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CLINICAL INVESTIGATIONS FROM THE RACP

Early detection and treatment of chronic kidney disease

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Key points

- **Chronic kidney disease (CKD) is common and often asymptomatic.**
- **CKD is associated with significant morbidity and mortality; prompt recognition and treatment can improve outcome.**
- **Estimated glomerular filtration rate (eGFR) is more sensitive than serum creatinine level alone in detecting early CKD.**
- **Treatment aims to reduce cardiovascular risk and slow CKD progression.**
- **Presence of one or more 'red flags' necessitates prompt referral to a nephrologist.**

In this series, we present authoritative advice on the investigation of a common clinical problem, especially commissioned for family doctors and written by members of the Royal Australasian College of Physicians.

Chronic kidney disease (CKD) is a major public health issue, with an estimated prevalence in Australia of 15% (based on AusDiab data for 2001 and 2005).[1] CKD is frequently asymptomatic, mostly undiagnosed, and one of the strongest risk factors for cardiovascular disease. There are treatments to slow progression of kidney disease, and early intervention and referral improve outcomes.

CKD is defined as:

- glomerular filtration rate (GFR) less than 60 mL/minute/1.73 m^2 for longer than three months with or without kidney damage, or
- evidence of renal damage, including microalbuminuria, proteinuria, glomerular haematuria, structural abnormalities such as polycystic kidneys or scarring, or pathological abnormalities such as an abnormal result on kidney biopsy.

Common causes of CKD include diabetic nephropathy, glomerulonephritis, hypertensive vascular disease and reflux nephropathy.[2] Conservative estimates of the prevalence of different stages of CKD among people in Australia are shown in Table 1.[1,3]

This article will discuss how to detect and manage early CKD. A suggested approach is outlined in the flowchart on page 17.[2] The goals of management are:

- early identification and quantification of CKD
- treatment to slow or prevent CKD progression
- modification of cardiovascular risk factors
- avoidance of nephrotoxic drugs and appropriate dosing of renally excreted drugs for the level of renal impairment.

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DETECTING CKD

Creatinine versus glomerular filtration rate

CKD is often diagnosed based on a raised serum creatinine level. However, creatinine is a relatively poor marker of kidney function, and GFR can be reduced by up to 50% before creatinine rises out of the normal range. Estimated GFR (eGFR) is a much better tool for assessing renal function and can be calculated using formulas such as the Cockcroft–Gault formula (based on creatinine level, age, sex and weight), or the Modified Diet in Renal Disease (MDRD) or recently developed CKD Epidemiology Collaboration (CKD-EPI) formulas (based on creatinine level, age and sex).

The CKD-EPI formula is currently recommended for calculating eGFR in Australian laboratories (Table 2).[4] This formula better estimates the risk of adverse outcomes, including end-stage kidney disease, cardiovascular outcomes and all-cause mortality, than previous equations, mostly by reclassifying some individuals previously considered high risk to low risk.[5] The CKD-EPI formula has been validated for use in several non-white populations but not in Aboriginal or Torres Strait Islander people. It performs poorly when renal function is changing rapidly. It should be noted that any formula is only a guide, and formal creatinine clearance should be tested if there is uncertainty.

The introduction of eGFR reporting has increased the use of ACE inhibitors and angiotensin II receptor antagonists (ARAs) in patients with CKD and also increased outpatient visits to nephrologists.[6,7]

Screening for CKD

CKD is generally asymptomatic; kidney function can be significantly reduced before symptoms are present. Screening is therefore imperative for patients who have risk factors for CKD, including:

- smoking
- diabetes
- hypertension
- obesity (body mass index of 30 kg/m^2 or more)
- established cardiovascular disease
- family history of kidney disease
- Aboriginal or Torres Strait Islander origin and age 30 years or older.

Patients who have one or more of these risk factors should be screened every one to two years (or annually for those with hypertension or diabetes). Initial screening includes:

- measuring blood pressure
- measuring serum creatinine level to calculate eGFR
- testing for protein or albumin in the urine by measuring urinary albumin to creatinine ratio (ACR), preferably in the first morning void. Urinary ACR correlates well with daily protein excretion in a 24-hour urine collection and is easier to measure in an outpatient setting.

There is a growing focus on identifying albuminuria (ACR, males 2.5 mg/mmol or above; females 3.5 mg/mmol or above), as increasing proteinuria is associated with an increased risk of progression of CKD. It is also an independent risk factor for cardiovascular disease.

Haematuria can also be an indicator of renal damage or inflammation but may have other causes such as urinary tract disease or malignancy. Persistent haematuria should be investigated.

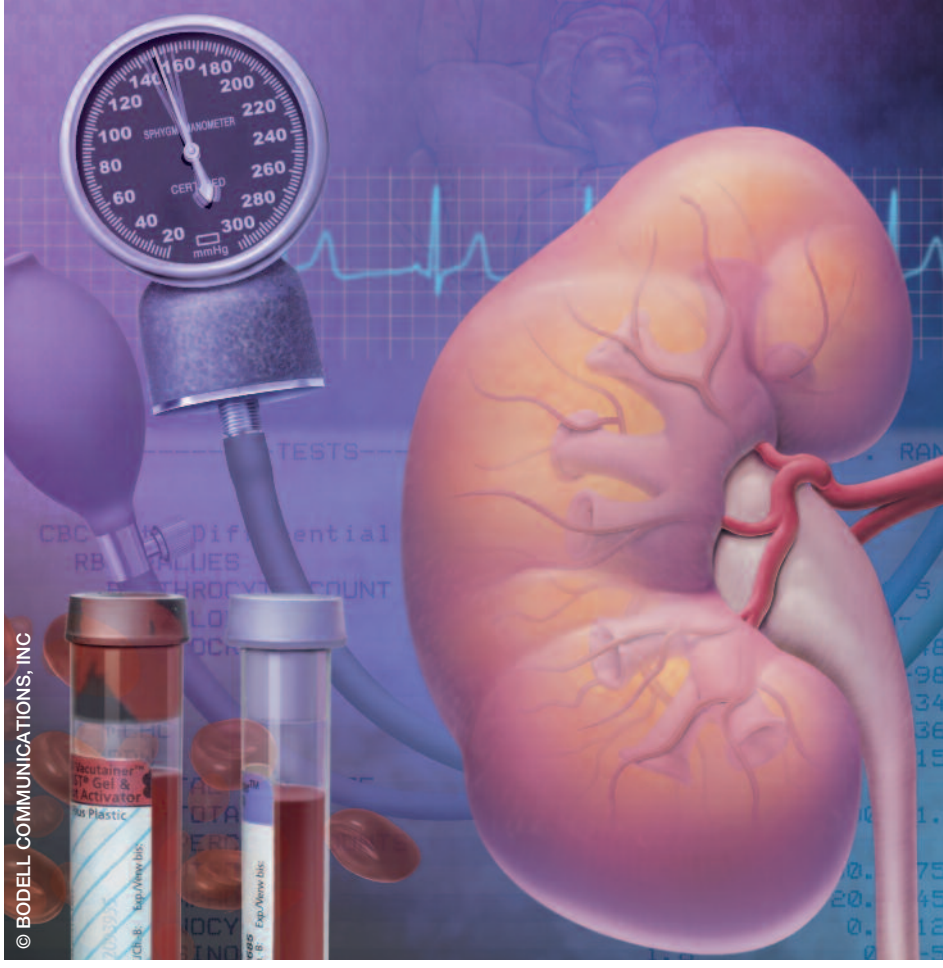


TABLE 1. PREVALENCE OF CHRONIC KIDNEY DISEASE IN PEOPLE AGED OVER 25 YEARS IN AUSTRALIA[1,3]

CKD stage*	Description	GFR (mL/min/1.73 m²)	Prevalence (%)†	Estimated number
1	Kidney damage with normal GFR	≥90	0.9	110,000
2	Kidney damage with mild reduction in GFR	60 to 89	4.9	610,000
3a	Moderate reduction in GFR	45 to 59	8.1	1,000,000
3b		30 to 44		
4	Severe reduction in GFR	15 to 29	0.2	30,000
5	Kidney failure	<15 or on dialysis	0.1	16,000

ABBREVIATIONS: CKD = chronic kidney disease; GFR = glomerular filtration rate.
* Disease stage defined by the Kidney Disease Outcomes Quality Initiative (K/DOQI).[3] † Prevalence determined using AusDiab data for 2001 and 2005.[1]

URGENT REFERRAL

It is important to recognise when a raised serum creatinine level needs immediate investigation and referral as it may represent life- or kidney-threatening disease. Red flags include:

- a marked elevation in serum creatinine level
- rapid progression of renal impairment, oliguria or anuria
- active urinary sediment (glomerular haematuria and/or cellular casts)
- systemic symptoms (fever, arthralgia or pulmonary symptoms)
- marked elevation in blood pressure.

A marked elevation in blood pressure could represent malignant hypertension with end-organ damage. Any of the other features could represent a potentially life- or renal function-threatening illness, such as systemic vasculitis.

INVESTIGATION OF REVERSIBLE CAUSES

Reversible causes of reduced renal function should be identified and corrected early after their discovery. Decreased renal perfusion from reduced intravascular volume, hypotension and drugs that lower GFR, especially NSAIDs, should be corrected. ACE inhibitors and ARAs may lower GFR, but this is expected and should not necessarily be a reason to withdraw them.

Symptoms of urinary obstruction necessitate early imaging. However, as obstruction may be asymptomatic, imaging should be included routinely in the investigation of an eGFR less than 60 mL/minute/1.73 m².

Evidence of hypercalcaemia, both symptomatic or biochemical, should be sought. Hypercalcaemia should be treated as it can lead to deterioration of renal function, as well as being a marker of possible malignancy.

SLOWING PROGRESSION OF CKD

CKD can progress to end-stage kidney disease, but the rate of progression is highly variable. Some interventions have been shown to delay this progression.

Blood pressure control

The most important intervention in CKD is adequate blood pressure control. There is good evidence that lower blood pressure is associated with slower decline in GFR in both diabetic and non-diabetic kidney disease.[8] The renoprotective effect of antihypertensive therapy is more marked in patients with significant proteinuria (protein excretion more than 1 g/day).

Blood pressure target values are:

- less than 130/80 mmHg for patients with albuminuria or diabetes
- less than 140/90 mmHg for other patients.

Blood pressure control should start with lifestyle interventions such as salt restriction, alcohol reduction, weight loss and exercise. Following these interventions, antihypertensive therapy should be introduced to achieve blood pressure target values.

ACE inhibitors and ARAs have a greater renoprotective effect in patients with proteinuria and should be the agents of choice in these patients. However, in patients without proteinuria, they seem to confer no advantage over other antihypertensive agents.[8] Despite the individual benefits, combining ACE inhibitors and ARAs has been associated with increased complications compared with either alone and should be commenced only in consultation with a nephrologist.[9]

Diabetes control

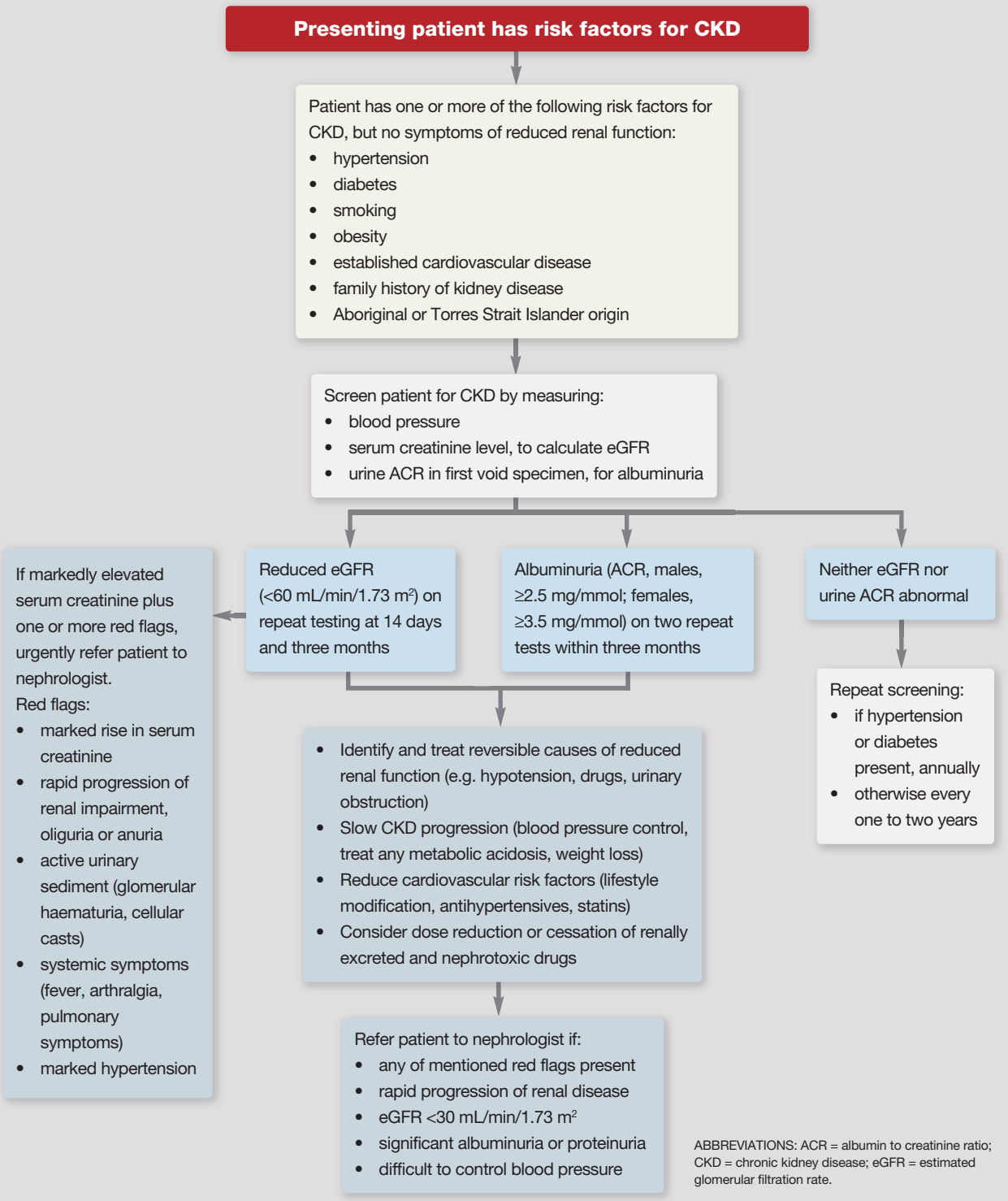
Good glycaemic control is advocated in people with diabetes and CKD for reducing diabetes complications and cardiovascular risk. There is evidence that normalising glucose levels can delay onset and progression of diabetic nephropathy.[10] The recommendation is to maintain the glycosylated haemoglobin level below 7%.

Treating metabolic acidosis with sodium bicarbonate has been shown to slow progression in CKD.[11]

Weight loss

There is evidence that weight loss decreases proteinuria as well as blood pressure.[12] Every kilogram of weight loss has been associated with a decrease in proteinuria

AN APPROACH TO INVESTIGATING CHRONIC KIDNEY DISEASE[2]



ABBREVIATIONS: ACR = albumin to creatinine ratio; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate.

TABLE 2. FORMULAS USED FOR CALCULATING EGFR, FROM THE CKD EPIDEMIOLOGY COLLABORATION (CKD-EPI)*[4]

Sex	Serum creatinine (μmol/L)	Formula for eGFR (mL/min/1.73 m²)
Female	≤62	$144 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.7)^{-0.329} \times (0.993)^{\text{age in years}}$
	>62	$144 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.7)^{-1.209} \times (0.993)^{\text{age in years}}$
Male	≤80	$141 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.9)^{-0.411} \times (0.993)^{\text{age in years}}$
	>80	$141 \times (\text{SCr in } \mu\text{mol/L} \times 0.0113/0.9)^{-1.209} \times (0.993)^{\text{age in years}}$

ABBREVIATIONS: CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; SCr = serum creatinine level.
* As recommended by the Australasian Creatinine Consensus Working Group.[4]

of 110 mg/day and in microalbuminuria of 1.1 mg/day. Although there are currently no data on the persistence of these reductions, weight loss is still recommended for the management of CKD as well as for cardiovascular risk reduction.

MODIFICATION OF CARDIOVASCULAR RISK FACTORS

CKD is an independent risk factor for cardiovascular disease. Good blood pressure control reduces cardiovascular risk as well as having beneficial effects on kidney disease. Interventions, including weight loss and antihypertensive therapy, should be introduced to achieve blood pressure target values, as outlined above.

Statins have been shown repeatedly to reduce cardiovascular risk in patients with raised serum cholesterol and also those with established coronary artery disease. The SHARP trial showed that the risk of cardiovascular events was reduced in patients with CKD to a similar degree as in patients without CKD.[13]

Smoking cessation is well established for cardiovascular risk reduction and there is also some evidence that it may slow progression of CKD.[14]

Aspirin has been used for reducing cardiovascular risk in patients with established coronary artery disease as well as for prevention in patients with cardiovascular risk factors. A reduced risk of cardiovascular events has also been shown in patients with CKD, but with an increased risk of bleeding events.[15]

Moderate exercise improves blood pressure, reduces cardiovascular events and improves survival.

DRUGS AND DOSING

The use of renally excreted drugs needs to be reviewed for possible dose reduction or cessation when eGFR falls below 60 mL/minute/1.73 m². These drugs include, but are not limited to, digoxin, opioid analgesics, antiviral agents, benzodiazepines and metformin.

Potentially nephrotoxic drugs should be used with care or avoided in patients with reduced renal function. These include NSAIDs and COX-2 inhibitors, lithium, aminoglycosides and radiographic contrast agents.

SPECIALIST REFERRAL

Early referral to a nephrologist has been shown to improve outcomes for patients with CKD stages 4 and 5, both slowing progression of renal disease and improving survival.[16-18] There is also evidence that late referral is associated with higher morbidity and mortality.[19] Referral to a nephrologist is appropriate in the presence of:

- any of the red flags mentioned above
- rapid progression of renal disease
- eGFR less than 30 mL/minute/1.73 m²
- significant albuminuria or proteinuria
- blood pressure that is difficult to control.

Anaemia should be investigated early, to exclude gastrointestinal blood loss in particular. If no cause is found other than CKD then the patient should be referred promptly for consideration of recombinant erythropoietin therapy.

When a patient is referred to a nephrologist, information on current kidney function as well as any renal imaging (ultrasound examination) should be sent with the patient to facilitate appropriate triage and management.

CONCLUSION

CKD is common and one of the strongest risk factors for cardiovascular disease; however, there are treatments and lifestyle modifications that can slow its progression. As CKD is often asymptomatic, screening is imperative for patients with risk factors. Screening should include determination of eGFR and urinary ACR. If screening suggests kidney disease then reversible causes should be sought and treated. Blood pressure control is the most important intervention to slow progression of CKD and also reduces cardiovascular risk. MT

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