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Original Article

KHA-CARI Guideline: Early chronic kidney disease: Detection, prevention and management

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SCOPE OF GUIDELINE

This guideline addresses issues relevant to the detection, primary prevention and management of early chronic kidney disease.

PART I. DETECTION OF EARLY CHRONIC KIDNEY DISEASE: NATURAL HISTORY, RISK FACTORS, SCREENING, DIAGNOSIS AND REFERRAL

Chronic kidney disease (CKD) is a major public health problem in Australia and throughout the world. Based on data from the Ausdiab study,[1] it is estimated that over 1.7 million Australian adults have at least moderately severe kidney failure, defined as an estimated glomerular filtration rate (eGFR) less than 60 mL/min per 1.73 m^2. This pernicious condition is often not associated with significant symptoms or urinary abnormalities and is unrecognized in 80–90% of cases.[1–3] CKD progresses at a rate that requires approximately 2300 individuals each year in Australia to commence either dialysis or kidney transplantation.[4] Furthermore, the presence of CKD is one of the most potent known risk factors for cardiovascular disease (CVD), such that individuals with CKD have a 2- to 3-fold greater risk of cardiac death than age- and sex-matched controls without CKD.[5–7] According to death certificate data, CKD directly or indirectly contributes to the deaths of approximately 10% of Australians and is one of the few diseases in which mortality rates are worsening over time.[8] However, timely identification and treatment of CKD can reduce the risks of CVD and CKD progression by up to 50%.[9]

Early detection of CKD may therefore have value, although criteria for a screening programme to detect the disease must be met to balance the aggregate benefits with the risks and costs of the screening tests. General practitioners, in particular, play a crucial role in CKD early detection and management. All people attending their general practitioner should be assessed for CKD risk factors as part of routine primary health encounters.

A number of studies[10–20] have further demonstrated that early referral of patients with more serious CKD to a multidisciplinary renal unit is associated with reduced rates of kidney failure decline, decreased need for and duration of hospitalization, increased likelihood of permanent dialysis access created prior to dialysis onset, reduced initial costs of care following the commencement of dialysis, increased likelihood of kidney transplantation, and decreased patient morbidity and mortality. Nevertheless, approximately one-quarter of CKD patients in Australia are referred 'late' to nephrologists (i.e. within 3 months of needing to commence kidney replacement therapy).[4] Such 'late referred' patients have markedly reduced survival rates on dialysis and are much less likely to receive a kidney transplant.[21]

The objective of this guideline is to identify what risk factors, present in an appreciable portion (>5%) of the community, are associated with the development of CKD and which are remediable or potentially modifiable, in order to detect early CKD and intervene at the earliest possible stage. Also, evidence regarding outcomes and complications of CKD is evaluated with particular emphasis on outcomes and symptoms that are likely to be deemed significant by people diagnosed with early stage of CKD. The role and cost-effectiveness of screening for CKD, the target population, setting and screening strategies are also addressed.

1. Symptoms, natural history and outcomes of early chronic kidney disease

Evidence Summary

a. CKD is associated with increased risks of death from any cause, cardiovascular events and progression to end-stage kidney disease (ESKD).
b. The risk of adverse outcomes increases with more severe stages of CKD.
c. At every stage of CKD the presence of proteinuria increases the risks of adverse outcomes.
d. The relative risks of death and ESKD differ according to patient age and comorbidities. The likelihood of death increases with advancing age.
e. Complications of stage 1–3 CKD include anaemia, secondary hyperparathyroidism, and vitamin D deficiency.
f. A large proportion of patients with early CKD experience pain, reduced quality of life and sleep disturbance. However, these symptoms are no worse than in patients with other medical problems.

2. Risk factors for early chronic kidney disease

Evidence Summary

a. The following risk factors are associated with an appreciable (20–40%) risk of CKD:

- Obesity
- Hypertension
- Diabetes mellitus
- Cigarette smoking
- Established CVD
- Age > 60 years
- Aboriginal and Torres Strait Islander peoples
- Maori and Pacific peoples
- Family history of stage 5 CKD or hereditary kidney disease in a first or second degree relative
- Severe socioeconomic disadvantage

b. Metabolic syndrome is associated with an increased risk for CKD but it is still not known whether this constellation improves risk prediction beyond that afforded by its individual components (hypertension, impaired glucose tolerance and dyslipidaemia).
c. The presence of kidney stones is associated with a modest increased risk of CKD (approximately 6% absolute risk).
d. There is conflicting evidence regarding the roles of alcohol consumption and benign prostatic hypertrophy as risk factors for CKD.

3. Screening for early chronic kidney disease

Guideline recommendations

a. We recommend screening for CKD as it is an effective strategy to allow earlier detection and management to reduce the increasing CKD burden (1C).
b. We recommend that screening for CKD be targeted and performed in individuals at increased risk of developing CKD, including those with diabetes mellitus, hypertension, and established CVD (1B).
c. We recommend screening in those with additional CKD risk factors identified in Guideline 2a (obesity, cigarette smoking, Aboriginal and Torres Strait Islander peoples, family history of stage 5 CKD or hereditary kidney disease in a first or second degree relative and severe socioeconomic disadvantage) (1D).
d. We recommend screening every 1–2 years in adults depending on their risk factor profile as per Table 1 (1D).
e. The tests recommended for CKD screening should include both a urine test for albuminuria and a blood test for serum creatinine to determine an eGFR (1C).
f. We recommend a urinary albumin : creatinine ratio (UACR) measurement in a first void specimen for the detection of proteinuria in both diabetic and non-diabetic patients (1C).
i. Where a first void specimen is not possible or practical, a 'spot' (random) urine specimen for UACR is recommended (1C).
g. We recommend that a positive UACR screening test should be repeated on 1–2 occasions over a period of three months to confirm persistence of albuminuria. If the first positive UACR is a random spot (as it may be for opportunistic screening), then repeat tests should ideally be first morning void specimens (1D).
i. We recommend following the algorithm depicted in Figure 1 (1D).

Table 1 Early detection of CKD using Kidney Health Check

Indication for testing†	Recommended tests	Frequency of testing
Smoker Diabetes Hypertension Obesity Established cardiovascular disease‡ Family history of CKD	Urine ACR¶, eGFR, blood pressure	Every 12 months
Aboriginal or Torres Strait Islander aged ≥30 years§		Every 24 months

Source: Modified from RACGP Red Book[22] and NACCHO: National Guide.[23]
†While being aged 60 years of age or over is considered to be a risk factor for CKD, in the absence of other risk factors it is not necessary to routinely test these individuals for kidney disease. ‡Established cardiovascular disease is defined as a previous diagnosis of coronary heart disease, cerebrovascular disease or peripheral vascular disease. §See National Guide to a Preventive Health Assessment in Aboriginal and Torres Strait Islander Peoples (NACCHO) 2012 for more detail regarding indication for testing in Aboriginal and Torres Strait Islander Peoples. ¶If Urine ACR positive, arrange two further tests over three months (preferably first morning void). If eGFR<60 mL/min per 1.73 m^2, repeat test within 14 days. ACR, albumin : creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

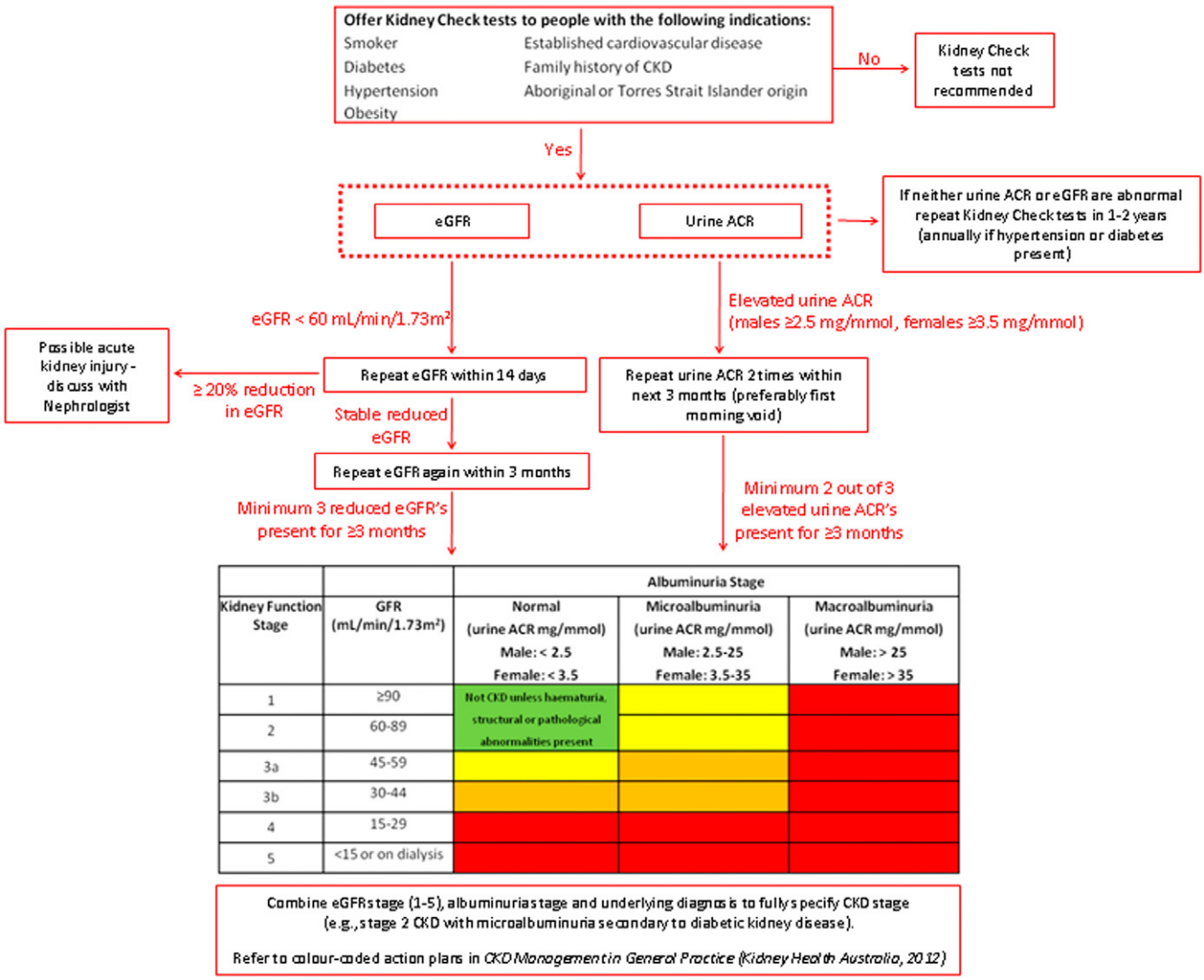

Fig. 1 Recommended screening algorithm for detection of CKD (chronic kidney disease). **Sources**: The Royal Australian College of General Practitioners (RACGP) 'Red Book' Taskforce.[22] National Aboriginal Community Controlled Health Organisation (NACCHO/RACGP).[23] ACR, albumin : creatinine ratio; eGFR, estimated glomerular filtration rate.

4. Diagnosis, classification and staging of chronic kidney disease

Guideline recommendations

Diagnosis

a. We recommend that CKD be diagnosed in all individuals on at least two occasions for a period of at least 3 months, irrespective of the underlying cause and on the basis of: (1C)

i. an estimated or measured GFR <60 mL/min per 1.73 m^2 and/or

ii. evidence of kidney damage (albuminuria, proteinuria, haematuria after exclusion of urological causes, or structural abnormalities on kidney imaging tests)

Note:

- These diagnostic criteria are the same for all races and gender.

Classification and staging

b. We recommend that the stages of CKD should be based on the combined indices of kidney function (measured or estimated GFR) (Table 2) and kidney damage (albuminuria/proteinuria) (Table 3), irrespective of the underlying diagnosis (1C).

c. We recommend that these staging criteria be used to stratify CKD patient risk (Table 4) and be linked with specific management plans according to that level of risk (1C).

d. We recommend that when CKD is initially diagnosed, to consider the underlying cause and to pursue the diagnosis sufficiently to exclude treatable pathology, such as obstruction, vasculitis, nephrotic syndrome and rapidly progressive glomerulonephritis (1C).

e. We recommend an early repeat of the eGFR test if there is any suspicion of an acute condition. It is particularly important to be sure that acute kidney disease is not missed by assuming the first abnormal eGFR represents a long-standing condition (1C).

f. We recommend that the above criteria for CKD diagnosis and staging be applied irrespective of age (1C).

Table 2 Indices for kidney function

Kidney function stage	GFR (mL/min per 1.73 m^2)	Description
1	≥90	Normal or increased GFR
2	60–89	Normal or slightly decreased GFR
3A	45–59	Mild-moderate decrease in GFR
3B	30–44	Moderate-severe decrease in GFR
4	15–29	Severe decrease in GFR
5	<15 or on dialysis	End-stage kidney failure

GFR, glomerular filtration rate.

Ungraded suggestions for clinical care

Diagnosis

i. The following diagnostic evaluation tests for CKD are always indicated:

- Full blood count
- Repeat (within 1 week) serum urea/electrolytes/creatinine/eGFR/albumin
- Urine ACR (preferably on a first morning void, although a random urine is acceptable)
- Fasting lipids and glucose
- Urine microscopy and culture
- Renal ultrasound scan

ii. The following diagnostic evaluation tests for CKD are sometimes indicated:

If patient:	Then carry out the following test:
Has diabetes	$HbA1_C$
Has eGFR <60 mL/min per 1.73 m^2	Serum calcium, phosphate, PTH, 25-hydroxy-vitamin D and iron studies
Is >40 years old	Serum and urine electrophoresis
Has rash, arthritis or features of connective tissue disease	Anti-nuclear antibodies, Extractable nuclear antigens, Complement studies
Has pulmonary symptoms or deteriorating kidney function	Anti-glomerular basement membrane antibody, Anti-neutrophil cytoplasmic antibody
Has risk factors for HBV, HCV and HIV	HBV, HCV, HIV serology
Has persistent albuminuria >60–120 mg/mmol (approximately equivalent to 24 h urinary protein >1–2 g/day)	Refer to Nephrologist for consideration of renal biopsy

5. When to refer for specialist renal care

Guideline recommendations

a. We recommend referral to a specialist renal service or nephrologist in the following situations:

i. Stage 4 and 5 CKD of any cause (eGFR < 30 mL/min per 1.73 m^2) (1C)

ii. Persistent significant albuminuria (ACR ≥ 30 mg/mmol, approximately equivalent to protein creatinine ratio (PCR) ≥50 mg/mmol, or urinary protein excretion ≥500 mg/24 h) (1C)

iii. A consistent decline in eGFR from a baseline of <60 ml/min per 1.73 m^2 (a decline > 5 ml/min per 1.73 m^2 over a 6-month period which is confirmed on at least three separate readings) (1C)*

b. We suggest referral to a specialist renal service or nephrologist in the following situations:

i. Glomerular haematuria with macroalbuminuria (2C)

ii. CKD and hypertension that is hard to get to target despite at least three anti-hypertensive agents (2C).

c. We suggest discussing management issues with a specialist by letter, email or telephone in cases where it may not be necessary for the person with CKD to be seen by the specialist (2D).

d. Once a referral has been made and a plan jointly agreed, routine follow-up could take place at the patient's General Practitioner surgery rather than in a specialist clinic. If this is the case, we recommend that criteria for future referral or re-referral should be specified (1D).

e. We suggest that the individual's wishes and comorbidities when considering referral, be taken into account (2D).

*It is important to note that intra-individual variation in eGFR readings can be as high as 15–20% between consecutive eGFR measurements, such that a number of readings are required before one can be confident that a decrease in eGFR of >5 ml/min per 1.73 m^2 in 6 months is real.

PART II: PRIMARY PREVENTION OF EARLY CHRONIC KIDNEY DISEASE: LIFESTYLE FACTORS, BLOOD PRESSURE, DIABETES MELLITUS, PATIENT EDUCATION, MULTIDISCIPLINARY CARE AND PREGNANCY

Chronic kidney disease is associated with considerable morbidity and increased mortality risk. Biochemical evidence of CKD (reduced estimated GFR, elevated serum creatinine)

Table 3 Indices for kidney damage

Kidney damage stage†	Urine albumin/creatinine ratio (mg/mmol)	24 h urine albumin (mg/day)	Urine protein: creatinine ratio (mg/mmol)	24 h urine protein (mg/day)
Normoalbuminuria	<2.5 (M) <3.5 (F)	<30	<4 (M) <6 (F)	<50
Microalbuminuria	2.5–25 (M) 3.5–35 (F)	30–300	4–40 (M) 6–60 (F)	50–500
Macroalbuminuria	>25 (M) >35 (F)	>300	>40 (M) >60 (F)	>500

†When reporting kidney function, stage (stages 1–5) is combined with kidney damage (albuminuria/proteinuria (Norm-/Micro-/Macro-albuminuria)) and clinical diagnosis to fully specify CKD (chronic kidney disease) stage (e.g. Stage 2 CKD with microalbuminuria secondary to diabetic nephropathy). *Note*: These staging criteria are the same for all races and gender.

Table 4 Staging criteria for CKD and patient risk

Kidney function stage	GFR (mL/min per 1.73 m^2)	Albuminuria stage		
		Normal (urine ACR mg/mmol)	Microalbuminuria (urine ACR mg/mmol)	Macroalbuminuria (urine ACR mg/mmol)
		Male: <2.5 Female: <3.5	Male: 2.5–25 Female: 3.5–35	Male: >25 Female: >35
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60–89			
3a	45–59			
3b	30–44			
4	15–29			
5	<15 or on dialysis			

Risks of progressive CKD denoted as low (green), moderate (yellow), high (orange) and very high (red). [For specific management plans refer to Chronic Kidney Disease Management in General Practice[24]] *Note*: (i) For patients with CKD, the combination of a low GFR and albuminuria or proteinuria places them at a greater risk of CKD progression at all ages, than those with just low GFR, albuminuria or proteinuria. (ii) A measured or estimated GFR < 45 mL/min per 1.73 m^2 is associated with increased risks of adverse renal, cardiovascular and other clinical outcomes, irrespective of age. ACR, albumin : creatinine ratio; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate.

usually indicates the presence of tubulointerstitial fibrosis within the kidney. Such pathology is irreversible, therefore the aim of treatment in many patients with CKD is to delay progression of disease rather than achieve a cure. In light of this it is clear that implementation of primary prevention measures to avoid development of CKD is a preferable strategy. While much information is available about risk factors for development of CKD (refer to Early CKD CARI Guideline Part I) it is less clear whether risk factor modification prevents development of CKD.

In addition to primary prevention strategies, the needs of patients and their families to access CKD education and information tailored to the stage and cause of CKD, has been highlighted by some studies. White *et al*.[25] conducted a cross sectional survey of participants of the AusDiab study to assess the level of awareness of the causes of kidney disease. The results indicated an overall low level of awareness of risk factors for kidney disease and low level of recall of kidney function testing even among subgroups of the cohort who were at greatest risk of CKD.[25] A study by Ormandy *et al*.[26] found that CKD patients had clear information needs, which changed according to their CKD stage. Moreover, Nunes *et al*.[27] reported disparity between perceived knowledge and objective knowledge in patients with CKD. Although information is crucial to knowledgeable decision-making by patients, how it is provided is also very important. Successful contemporary educational interventions for people with a chronic disease typically incorporate psychological methods to empower patients and change behaviour.[28]

The aim of this guideline was to evaluate currently available clinical evidence of interventions relevant to lifestyle modification, patient education, elevated blood pressure, diabetes mellitus, referral to multidisciplinary care and the effect of pregnancy in the primary prevention of CKD. In this guideline prevention of CKD is defined as a normal serum creatinine, eGFR above 60 mL/min and absence of urinary albumin, protein or haematuria.

6. Primary prevention of chronic kidney disease: modification of lifestyle factors

Guideline recommendations

Weight management

a. We suggest the maintenance of a stable (within 5%), healthy weight as it is associated with a lower risk of developing CKD (2C)

b. We suggest, where weight loss is required, the use of medications such as topiramate (if available) in conjunction

with a non-pharmacological weight loss programme to increase weight loss and reduce the risk of developing CKD (2B)

Dietary modification

c. We suggest adherence to a low salt diet (<100 mmol or 2300 mg/day) to reduce the risk of developing CKD (2C)

d. We suggest a normal dietary protein intake, as the relative benefits *versus* harms of dietary protein restriction has not been adequately established (2D)

Lifestyle modification

e. We recommend avoidance or cessation of cigarette smoking to reduce the risk of developing CKD (1D)

f. We suggest that patients with identified excessive alcohol consumption should receive psychological support and interventions to minimise excessive intake (2D)

g. We suggest that patients be encouraged to undertake regular physical exercise to reduce the risk of developing CKD. Exercise needs to be appropriate for their physical ability and medical history (2C)

7. Primary prevention of chronic kidney disease: blood pressure targets

Guideline recommendations

a. We recommend that patients achieve standard BP targets <140/90 as this reduces mortality and morbidity outcomes (1A).

Ungraded suggestions for clinical care

- Patients in Stages 1–2 CKD should have their blood pressure checked annually
- Patients in Stages 3A and 3B should have their blood pressure checked 3–6 monthly

8. Primary prevention of chronic kidney disease: managing diabetes mellitus to reduce the risk of progression to CKD

Guideline recommendations

a. We suggest that patients with diabetes mellitus aim to achieve an HbA1c <7.0% or <53 mmol/mol* (2B).

*SI units recommended as per The International HbA1c Consensus Committee.[29,30]

9. Education Strategies

Guideline recommendations

a. We suggest early, comprehensive and structured CKD education about management of hypertension, diabetes, obesity and smoking and other risk factors as this may delay CKD progression (2C).

b. We recommend education that includes information on CKD as well as the psychological aspects of CKD, for predialysis and dialysis patients (1C).

c. We suggest that the provision of CKD education is conducted by primary care providers who are involved in the screening process (2D).

d. We suggest educational programmes be provided based on consideration of (2C)

- **i.** CKD stage
- **ii.** The individual's risk factors and health requirements
- **iii.** The individual's cultural and social background

e. We recommend education and self-management programmes for patients with diabetes mellitus and hypertension to prevent CKD development and progression (1B).

f. We recommend CKD and hypertension management education be given to individuals with multiple cardiovascular risks and hypertension (1C)

g. We recommend that education on hypertension management include the following:

- **i.** Promoting lifestyle changes (salt restriction, regular physical activity, weight reduction, alcohol moderation) which help to prevent and control hypertension (1C)
- **ii.** Encourage all diabetic patients with CKD to use home blood pressure measurement to ensure that recommended blood pressure targets are consistently being reached (1C)

h. We suggest diabetes management education include the following:

- **i.** Regular physical activity, most days of the week, as it is an important component of diabetes mellitus self-management programmes (2D).
- **ii.** Early CKD diabetic patients should be educated about target levels for blood pressure, cholesterol and glycaemic control (2C) (see medical therapies to reduce CKD guideline).

10. Multidisciplinary or multifaceted renal care in early chronic kidney disease

Guideline recommendations

a. We recommend an individualized, structured care plan with appropriate prescription of medications and interventions targeting cardiovascular and renal risk modification, for all patients with early CKD (1D).

b. We suggest the involvement of a multidisciplinary healthcare team (e.g. doctor, practice nurse, dietician and social worker) in the management of patients with early CKD as this results in improved clinical outcomes compared with care provided by a health practitioner working in isolation (2C).

Ungraded suggestions for clinical care

Patients with diabetes should be referred to other professionals specializing in diabetes (e.g. diabetologist, diabetes educator and dietician) as soon as practicable.

11. Pregnancy and early chronic kidney disease

Guideline recommendations

a. We suggest that women with early CKD who have normal or near-normal renal function (eGFR > 60 mL/min per 1.73 m^2) and who wish to fall pregnant be advised that they can provided their blood pressure is well controlled (2C).

b. We recommend that women with CKD who have poorly controlled hypertension or markedly impaired kidney function (eGFR < 30 mL/min per 1.73 m^2) be advised against falling pregnant on the basis of risk of renal functional decline, as well as increased risks of adverse foeto-maternal outcomes, such as pre-ecclampsia, eclampsia, preterm delivery, need for Caesarian section, need for neonatal intensive care, stillbirths and low birth weight babies (1C).

c. We recommend that women with CKD receive pre-conception counselling that pregnancy is associated with increased risks of adverse maternal outcomes (gestational hypertension, pre-eclampsia, eclampsia and maternal death) and adverse foetal outcomes (premature births, intra-uterine growth retardation, small-for-gestational age, neonatal mortality, stillbirth and low birth weight) (1C).

Note:

The degrees of increased risk of each outcome in pregnant women with CKD are difficult to precisely quantify, although have generally been reported in each study to be at least 2-fold higher than in pregnant women without CKD.

d. We recommend that patients with CKD planning to fall pregnant should have their medications reviewed and modified prior to conception. The anticipated benefits of each medication should be weighed against its potential risks. In particular, angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) should be discontinued (1D).

e. We recommend that pregnant patients with CKD should be carefully monitored for the development of hypertensive disorders of pregnancy and renal functional deterioration, and should also be referred to a nephrologist (1D).

f. The above recommendations also apply to women with functioning kidney transplants (1D).

PART III: MANAGEMENT OF EARLY CHRONIC KIDNEY DISEASE: MODIFICATION OF LIFESTYLE AND NUTRITION INTERVENTIONS, MEDICAL THERAPIES (ANTI-HYPERTENSIVES, LIPID-LOWERING, HYPOGLYCAEMICS, ANTI-PLATELET, URIC ACID-LOWERING AGENTS, VITAMIN D)

Chronic kidney disease is a significant contributor to morbidity and mortality, and represents a major expense to the healthcare system. Early intervention with appropriate medical therapies is essential to address this public health burden and may reduce the progression of CKD and cardiovascular risk by up to 50%.[9]

Important risk factors for CKD include diabetes mellitus, hypertension, obesity and smoking. Modification of lifestyle habits (e.g. healthy diet, physical exercise, smoking cessation, moderate alcohol consumption and weight loss in obese people) may therefore be of value in retarding the progression of CKD. In addition, restriction of dietary protein[31] and augmentation of fluid intake[32] have been recommended as a treatment for retarding CKD progression for over 50 years. While the National Health and Medical Research Council (NHMRC) Dietary Guidelines for Australian Adults (http://www.nhmrc.gov.au/guidelines/publications/n29-n30-n31-n32-n33-n34) provide useful generalized, evidence-based information about healthy food choices, patients with CKD often require individualized diet prescription by an appropriately qualified dietitian.

Diabetes mellitus, particularly type 2, is increasing in prevalence and associated with significant cardiovascular morbidity and mortality. It also represents the leading cause of CKD worldwide. Evidence from large, prospective trials indicates that tight glycaemic control in type 1[33] and, to a lesser extent, type 2[34,35] diabetic patients results in clinically significant preservation of renal function. The optimal level to which glycosylated haemoglobin (HbA1c) should be targeted (<7.0%) is largely based on the Diabetes Control and Complications Trial (DCCT) and UKPDS trials[33–35] but the threshold below which the benefit is lost or at which the incidence of side-effects becomes unacceptable is not clear.

Chronic kidney disease is also a well-established independent cardiovascular risk factor. Evidence[36,37] for anti-platelet therapy suggests that low-dose aspirin reduces the risk of CVD by 25–33%, particularly in patients with established CVD (secondary prevention) or those at high risk (primary prevention). However, these potential benefits need to be weighed against an increased risk of bleeding in CKD.[38] With regard to blood pressure management new evidence reviewed in this updated guideline has led to an upward revision of the recommended BP targets. These new targets are in line with those recommended by the NHMRC.[39]

There are a number of epidemiological studies[40,41] which have established that asymptomatic hyperuricaemia is associated with both CKD and ESKD. However, hyperuricaemia is a ubiquitous finding in CKD[42] and could be a consequence of reduced excretion, diuretic therapy, or oxidative stress. Although it is not clear whether urate plays a causative role or is an indirect marker of kidney function, uric acid lowering therapy has emerged as a potentially novel therapeutic treatment for slowing the progression of CKD.[41]

In the CKD population, both vitamin D deficiency and insufficiency are common. As GFR falls, hydroxylation/activation of vitamin D is impaired leading to hyperparathyroidism and CKD mineral and bone disorder (CKD-MBD). Retention of phosphate may begin to occur when renal function falls below 80% of normal. Changes in any of these laboratory values may begin in stage CKD 3, although the presence, rate of change and severity of these abnormal

parameters are highly variable among individuals. In a study of 168 consecutive new referrals of patients with stages 2–5 CKD to a CKD clinic, Ravani *et al.*[43] observed that both 25-hydroxyvitamin D and 1,25-dihydroxyvitamin-D levels were significantly, inversely associated with eGFR. Consequently, the prevalence rates of vitamin D insufficiency and deficiency increased from 62% and 25% in stage 2 CKD to 88% and 56% in stage 5 CKD. Similarly, a cross-sectional study of 15 068 adults participating in the Third National Health and Nutrition Examination Survey (NHANES) reported a strong, inverse association between albuminuria and serum 25-hydroxyvitamin D concentrations.[44]

The objective of this guideline is to review currently available evidence with regards to medical therapies for the management of: hypertension, hypercholesterolaemia, diabetes mellitus, CVD, hyperuricaemia and vitamin D insufficiency and deficiency in patients with stage 1–3 CKD. Evidence for lifestyle modification and nutrition is also reviewed.

12. Modification of lifestyle and nutrition interventions for management of early chronic kidney disease

Guideline recommendations

Dietary modification

Protein

a. We suggest that patients with progressive CKD have individualized diet intervention involving an appropriately qualified dietitian (2C).

b. We recommend adults with early CKD consume a normal protein diet, consisting of 0.75–1.0 g/kg per day, with adequate energy. This is in line with the Recommended Daily Intake (RDI) for the general population (1C).

c. A low protein diet (≤0.6 g/kg per day) to slow down CKD progression, is not recommended because of the risk of malnutrition (1C).

d. We suggest people with excess protein intakes reduce their intakes to the RDI levels as a high protein diet may accelerate renal function decline in mild renal insufficiency (2C).

Salt

e. We recommend that early CKD patients restrict their dietary sodium intake to 100 mmol/day (or 2.3 g sodium or 6 g salt per day) or less, as it reduces blood pressure and albuminuria in patients with CKD (1C).

f. We recommend that patients with CKD should not use salt substitutes that contain high amounts of potassium salts (1D).

Phosphate

g. We suggest that early CKD patients (stages 1–3) should not restrict dietary phosphate intake as restriction of dietary phosphate does not influence renal or cardiovascular outcomes in these patients (2C).

Potassium

h. We suggest that early CKD patients with persistent hyperkalaemia restrict their dietary potassium intake with the assistance of an appropriately qualified dietitian (2D).

Polyphenol-enriched diets

i. We suggest that in early CKD patients with diabetic nephropathy, consumption of a carbohydrate-restricted, low-iron-available, polyphenol-enriched (CR-LIPE) diet may slow the progression of diabetic nephropathy (2C).

Caloric restriction

j. We recommend that overweight/obese patients with CKD should be prescribed caloric restriction under the management of an appropriately qualified dietitian. A reduction in weight can mean improvement of CKD (1C).

k. We suggest that, in the absence of specific recommendations for CKD, overweight or obese patients are encouraged to lose body fatness to aim for a body mass index (BMI) closer to 18.5–24.9 kg/m^2 and waist circumference ≤102 cm for men and ≤88 cm for women (2C).

- This is in line with the Dietary Guidelines for Australian Adults recommended by the NHMRC and Australian better health initiatives.

Fruit and vegetables

l. We suggest adults with early CKD consume a balanced diet rich in fruits and vegetables, as these appear to reduce blood pressure and have renoprotective effects comparable to sodium bicarbonate (2C).

Mediterranean diet

m. We suggest adults with early CKD consume a Mediterranean style diet to reduce dyslipidemia and to protect against lipid peroxidation and inflammation (2C).

Dietary fibre

n. We suggest adults with early CKD consume a diet rich in dietary fibre that is associated with reduced inflammation and mortality in patients with CKD (2D).

Lifestyle modification

Physical exercise

o. We suggest that patients with CKD be encouraged to undertake regular physical exercise that is appropriate for their physical ability and medical history (2B).

p. We suggest that, in the absence of specific exercise recommendations, patients are encouraged to include a minimum of 30 min of moderate physical activity each day in line with the Guidelines for Australian Adults recommended by the NHMRC (2C).

Smoking

q. We recommend that patients with CKD stop smoking to reduce their risk of CKD progression and cardiovascular risk (1C).

Alcohol

r. There is no specific evidence for alcohol consumption in patients with CKD. However, we suggest the recommendations made by the NHMRC Australian Guidelines to Reduce Health Risks from Drinking Alcohol be applied to patients with early CKD (2C).

Carbonated beverages

s. We suggest patients with CKD minimize their intake of cola beverages to a maximum of one glass (250 ml) or less of cola per day (2C).

Fluid intake

t. We suggest that patients drink fluid in moderation. For most patients with early CKD, a daily fluid intake of 2–2.5 L (including the fluid content of foods) is sufficient, although this might need to be varied according to individual circumstances (2C).

Note:

- There is no convincing evidence to date that pushing oral fluid intake beyond this amount, except in states of excessive fluid loss (e.g. sweating or diarrhoea), is beneficial for long-term kidney health.

13. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: anti-hypertensive agents

Guideline recommendations

Non-diabetic Kidney Disease

a. We recommend that either ACEI or ARB should be used as first line therapy (1B)

b. We recommend that combination therapy with both ACEI and ARB should be avoided (1C)

Blood pressure targets

c. We recommend BP ≤ 140/90 (1B)

d. We recommend BP ≤ 130/80 in people with micro or macroalbuminuria (UACR > 3.5 mg/mmol in women; UACR >2.5 mg/mmol in men) (1B)

Diabetic Kidney Disease – Type I and Type II Diabetes

a. We recommend that either ACEI or ARB should be used as first line therapy (1A)

b. We recommend that combination therapy with both ACEI and ARB should be avoided (1C)

c. β-Blockers, calcium channel blockers and thiazide diuretics are all appropriate second line therapy (1B)

Blood pressure targets

d. We recommend a blood pressure target of ≤130/80 in all people with diabetes (1B)

14. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: lipid lowering therapy

Guideline recommendations

a. We recommend that patients with early CKD (stage 1–3) should be treated with statin therapy (with or without ezetimibe) to reduce the risk of atherosclerotic events (1A).

15. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: glycaemic control

Guideline recommendations

a. We recommend that patients with early (stage 1–3) CKD because of type 1 or type 2 diabetes mellitus aim to achieve a HbA1c target of approximately 7.0% or 53 mmol/mol* (1B).

b. We recommend caution against intensively lowering HbA1c levels appreciably below 7.0% in view of demonstrated increased risks of hypoglycaemia (1B) and possibly death (1C).

c. We recommend that multifactorial interventions targeting cholesterol and blood pressure as well as glycaemic control should be instituted to improve renal and cardiovascular outcomes in patients with early (stage 1–3) CKD because of diabetes mellitus, particularly type 2 diabetes mellitus (1B).

*SI units recommended as per The International HbA1c Consensus.[29,30]

16. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: anti-platelet therapy

Guideline recommendations

a. We suggest that aspirin therapy should not be routinely recommended as the risk : benefit for primary prevention of CVD in patients with early (stage 1–3) CKD is uncertain (2C).

17. Medical therapies to reduce chronic kidney disease progression and cardiovascular risk: uric acid-lowering agents

Guideline recommendations

a. We suggest that use of uric acid lowering agents (such as allopurinol, rasburicase or feboxostat) should not be routinely recommended in people with early (stages 1–3) CKD who have asymptomatic hyperuricaemia (2C).

18. Vitamin D therapy (supplementation) in early chronic kidney disease

Guideline recommendations

a. We suggest vitamin D deficiency (25-hydroxyvitamin D <37.5 nmol/L) and insufficiency (25-hydroxyvitamin D 37.5–75 nmol/L), if present, be corrected using treatment strategies recommended for the general population (2C) as outlined below:

Vitamin D found in foods:

b. We suggest a daily oral intake (total) of vitamin D for patients with early CKD who are not exposed to direct sunlight for at least 1–2 h per week, as per NHMRC recommendations (2D).

- 19–50 years – 5 μg (200 IU)
- 51–70 years – 10 μg (400 IU)
- >70 years – 15 μg (600 IU)
- (where 1 μg = 40 IU)

Note:

Few foods contain significant amounts of vitamin D, the major sources being fatty fish (salmon, sardine, herring and mackerel), liver, eggs and fortified foods, such as margarine and some varieties of low-fat milk. There are limited data on vitamin D content of local foods. It is exceedingly difficult to obtain sufficient vitamin D from the diet alone.

Sun exposure for Vitamin D:

c. To strike a balance between achieving adequate vitamin D from sun exposure and avoiding the risk of skin cancer, we suggest that the recommendations made in the joint positions statements of the Australian and New Zealand Bone and Mineral Society, Osteoporosis Australia, the Australasian College of Dermatologists and the Cancer Council of Australia be applied to patients with early chronic kidney disease (2D):

- Fair-skinned people can get enough vitamin D in summer from a few minutes of sunlight on their face, arms and hands before 10:00 h or after 15:00 h on most days of the week.
- In winter in southern regions of Australia, when UV radiation levels are below 3, people need about 2–3 h of sunlight to their face, arms and hands over a week.

Note:

- Endogenous synthesis (activation) of vitamin D is reduced in CKD, but it is not sure if extended sunlight exposure could overcome such insufficiency.

Vitamin D supplementation:

d. We recommend a prescription of vitamin D therapy for early CKD patients with secondary hyperparathyroidism, as it has been shown to be effective in suppressing elevated levels of parathyroid hormone (PTH) (1A).

Note:

- However, there has been insufficient evidence to date to determine whether this intervention improves patient-level outcomes (e.g. bone pain, fracture, need for parathyroidectomy, progression to renal replacement therapy, cardiovascular events or all-cause mortality).
- These potential benefits of vitamin D therapy must be weighed against its potential deleterious effects, including hypercalcaemia, hyperphosphataemia, vascular calcification, adynamic bone disease and accelerated progression of CKD.

e. We recommend that early CKD patients on vitamin D therapy have their calcium, phosphate, PTH, alkaline phosphatase and 25-hydroxy-vitamin D levels monitored regularly (1C).

CONFLICT OF INTEREST

Emelia Atai, Graeme Turner, Kate Wiggins, Maria Chan, Tim Usherwood, Clodagh Scott and Nigel Toussaint have no relevant financial affiliations that would cause a conflict of interest according to the conflict of interest statement set down by KHA-CARI.

Richard Phoon has a level II b. conflict of interest for receiving speaker fees and honoraria from several companies related to anaemia, CKD-MBD and cardiovascular disease between 2008 and 2010.

David Johnson has a level II b. conflict of interest for receiving speaker honoraria and advisor's fees from several companies related to anaemia, CKD-MBD, hypertension and cardiovascular disease between 2008 and 2012.

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