing clinical trials.

Several studies have demonstrated the efficacy of GLP-1 receptor agonists in reducing major cardiovascular events in people with type 2 diabetes and HbA_{1c} below 7%, and in reducing proteinuria, which suggests potential kidney protective benefits.[41-43] The recently completed FLOW trial aims to assess the impact of semaglutide on kidney function decline in people with type 2 diabetes, with key finding expected later in 2024.[44] GLP-1 receptor agonists are currently only TGA approved for type 2 diabetes. Tips for prescribing and monitoring GLP-1 receptor agonists are highlighted in Box 5.

5. PRESCRIBING AND MONITORING TIPS FOR GLP-1 RECEPTOR AGONISTS

- Manage and mitigate gastrointestinal side effects of GLP-1 receptor agonists:
  - start therapy at the lowest dose and up-titrate slowly to the maximal tolerated dose
  - encourage a change in eating patterns from eating out of habit to eating only when hungry and stopping when full
  - aim for slower, smaller, lighter meals
- Manage the (low) risk of hypoglycaemia:
  - consider reducing the dose of sulfonylureas or insulins
- GLP-1 receptor agonists should not be concomitantly prescribed with DPP-4 inhibitors
- GLP-1 receptor agonists are currently PBS listed for type 2 diabetes

Abbreviations: CKD = chronic kidney disease; DPP-4 = dipeptidyl peptidase-4; GLP-1 = glucagon-like peptide-1.

Multidisciplinary team input

This article aims to support clinicians to care for people with CKD or those who may have risk factors for CKD and does not provide exhaustive advice for managing people with kidney failure and advanced comorbid conditions that occur with CKD. Working within a multidisciplinary team that includes (but is not limited to) a nephrologist, a CKD nurse, a psychologist, endocrinologists, cardiologists and allied health professionals, can assist GPs in developing individualised care plans and in managing people with complex conditions.

Conclusion

The rising incidence of CKD is a significant public health concern. Addressing this growing problem involves a holistic approach to management that includes implementing nonpharmacological and pharmacological therapies, and input from a multidisciplinary team. Regular screening can help with early diagnosis and management. Optimising holistic care through nonpharmacological measures, including nutritional management and supporting lifestyle changes, is a mainstay for improving patient outcomes. Providing culturally responsible care to vulnerable at-risk populations, specifically Aboriginal and Torres Strait Islander people, is important for ensuring that care is effective, accessible, continuous and sustainable. A growing suite of pharmacological therapies are available for CKD and common comorbidities, and should be used to aggressively manage this disease and its associated risk factors. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

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