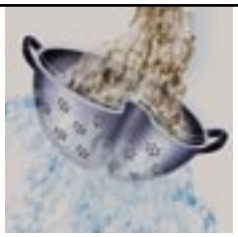

Chronic kidney disease

Management update

BACKGROUND Chronic kidney disease (CKD), defined as a glomerular filtration rate less than 60 mL/min/1.73 m2 and/or evidence of kidney damage for a period of at least 3 months, is an increasingly common, serious and under-recognised condition. A recent population study demonstrated that one in every 6 Australian adults has CKD (of which the vast majority are unaware).

OBJECTIVE This article aims to provide timely information to health professionals about how to classify and manage CKD.

DISCUSSION Management of CKD involves regular monitoring of cardiovascular and renal risk factors, identifying and treating common CKD complications, and avoiding medications that may worsen CKD. Early detection and timely appropriate management of CKD (especially with respect to blood pressure control) will substantially reduce kidney failure progression and cardiovascular risk by up to 50%.

Chronic kidney disease (CKD) is defined as a glomerular filtration rate (GFR) less than 60 mL/min/1.73 m2 and/or evidence of kidney damage for a period of at least 3 months (*Table 1*). Glomerular filtration rate can either be measured directly (eg. by clearance of creatinine, iohexol, EDTA, DTPA or iothalamate) or estimated by a validated prediction formula (eg. Cockcroft-Gault or Modification of Diet in Renal Disease [MDRD] equations).[1] Evidence of kidney damage includes microalbuminuria, macroalbuminuria, persistent haematuria (where other causes such as urologic conditions have been excluded), or radiological abnormalities (eg. the presence of scarring or polycystic kidneys on a renal ultrasound scan). Chronic kidney disease is classified into five stages according to the GFR level (*Table 2*).

Chronic kidney disease is a major public health problem in Australia and throughout the world. Based on data from the Ausdiab study,[2] it is estimated that over 2.3 million Australian adults have at least one manifestation of CKD (*Table 1*). This includes over 1.4 million individuals with at least moderate kidney failure (defined as a GFR <60 mL/min/1.73m2), 800 000 with microalbuminuria, 80 000 with macroalbuminuria and 600 000 with persistent haematuria. Moreover, approximately 6 million individuals have at least one of the major risk factors for CKD (*Table 3*). Chronic kidney disease is often not associated with significant symptoms and is unrecognised in 80–90% of cases.[2–4]

The role of the GP

With over 1.7 million adults with stage 3 CKD (GFR 30–60 mL/min) and only 180 nephrologists in Australia, it is clear that the majority of CKD patients (stages 1, 2 and 3) will be managed primarily by

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general practitioners (*Table 4*). Principal goals of CKD management are:

- reduction of cardiovascular and renal risk
- early detection and management of CKD complications
- avoidance of nephrotoxic medications and ensuring that dosages of other prescribed drugs are appropriate for the level of kidney function, and
- timely referral of CKD patients to a nephrologist.

Table 1. Definition of chronic kidney disease

- GFR <60 mL/min/1.73 m2 for ≥3 months with or without evidence of kidney damage*, OR
- Evidence of kidney damage (with or without decreased GFR) for ≥3 months, as evidenced by any of the following:
  - microalbuminuria (urinary albumin excretion rate 30–300 mg/day)
  - macroalbuminuria (urinary albumin excretion rate >300 mg/day)
  - persistent haematuria (where other causes such as urologic conditions have been excluded)
  - pathologic abnormalities (eg. abnormal renal biopsy)
  - radiologic abnormalities (eg. scarring or polycystic kidneys on renal ultrasound scan)

* Methods for measuring or calculating GFR[1]

Table 2. Stages of CKD (based on the CARI guidelines[12])

Stage	Description	GFR (mL/min/1.73 m2)	Prevalence from AusDiab[2]	Numbers in Australia
1	Kidney damage[a] with normal or ↑ GFR	≥90	3.1%	400 000
2	Kidney damage[a] with mild ↓ GFR	60–89	4%	500 000
3	Moderate ↓ GFR	30–59	10.9%	1 400 000
4	Severe ↓ GFR	15–29	0.3%	40 000
5	Kidney failure	<15 or on dialysis	0.02%	13 200

a = kidney damage is defined as persistent microalbuminuria, persistent proteinuria, persistent haematuria after exclusion of urological causes, or structural abnormalities on kidney imaging tests

Table 3. Major risk factors for chronic kidney disease[2–4]

	Percentage of Australian population affected
Hypertension	29
Diabetes mellitus	7.5
Age over 50 years	30
Smoking	16
Aboriginal or Torres Strait Islander	2

Reduction of cardiovascular and renal risk in CKD

All patients with CKD should undergo cardiovascular and kidney disease risk factor modification.[5,6] The presence of CKD is one of the most potent known risk factors for cardiovascular disease[7,8] such that individuals with CKD have a 10–20 fold greater risk of cardiac death than age and sex matched controls without CKD.[9] Moreover, patients with CKD are at least 20 times more likely to die from cardiovascular disease than survive to reach dialysis.[10] There is strong randomised controlled trial evidence that timely intervention in this group of patients can substantially reduce kidney failure progression and cardiovascular risk by up to 50%.[11] Once GFR is substantially reduced (≤60 mL/min/1.73 m2), the natural history is a continuing decline. The steps outlined below will slow the decline, but regular monitoring (at least every 3 months) is essential.

Blood pressure reduction

The most important goal in patients with CKD is to reduce arterial blood pressure to target levels (<130/85 mmHg if proteinuria <1 g/day or <125/75 mmHg if proteinuria >1 g/day or diabetic).[12] In order to reach currently recommended blood pressure targets, multiple (often 3–4) antihypertensive medications are frequently required.[11] Meta-regression analyses[13–16] have indicated that blood pressure reduction accounts for 50% of the variance in GFR decline and that each 10 mmHg reduction in mean arterial pressure (down to 92 mmHg) confers a benefit in GFR preservation of 3.7–5.0 mL/min/year. Based on the weight of accumulated evidence to date, angiotensin converting enzyme (ACE) inhibitors remain the first line therapy for patients with CKD,[17] although recent new evidence in type 2 diabetic nephropathy suggests that angiotensin receptor blockers (ARB) may provide comparable renoprotection.[18–20]

Antiproteinuric agents

The benefits of ACE inhibitors and ARB seem to be disproportionate to the degree of blood pressure reduction[16,18,21–23] and proportional to the degree of baseline proteinuria[24–26] and its reduction following treatment.[18,24] Several studies have found that ACE inhibitors and ARB are more effective than other specific antihypertensive agents, including diuretics, ß-blockers and calcium channel blockers, in reducing protein excretion and in slowing the decline of kidney

function.[16,27–29] The degree of renoprotection afforded also appears to be greater in patients with more severe degrees of kidney failure[14,30–32] and in those who experience a greater initial increase in serum creatinine concentration following the commencement of treatment.[14] It is therefore important to avoid withdrawal of ACE inhibitors or ARB in CKD patients who experience an acute rise in plasma creatinine concentration of less than 30% that stabilises within the first 2 months of therapy, as these patients are the ones who are most likely to derive the greatest renoprotective benefit.[14] Angiotensin converting enzyme inhibitors should be ceased:

- if the rise in creatinine level exceeds 30% above the baseline value (consider bilateral renal artery stenosis[14]), or
- if the serum potassium concentration exceeds 6 mmol/L (despite dose reduction, dietary potassium restriction and concomitant diuretic therapy).

However, the frequency of this complication in CKD patients is less than 2%, with the average rise in serum potassium levels being of the order of 0.5 mmol/L.

A number of randomised controlled studies have demonstrated that combining an ACE inhibitor and ARB may result in superior treatment of hypertension, proteinuria and/or kidney failure progression compared with monotherapy.[33–39]

Lipid lowering treatments

A number of small randomised controlled trials[40–47] and a meta-analysis[48] suggest that the use of statins in CKD patients with hypercholesterolaemia results in clinically and statistically significant slowing of kidney failure progression. It is presently uncertain whether statins reduce cardiovascular risk in CKD patients, but this question will be addressed in the next few years by the Studies of Heart and Renal Protection (SHARP) trial.[49] There is insufficient evidence available to define cholesterol targets in CKD patients, but it seems reasonable to adopt the targets recommended by the National Heart Foundation for patients with increased cardiovascular risk (total cholesterol <4.0 mmol/L and LDL cholesterol <2.5 mmol/L).

Glycaemic control

Several randomised controlled trials have demonstrated that intensive blood sugar control significantly reduces the risk of developing microalbuminuria, macroalbuminuria and/or overt nephropathy in patients with type 1 diabetes mellitus[50,51] and type 2 diabetes mellitus.[52,53] Based on these studies, the draft Caring for Australians with Renal Insufficiency (CARI) guidelines recommend targeting pre-prandial blood glucose levels between 4.4 and 6.7 mmol/L, and HbA1c values ≤7% for all diabetics.[12] However, there is no evidence that intensive glycaemic control alters renal outcomes once a patient has reached stage 3 CKD.

Cessation of smoking

Although there have been no randomised controlled trials, a large case control study[54] has demonstrated that current smoking is a significant, independent risk factor for more severe proteinuria and clinically important deterioration in renal function. Former smokers were not at increased risk,[54] suggesting that cessation of smoking may be associated with a reduction in risk of progressive renal disease. In retrospective studies of diabetic patients, smoking has been associated with an increased risk of albuminuria and more rapid deterioration of renal function.[55,56] Smoking cessation has been associated with a reduction in albumin excretion[55] and renal failure progression in diabetics.[57]

Weight reduction

Obesity has been shown to be a significant, independent risk factor for the development of de novo CKD[58–60] and an important accelerant of established CKD.[61,62] It is therefore important to encourage patients with CKD to lose weight through caloric restriction and physical exercise (*Table 5*).

Dietary protein restriction

Dietary protein restriction has been shown to result in modest slowing of CKD progression by meta-analyses.[63–65] However, this beneficial effect is generally considered to be outweighed by the deleterious consequences of nutritional restriction in CKD patients.[24,66] For these reasons, the CARI guidelines recommend a normal dietary protein intake (0.75–1.0 g/kg body weight/day).[12]

Correction of anaemia

Limited studies[67,68] have reported that correction of uraemic anaemia by erythropoietin slows the progression of CKD, although this finding has not been confirmed by other studies. However, patients certainly feel better.[69]

Table 4. Approach to CKD patients according to stage

CKD stage	**1**	**2**	**3**
Description	**Kidney damage + normal/ ↑ GFR**	**Kidney damage + mild ↓ GFR**	**Moderate ↓ GFR**
GFR (mL/min/1.73 m2)	>90	60–89	30–59
Common signs and symptoms	Nil	Nil	Nil or nocturia, mild malaise, anorexia
Common complications	Hypertension	Hypertension	Hypertension, hyperparathyroidism, renal osteodystrophy, anaemia, sleep apnoea, restless legs, CVD, malnutrition
Clinic assessment	BP, weight, volume assessment, urine dipstick	BP, weight, volume assessment, urine dipstick	BP, weight, volume assessment, urine dipstick
Lab assessment	UEC, eGFR Glucose Lipids	UEC, eGFR Glucose Lipids	UEC, eGFR Glucose Lipids FBC Iron stores Ca/PO4 PTH (quarterly)
Management	Diagnosis Cardiac and kidney risk factor modification	Diagnosis Cardiac and kidney risk factor modification	Diagnosis Cardiac and kidney risk factor modification
Frequency of clinical review	4–6 months	3 months	1–3 months
Nephrologist referral	Consider referral if any criteria listed in *Table 7* are present	Consider referral if any criteria listed in *Table 7* are present	Consider referral if any criteria listed in *Table 7* are present

BP = blood pressure, Ca/PO4 = serum calcium and phosphate, CVD = cardiovascular disease, echo = echocardiograph, FBC = full blood count, GIT = gastrointestinal tract, PTH = serum parathyroid hormone level, UEC = blood urea electrolytes creatinine

Early detection and management of CKD complications

Aside from the fact that the opportunity for renal function preservation is greatest when intervention is instigated early, many of the known complications of CKD such as hypertension, secondary hyperparathyroidism, renal osteodystrophy, anaemia, sleep apnoea, restless legs, cardiovascular disease, and malnutrition, are often already evident by stage 3 (GFR 30–59 mL/min/1.73 m2).[11] Other complications, such as hyperkalaemia, acidosis and hyperphosphataemia, usually become apparent in stage 4 CKD (GFR 15–29 mL/min/1.73 m2).[11] Regular monitoring for all of these complications (at least 3 monthly in stage 3 and monthly in stage 4) is essential. Recommended treatment goals and strategies are listed in *Table 5*. The NHMRC also recommends immunisation against influenza and invasive pneumococcal disease for patients with diabetes and/or chronic kidney failure.

4 **Severe ↓ GFR**	5 **End stage kidney failure**
15–29	<15 or on dialysis
Nil or nocturia, malaise, anorexia, nausea, pruritus, restless legs, dyspnoea	Nocturia, mild malaise, anorexia, nausea, vomiting, pruritus, restless legs, dyspnoea
Hypertension, hyperparathyroidism, renal osteodystrophy, anaemia, sleep apnoea, restless legs, CVD, malnutrition, hyperphosphataemia, acidosis, hyperkalaemia	Hypertension, hyperparathyroidism, renal osteodystrophy, restless legs, CVD, malnutrition, hyperphosphataemia, acidosis, hyperkalaemia, anaemia, sleep apnoea, paricarditis, GIT bleeding, encephalopathy, neuropathy
BP, weight, volume assessment, urine dipstick	BP, weight, volume assessment, urine dipstick
UEC, eGFR Glucose Lipids FBC Iron stores Ca/PO4 PTH (quarterly) Echo (annually)	As per monthly blood schedule specified by renal unit
Diagnosis Cardiac and kidney risk factor modification Treat complications Dialysis education	Dialysis or transplantation (or conservative medical management) Treat complications Dialysis access surgery Cardiac and kidney risk factor modification
Monthly	Monthly (shared with renal unit)
All patients should be referred to a nephrologist	All patients should be referred to a nephrologist

GFR = glomerular filtration rate, eGFR = estimated GFR (as determined by Cockcroft-Gault or MDRD formulae)

Medications review

Dosage reduction or cessation of renally excreted medications is generally required once the GFR falls below about 50 mL/min/1.73 m2. A list of commonly prescribed, renally excreted medications requiring review in CKD patients is provided in *Table 6*. It is also important to avoid nephrotoxic medications (*Table 6*).

Indications for referral

The CARI guidelines recommend that patients with:

- severe kidney failure (eGFR <30 mL/min; stage 4 or 5 CKD)
- diabetic nephropathy
- rapidly deteriorating renal function, or
- features suggestive of an underlying glomerulonephritis (eg. haematuria, casts or proteinuria in excess of 1g/day)

should be referred to a nephrologist (*Table 7*).

A number of studies[70–72] have demonstrated that early referral of patients with severe CKD to a

multidisciplinary renal unit is associated with reduced rates of kidney failure decline, decreased need for and duration of hospitalisation, increased likelihood of permanent dialysis access created before dialysis onset, reduced initial costs of care following the commencement of dialysis, increased likelihood of kidney transplantation, and decreased patient morbidity and mortality. The CARI guidelines recommend that patients should be referred to renal units at least 12 months before the anticipated commencement of dialysis and/or kidney transplantation (ie. GFR ≤30 mL/min/1.73 m2). Nevertheless, in spite of this, approximately 30% of CKD patients in Australia are referred 'late' to nephrologists (ie. within 3 months of needing to commence kidney replacement therapy). Such 'late referred' patients have markedly reduced survival rates on dialysis and are much less likely to receive a kidney transplant.[73]

Table 5. Treatment targets for CKD patients

Parameter	Target	Treatment
Lifestyle factors	Cease smoking	Lifestyle counselling
• Smoking	BMI <25 kg/m2	
• Nutrition	WC <102 cm (male), <88 cm (female)	
• Alcohol	Dietary salt intake <1 mmol/kg/day	
• Physical activity	≤2 standard glasses alcohol/day	
	≥30 mins/day physical activity	
Blood pressure modification	≤130/85 mmHg (≤125/75 mmHg if proteinuria >1 g/day or diabetes)	ACE inhibitor and/or ARB first line + lifestyle
Proteinuria	≥50% reduction of baseline value	ACE inhibitor and/or ARB first line
Cholesterol	Total <4.0 mmol/L	Dietary advice
	LDL <2.5 mmol/L	Statins
Blood sugar (diabetics)	Pre-prandial BSL 4.4–6.7 mmol/L	Lifestyle modification
	HbA1c ≤7.0%	Oral hypoglycaemics
		Insulin
Dietary protein	0.75–1.0 g/kg body weight/day (normal)	Dietary advice
Anaemia	Hb 110–120 g/L	Correct iron deficiency
		Erythropoietin/darbepoietin
Acidosis	HCO3 >22 mmol/L	NaHCO3 tablets
Hyperkalaemia	K^+ ≤6.0 mmol/L	Dietary advice
		Diuretics
		Resonium
		Cease ACE inhibitor/ARB if K^+ persistently >6.0 mmol/L
Hyperparathyroidism/ osteodystrophy	PO4 ≤1.75 mmol/L	Calcitriol
	PTH 2–5 times upper limit of normal	Phosphate binders (calcium carbonate, aluminium hydroxide, magnesium trisilicate, sevelamer)
		Cinacalcet
Malnutrition	Albumin ≥35 g/L	Dietary advice
Restless legs	Control symptoms	Correct iron deficiency
		Dopaminergic agents
Sleep apnoea	Prevent apnoeic episodes	Weight reduction
		Avoid central nervous system depressants
		CPAP therapy (if obstructive pattern)

Table 6. Frequently used drugs that may accumulate in kidney failure or damage the kidneys further

Commonly prescribed drugs that need to be reduced in dose or ceased in kidney failure

- Acetazolamide
- Aciclovir
- Colchicine
- Digoxin
- Gabapentin
- Lithium
- Sotalol
- Sulphonylureas
- Metformin (significantly increased risk of lactic acidosis when GFR <50 mL/min/1.73 m2)

Commonly prescribed drugs that can damage kidneys in patients with CKD

- Nonsteroidal anti-inflammatories, COX-2 inhibitors
- ACE inhibitors and angiotensin 2 receptor antagonists
- Beware, especially, the 'triple wammy' of NSAID/COX-2 inhibitor, ACE inhibitor and diuretic
- Radiographic contrast agents
- Aminoglycosides

Table 7. Indications for referral of CKD patients to a nephrologist

- eGFR <30 mL/min/1.73 m2 (stage 4 or 5 CKD)
- Rapidly declining kidney function (>15% ↓ in GFR over 3 months)
- Significant proteinuria >1 g/24 hours
- Glomerular haematuria
- Kidney impairment plus hypertension that proves difficult to control
- Diabetes with kidney impairment or proteinuria/albuminuria

Conclusion

Chronic kidney disease is a common, under-recognised and eminently treatable condition that affects over 2.3 million Australians. It is also a major risk factor for cardiovascular disease, such that CKD patients are far more likely to die of ischaemic heart disease than to end up on dialysis. General practitioners are the key health care providers for patients with CKD and need to be aware of: strategies for modifying the risk of cardiovascular disease and kidney failure progression in CKD patients; strategies for detecting and treating complications at each of the various stages of CKD; commonly prescribed medications that are nephrotoxic or require dose reduction/cessation in CKD; and the indications for nephrologist referral.

Summary of important points

- Patients with stages 1–3 CKD are likely to be asymptomatic and diagnosis should be actively sought in patients with CKD risk factors.
- CKD is the strongest known risk factor for cardiovascular disease, such that CKD patients are far more likely to die of ischaemic heart disease than to end up on dialysis.
- ACE inhibitors remain the first line antihypertensive agents in patients with CKD.
- Proven effective interventions include reduction of blood pressure (most important), prescription of an ACE inhibitor and/or ARB as antiproteinuric agents, lowering of serum cholesterol, cessation of smoking, correction of anaemia and intensive glycaemic control (in diabetics before the development of macroalbuminuria).
- Nephrotoxic drugs should be avoided in CKD patients.
- Many commonly prescribed medications are renally excreted and should have their dosages reduced when the GFR falls below 50 mL/min/1.73 m2.

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