NEPHROLOGY CLINICAL GUIDELINES:

CHRONIC KIDNEY DISEASE MANAGEMENT IN FIJI PRIMARY CARE

2022

Table of Contents

BACKGROUND

In 2017 an estimated 13.6% of the entire Fiji population had chronic kidney disease (**CKD**). [1] This is significantly higher than the estimated global CKD prevalence of 9.1%. [1] The annual incidence of stage 5 kidney failure in Fiji is also thought to be markedly elevated at 753-938 per million population, which is four to five times the incidence reported from nearby Australia in 2013. [2] The health complications associated with CKD has led it to be the 5th leading cause of years of life lost in Fiji. [3]

The high prevalence rates in Fiji reflect an equally high burden of non-communicable diseases, particularly diabetes mellitus and hypertension. In Fiji, and globally, these two diseases are responsible for the vast majority of CKD cases. Other less common, but still important causes include glomerulonephritis, polycystic kidney disease and obstructive nephropathy.

Kidney disease has a major effect on general health both as a direct cause of morbidity and mortality, but also as an important risk factor for cardiovascular disease. In fact, CKD is a stronger risk factor for future coronary events and all cause mortality than diabetes [4], and people with CKD have a 2-3 fold greater risk of cardiac death than people without the condition. [5] If allowed to progress, stage 5 kidney failure requires either dialysis or kidney transplantation to sustain life, access to which is limited in Fiji due to high costs.

Unfortunately <10% of adults with CKD are aware of their diagnosis [1] and as such, opportunities to alter the natural history of the disease and its complications are often not taken. Studies have found that if CKD is detected early and managed appropriately, then the otherwise inevitable deterioration in kidney function can be reduced by as much as 50% and may even be reversible. [6]

The purpose of this guideline is to assist the primary care team in carrying out their critical role in the management of an important and widespread chronic disease. The tasks in front of them that we aim to guide are:

1. Identify cases of CKD as early as possible in their disease history;
2. Implement evidence-based management strategies proven to slow CKD progression and reduce cardiovascular complications; and
3. Refer for specialist input in a timely manner.

The recommendations outlined in this guideline are based predominantly on the internationally recognised KDIGO (Kidney Disease Improving Global Outcomes) guidelines but have been adapted for the Fiji health system.

1. SCREENING

Early detection of disease enables clinicians to initiate effective treatment in mild disease, delaying or avoiding progression to kidney failure, and as such, screening patients at high risk for kidney disease has been found to be cost-effective. [7]

As patients can remain asymptomatic until >90% of kidney function has been lost, screening for CKD is recommended for those who have one of the following risk factors:

Diabetes | Hypertension | Cardiovascular disease | Family history of kidney failure | ≥60 years

Screening should be completed at the first appointment, repeated at least annually thereafter and include the kidney health triad of blood pressure measurement, eGFR and proteinuria assessment (figure 1). Urine dipstick is used to detect proteinuria in the Fiji setting due to its easy access and low cost. Urine dipstick though is not a sensitive test for low-grade proteinuria and so if the result is trace or negative ideally a urine albumin-to-creatinine ratio (**ACR**) should be conducted to exclude the presence of mild/moderate albuminuria missed on the dipstick.

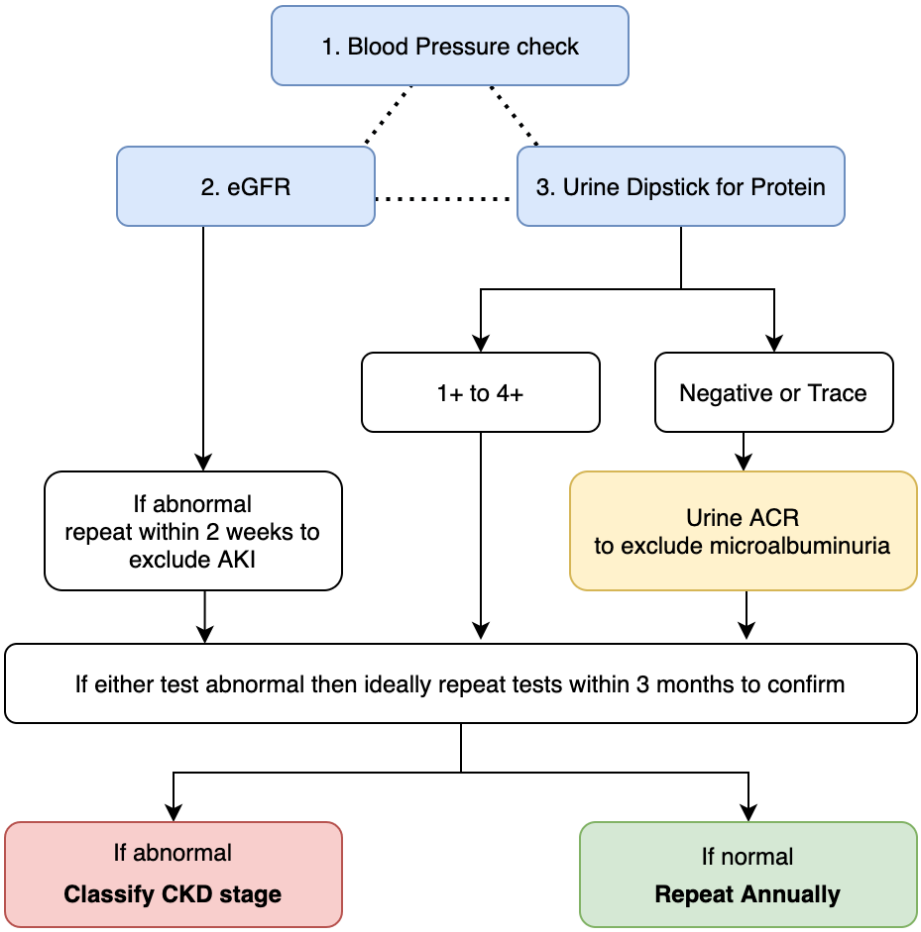


Figure 1. A pragmatic approach to CKD screening in Fiji.
ACR, albumin-to-creatinine ratio; eGFR, estimated glomerular filtration rate as calculated from serum creatinine using CKD-EPI or MDRD equations

2. DIAGNOSIS & CLASSIFICATION

CKD is defined as EITHER:

1. eGFR < 60ml/min/1.73m^2 for ≥3 months; and/or
2. Evidence of kidney damage, with or without decreased eGFR, as evidenced by one or more of the following:
    - Proteinuria
    - Haematuria, after exclusion of urological causes
    - Structural abnormalities on imaging
    - Pathological abnormalities on kidney biopsy

Once diagnosed, the clinician should then classify the stage of CKD using both eGFR and albuminuria assessment (figure 2). Assigning a CKD stage provides important prognostic information as the risk of outcomes such as cardiovascular death, kidney disease progression and kidney failure increase with each stage. Notably, the presence of albuminuria independently worsens prognosis significantly. Online tools can also be used to quantify an individual patient's risk of progressing to kidney failure and to show patients how that risk is lowered by treatment (e.g. kidneyfailurerisk.com).

For example:

- Mr AB with eGFR 70ml/min/m^2 and urine protein dipstick of 3+ is classified as CKD G2A3, which puts him at high risk of an adverse outcome (orange)
- Ms CD with eGFR 40ml/min/m^2 has a negative urine protein dipstick, so urine ACR is conducted with a result of 20mg/mmol. This puts her classification as CKD G3bA2 and at very high risk of an adverse outcome (red).

Staging will also help guide management and minimum follow-up intervals. Using the colouring in Figure 2 the following is a general guide to follow-up once initial management plan is in place

- Yellow = every 12 months
- Orange = every 3-6 months
- Red = every 1-3 months

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012

GFR categories (ml/min per 1.73 m²) Description and range				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				Urine ACR <3mg/mmol	Urine ACR 3-30mg/mmol	Urine ACR >30mg/mmol Dipstick ≥1+
	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

Figure 2. Classification and predicting prognosis of CKD - Adapted from KDIGO 2012 Clinical practice guideline for management of CKD. [8] *Colouring reflects the risk of progression and cardiovascular death – Green: low risk, Yellow: moderately increased risk; Orange: high risk; Red: very high risk.*

3. IDENTIFY CAUSE

CKD in itself is not a diagnosis. Attempts should be made to identify the underlying cause(s).

Although diabetes and hypertension are the most common causes of kidney disease in Fiji, other conditions can cause CKD, even in patients with these co-morbidities. The clinician must therefore evaluate for other causes, especially when the patient's duration of diabetic or hypertensive history, glycaemic or BP control and other end-organ complications (such as retinopathy) do not correspond with the severity of CKD found.

In addition to a good history and examination, it is recommended the following steps be taken for all patients with new diagnosis of CKD:

1. **Repeat eGFR**/electrolytes within 2 weeks to exclude acute kidney injury
2. **Proteinuria** assessment
    a. The presence of proteinuria reflects kidney disease and testing assists in disease detection prior to eGFR decline, prognosticating (figure 2), assessing treatment response and identifying different clinical syndromes.
    b. Urine protein dipstick, although accessible and cheap, is not a sensitive test for low-grade proteinuria. Therefore, if the dipstick result is trace/negative, urine ACR should be conducted to exclude the presence of moderate albuminuria (A2). A dipstick result of ≥1+ is suggestive of severe albuminuria (A3) (table 1).
    c. If heavy proteinuria and oedema are present it is recommended to check the serum albumin and consider a 24 hour urine collection for formal proteinuria quantification and exclusion of nephrotic syndrome.
3. **Haematuria** assessment (e.g., dipstick, microscopy)
    a. Haematuria can be either glomerular or non-glomerular in origin.
    b. When persistent haematuria is present with significant proteinuria (A2/A3) an underlying glomerulonephritis should be considered.
    c. Persistent haematuria mandates imaging of the renal tract, urine cytology and urologist advice.
4. **Ultrasound** of kidneys and urinary tract
    a. Ultrasound is used to exclude obstructive uropathy and other anatomical pathology.
    b. Normal kidney length is 10-12cm but can vary with patient height. Normal cortical thickness is 0.7-1.0cm.
    c. Kidney length <9cm and/or cortex thickness <0.7cm is suggestive of CKD. Other ultrasound signs are less reliable.
5. **Discuss** with a specialist if advice is needed (section 6)

Table 1. Interpreting and comparing different proteinuria assessments [8]

Albuminuria Categories	Protein Dipstick	ACR (mg/mmol)	24-hr Proteinuria
Normal/Mild (A1)	Negative*	< 3	<150mg/d
Moderate (A2)	Trace*	3-30	150-500mg/d
Severe (A3)	≥1+	30 70 >220	0.5g/d 1g/d >3.5g/d

**Dipsticks are only semi-quantitative and are not accurate for detecting mild/moderate albuminuria*
The relationship among these testing methods is an approximate only. ACR; albumin-to-creatinine ratio

4. EDUCATE PATIENTS ABOUT CKD

All patients should be informed of their CKD diagnosis and status at the time of diagnosis and at each follow-up. This is not only an ethical obligation, but also can be used to motivate patients to adhere to management plans and attend follow-up appointments.

During patient education it may be useful to use the eGFR as a marker of remaining percentage of kidney function. For example, eGFR of 50ml/min/m^2 can be discussed with the patient as 50% of remaining kidney function. Although not completely accurate (as normal eGFR is 120-130 ml/min/m^2), patients tend to understand their situation more easily using this method and can often remember the percentage value when discussing their medical history with other health professionals.

Table 2. Key Concepts & Example Talking Points [9]

1. What is CKD	CKD means the kidneys are damaged and may no longer filter blood well to remove wastes and excess water. This damage happens over many months to years. As more damage occurs, the kidneys are unable to keep the body healthy.
2. Importance of testing	Most people with CKD have no symptoms until their kidneys are close to failing. The only way to know if you have kidney disease and how it is changing is to get blood and urine tests at follow-up appointments.
3. Progressive nature of CKD	Kidney function in CKD usually does not get significantly better over time as most of the damage is permanent. In fact, for many people is likely to get worse as the remaining parts of the kidneys are increasingly overworked.
	When the kidneys fail altogether people need a treatment (either dialysis or kidney transplant), which can do the work their kidneys normally would do to keep them alive and maintain health.
4. Importance of treatment & follow-up	Treatment is focused on helping slow kidney function decline, keeping the kidneys working for as long as possible, and reducing the risk of heart disease.
	Treatment includes eating a healthy diet with less salt, keeping blood pressure well controlled, and controlling blood sugars if you have diabetes. Taking medications as prescribed is usually important to achieve these goals.
	It is very important to work together to manage your CKD as best as we can. With proper management and regular follow-up, you may never need dialysis or, we can at least delay it for as long as possible.

5. KEY MANAGEMENT STEPS

Summary of Key Management Steps

1. Aim systolic BP < 130 mmHg
2. Use maximum tolerated dose of ACEi or ARB
3. Use SGLT2 inhibitor if eGFR >20 ml/min/1.73m^2
4. Statin therapy should be prescribed for all adults with CKD
5. Individualise glycaemic target between HbA1c <6.5% to <8.0%.
6. Discuss dietary advice and regularly encourage lifestyle change
7. Educate patients about medications – to avoid NSAIDs, provide sick day plan and ask them to inform their caregivers of their CKD status when prescribing
8. Follow-up regularly based on staging classification
9. Refer to a specialist if eGFR < 30 ml/min/1.73m^2, rapidly worsening function or the cause of CKD is unclear

5.1. BLOOD PRESSURE CONTROL

Hypertension is both a cause of CKD and a common complication of it. Regardless, elevated blood pressure (BP) increases the risk of worsening kidney function and cardiovascular disease and achieving recommended targets is one of the most important goals in the management of CKD.

> Adults with high BP and CKD should be treated with a target systolic BP < 130 mmHg [10]

BP target
Long-term achievement of this target blood pressure has been shown to significantly reduce cardiovascular events, risk of kidney failure and all-cause mortality. [10,11] An even lower target of SBP < 120mmHg may be superior in improving outcomes but requires consistent use of standardized blood pressure measurements to avoid the risks of overtreatment. [11,12]

To achieve this target patients often initially require frequent follow-up for proactive up-titration of drug therapy and reinforcement of lifestyle change. Guidelines for selecting anti-hypertensive drug treatment can be found in the Fiji Cardiovascular Therapeutic Guidelines section 5.2, but in general ACEi/ARB therapy should be maximised first in patients with CKD (section 5.2), followed by either a calcium channel blocker (amlodipine/nifedipine) or diuretic (hydrochlorothiazide/frusemide).

Home BP measurement
Blood pressure measurements from home correlate better with cardiovascular and kidney outcomes than office measurements and will help overcome “white-coat syndrome” which is present in 15-30% of adults. [11] Thus, whenever possible, patients should be encouraged to purchase their own BP machines and bring records of morning and evening measurements done at home for review at follow-up appointments.

Salt Restriction
A very important aspect of blood pressure control is restriction of salt intake to <5g/day (equivalent to sodium <2g/day or <100mmol/day). Lowering salt intake can both lower BP substantially and enhance the response to anti-hypertensive medications, particularly ACEi/ARB.

The average daily intake of salt in Fiji is 11.7g/day – more than twice the WHO and KDIGO recommendations. A recent Cochrane Library review found reducing salt intake by approximately 4.2g/day lowered BP by 7/4mmHg and albuminuria by 35% in people with CKD. [13] This is comparable to single antihypertensive drug therapy. Even greater BP lowering effects with salt restriction are expected the higher the patient’s baseline BP. [14]

5.2. ACE-INHIBITOR OR ARB USE

All patients with CKD with albuminuria should be treated with an ACE inhibitor or ARB as they have been shown to improve kidney outcomes *independent* of their blood pressure lowering effects. [11,17]

Maximising Dose

The albuminuria-lowering effect of ACEi/ARB is dose dependent. Therefore, to get the most benefit from these medications they should be increased every 2-4 weeks to achieve the maximum tolerated dose, ideally whilst monitoring creatinine and potassium (figure 3). It may also reasonable to treat people with CKD without albuminuria with ACEi/ARB to derive cardiovascular benefits. [11]

Side Effects

A rise in creatinine of up to 30% is common and should not be a deterrent in using ACEi/ARB therapy. Moreover, clinical trials suggest the greatest benefit in slowing CKD progression is seen in those with the lowest eGFR at initiation. [15] The most common cause of an acute rise in creatinine following initiation is decreased effective blood volume (relative dehydration), or the use of NSAIDs. The clinician should evaluate for these causes and others with the aim to continue ACEi/ARB treatment if possible.

Hyperkalaemia occurs in up to 10% of outpatients commencing ACEi/ARB, and those with a baseline potassium > 5.2mmol/L are at highest risk. [15] Stopping ACEi/ARB though has also been associated with increased risk of cardiovascular events in observational studies. Therefore, it is recommended to institute measures to manage hyperkalaemia as best as possible before dose reduction or cessation is used as a last resort. [15]

The combination of both ACEi and ARB use simultaneously is not recommended as it does not provide additional benefit but is associated with more risk of hyperkalaemia and AKI. [11]

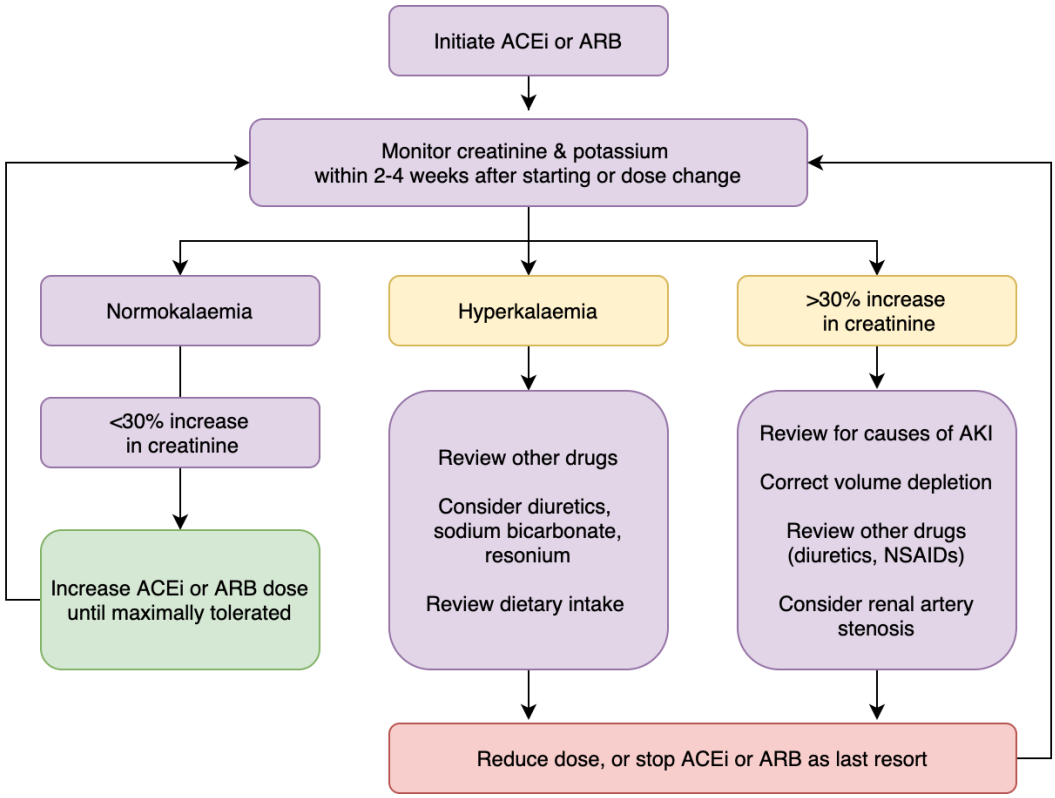


Figure 3. Monitoring of creatinine and potassium whilst achieving maximally tolerated ACEi/ARB dose – adapted from KDIGO 2020 Clinical practice guideline for management of diabetes management in chronic kidney disease [15]

5.3. SGLT2 INHIBITORS

All patients with CKD (eGFR >20 ml/min/1.73m^2), with or without diabetes, should be treated with an SGLT2 inhibitor [16,17]

The Sodium-Glucose Co-transporter-2 (SGLT2) inhibitors cause glucose and salt excretion by blocking the main transporter responsible for tubular glucose re-uptake. The SGLT2 inhibitors therefore result in a reduction in HbA1c, systolic blood pressure and weight.

Although originally designed purely as an anti-glycaemic medication, SGLT2 inhibitors have since been widely recognised to have significant cardiac and kidney benefits. Specifically, SGLT2 inhibitors have been shown to reduce the risk of kidney disease progression (defined as sustained >50% decrease in eGFR, end-stage kidney disease or death from kidney failure) by 37% and the risk of AKI by 23%. [16] In addition, their use lowers the risk of cardiovascular death or hospitalisation for heart failure by 23%. [16] The benefits seen were similar in patients *with and without* diabetes.

Table 3. Practical Tips for Prescribing SGLT2 inhibitors [17]

When to Start	When to Stop	Dosing	Precautions
eGFR > 20 ml/min/1.73m^2	Dialysis or kidney transplant	Empagliflozin 10mg daily* Dapagliflozin 10mg daily* Canagliflozin 100mg daily**	Dehydration, sick days, fasting Surgery (withhold >48hrs prior) Euglycemic DKA Fungal genitourinary infection

**Dose escalation is not required to derive the kidney and cardiac benefits. **Higher doses are not recommended in CKD*

Side Effects
SGLT2 inhibitors should not be initiated in hypotensive or hypovolaemic patients. Indeed, diuretics may need to be reduced at the time of commencement to avoid dehydration. SGLT2 inhibitors can also cause an acute drop in eGFR (up to 30%) due to haemodynamic changes in the glomerulus (similar to ACEi/ARB). [18] This though does not represent kidney damage and prescribers should feel confident that continuation of SGLT2i will attenuate decline over time.

Notably, SGLT2 inhibitors have *not* been shown to cause hypoglycaemia in patients without diabetes [18] due to a compensating reabsorption of glucose by SGLT1 when blood glucose levels are too low. However, patients with diabetes taking other anti-glycaemic agents may need these medications reduced if they are already achieving glycaemic targets or have a history of frequent hypoglycaemia.

In patients with diabetes SGLT2 inhibitors can rarely cause euglycaemic diabetic ketoacidosis. The absence of hyperglycaemia may result in a delay in diagnosis. Therefore, any patient on SGLT2 inhibitor with symptoms of DKA (nausea, vomiting, abdominal pain) should be evaluated for ketosis, and prescription of SGLT2 inhibitors in patients with type 1 diabetes should be done cautiously. [18]

5.4. GLYCAEMIC MANAGEMENT

An individualized HbA1c target ranging from <6.5% to <8.0% in patients with diabetes and CKD not treated with dialysis is recommended [17]

Most patients with CKD in Fiji have concurrent diabetes. In such patients achieving recommended glycaemic targets is associated with lower albuminuria, lower risk of CKD progression, less cardiovascular outcomes, and better survival. [17] These benefits of good glycaemic control only manifest over many years of treatment and so long-term adherence should be actively encouraged.

On the other hand, patients with advanced CKD are at a higher risk of hypoglycaemia with traditional glucose lowering drugs. Therefore, the glycaemic target in patients with CKD needs to be individualised taking into several factors outlined in figure 4. [17] For example, a higher target of <8.0% is often preferred in patients with advanced CKD (eGFR <30 ml/min/m^2), multiple comorbidities, short life expectancy and with risk factors for hypoglycaemia.

<6.5%	**HbA1c target**	**<8.0%**
CKD stage 1	**Severity of CKD**	CKD stage 5
Long	**Life expectancy**	Short
Absent/minor	**Macrovascular complications**	Present/severe
Few	**Comorbidities**	Many
Present	**Hypoglycaemia awareness**	Impaired
Available	**Resources for hypo management**	Scarce
Low	**Propensity of treatment to cause hypoglycaemia**	High

Figure 4. Factors guiding decisions on individual HbA1c targets – adapted from KDIGO 2022 Clinical practice guideline for management of diabetes management in CKD [17]

Drug Choice

For most patients the recommended first line glycaemic medications are metformin and SGLT2 inhibitors. If glycaemic targets are not achieved with these then other medications such as glipizide and/or insulin can be used instead, taking note they have an increased risk of hypoglycaemia compared to the first line options, and it is therefore advisable to start with lowest possible dose and titrate gradually.

Metformin is safe and effective in CKD with potential additional cardiovascular benefits beyond its effects on glycaemic control. [15] Metformin is not nephrotoxic per se but should be discontinued if eGFR <30ml/min/1.73m^2 or during a dehydrating illness because of a very small risk of lactic acidosis.

SGLT2 inhibitors are strongly recommended for all patients with diabetes and CKD with eGFR >20 ml/min/1.73m^2 (Section 5.3). This class of medication has been shown to significantly improve both kidney and cardiovascular outcomes *independent* of their effect on glycaemic control. [15]

5.5. CARDIOVASCULAR RISK REDUCTION

Patients with CKD have a 2-3-fold higher risk of cardiac death than those without CKD, and the risk of dying from cardiovascular events is up to 20 times greater than the risk of requiring dialysis or transplantation. [19] Therefore, a key component of the management of patients with CKD is cardiovascular risk reduction.

Tools such as the WHO cardiovascular risk assessment (Fiji Cardiovascular Therapeutic Guidelines section 1.3) or www.cvdcheck.org.au can be used to quantify an individual patient's risk to encourage patient engagement and adherence to treatment.

Lifestyle Change

Providing patients with lifestyle advice is a critical step in reducing cardiovascular risk in patients with CKD. [18] Focus areas to encourage include:

1. Smoking cessation
2. Healthy diet – section 5.5
3. Regular physical activity – moderate-intensity for at least a cumulative of 150 minutes per week, or at a level compatible with their cardiovascular and physical tolerance [15]
4. Maintaining a healthy weight of BMI 20 to 25 [22]
5. Limiting alcohol intake – ≤2 standard drinks per day for men and ≤1 per day for women [22]

Statin Therapy

Statins are recommended for all patients with CKD not requiring dialysis

Statin therapy has been shown to significantly reduce cardiovascular events in the non-dialysis dependent CKD populations. [20] Lipid targets have not been established for patients with CKD and so once statin therapy is initiated it is not recommended to routinely repeat the lipid profile. Instead, due to a higher risk of medication adverse events in those with eGFR <60ml/min/1.73m^2, the statin should generally be maintained long term at a reduced dose – e.g., simvastatin 20mg daily, atorvastatin 40mg daily or rosuvastatin 10mg daily. [20]

Adults with dialysis-dependent CKD should not be initiated on statins as current evidence suggests they do not reduce cardiovascular endpoints in this population group. [20] However, in patients already receiving statins at the time of dialysis initiation it is reasonable they be continued. [20]

Aspirin

Aspirin generally should be used lifelong as secondary prevention for those with a known history of cardiovascular disease. [15,21]

This recommendation is because patients with CKD, especially those with advanced CKD, have an increased bleeding risk, which may equal or outweigh the uncertain benefits of aspirin when used for primary prevention. Aspirin should be considered as primary prevention in individuals at high risk of cardiovascular disease (≥30% 10-year CVD risk) but it should be balanced against an increased risk of bleeding from low eGFR. [15,21]

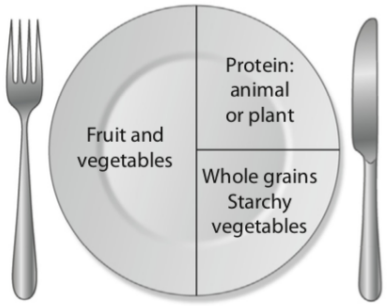
5.6. DIETARY ADVICE

Dietary patterns can have a significant impact on the risk of CKD progression, the severity of its complications, and the risk of all-cause mortality. [23,24] A diet focusing on whole plant foods has many benefits in CKD and has been established as effective therapy for the two most common causes of CKD in Fiji – type 2 diabetes and hypertension. [23,25]

> Patients with CKD, including those with diabetes, should eat an individualised diet high in vegetables, fruits, wholegrains, legumes, plant-based proteins and unsaturated fats, and nuts. [17]
>
> Salt intake should be limited to <5g/day (or sodium <2g/day) to lower BP and enhance the response to ACEi/ARB therapy

Meats, refined carbohydrates, and sweetened beverages should be limited or avoided. Observational studies have reported that high consumption of red and processed meat is associated with increased risk of CKD progression. [17,25]

Protein intake should be limited to 0.8g/kg of body weight per day in those who are non-dialysis dependent. High protein diets (>0.8g/kg/d) may be associated with progression of CKD. [17,25] In general, the above-described diet rich in plant-foods is naturally lower in protein content whilst remaining adequate.



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Potassium
Dietary potassium restriction is <u>not</u> routinely required for all CKD patients, but rather can be considered in those where significant hyperkalaemia is persistent. For information on managing hyperkalaemia, including dietary restriction, please see section 7.3.

Table 4. What does a healthy kidney diet look like? – adapted from Joshi et al [25]

Daily servings of food type	**Rationale**
2-4 servings of fruits	Minimally processed plant foods are the foundation of many healthy eating patterns due to their low caloric density and high content of fiber, healthy fats, vitamins, minerals, and antioxidants. These foods tend to be low in sodium, have lower phosphate bioavailability, and have plant proteins, which may reduce glomerular hyperfiltration and uremic toxin production.
5+ servings of non-starchy vegetables	
2+ servings of wholegrains & starchy vegetables	
3+ servings of legumes	
Foods to Avoid	**Rationale**
Highly processed foods	Often contain added sodium and phosphorus. Calorically dense and nutritionally poor.
Fruit juices, vegetable sauces, coconut products	Increase the rate of potassium ingestion (dried fruit may carry a similar risk); lack fiber; often prepared with added sugars.
Meat	May worsen blood pressure, associated with adverse kidney-related outcomes, higher phosphate bioavailability.
Dairy products	Higher phosphate bioavailability, calorically dense.

5.7. MEDICATION ADJUSTMENTS AND SICK DAY PLAN

Medication adjustments are often needed in people with CKD, either to avoid drug toxicity or to prevent compromising kidney function. Patients should be made aware of this and informed to flag their CKD with their healthcare providers to ensure medications are prescribed appropriately. In addition, it is recommended that clinicians use a reference, such as The Renal Drug Handbook [27], when prescribing medications for patients with CKD.

NSAIDs
Patients with CKD should be made aware to avoid all non-steroidal anti-inflammatory medications (e.g. ibuprofen, voltaren, indomethacin) as these are both readily available without a prescription and are associated with an increased risk of AKI and worsening CKD progression.

Sick Day Plan
When patients become sick and are unable to maintain adequate fluid intake certain medications can increase the risk of AKI, or have reduced clearance with increased risk of drug adverse events. Patients should be provided an individualised plan on how to manage their medications during any dehydrating or septic illness. For example it is often prudent to discontinue the following medications when acutely sick and recommence once well again:

- ACE inhibitors & ARB
- SGLT2 inhibitors
- Metformin
- Diuretics

6. REFERRAL FOR SPECIALIST REVIEW

Referrals for specialist input is associated with positive outcomes including slowing of GFR decline and better survival. [28] In Fiji specialist care should be provided by a nephrologist or internal medicine physician. Specialist care includes early detection and management of CKD complications and preparation for kidney replacement or non-dialysis supportive care.

In cases where it may not be necessary for the patient to be seen by the specialist in-person, the primary health care team is encouraged to contact a specialist by telephone or email for advice.

Indications for specialist referral:

1. CKD stage 4 or 5 (eGFR < 30ml/min/1.73m^2)
2. Worsening kidney function despite optimal management as described in section 5
    a. A sustained decrease per year of eGFR > 25% or 15 mL/min/1.73m^2
3. If the cause of CKD is unclear
    a. Severity of CKD is significantly greater than would be expected from the history of diabetes and/or hypertension
    b. Nephrotic syndrome
    c. Persistent haematuria
    d. Presence of another relevant condition (e.g., polycystic kidneys, SLE)
4. The presence of complications attributable to CKD as outlined in section 7
5. Kidney transplant recipient or donor

7. MANAGEMENT OF ADVANCED CKD COMPLICATIONS

Many of the complications of CKD become clinically apparent once the eGFR falls below 30ml/min/1.73m^2. In such patients it is essential to check for the development of complications at follow-up appointments and seek specialist advice when managing them.

7.1. ANAEMIA

Anaemia of CKD is due to both reduced EPO production and a high prevalence of absolute and/or functional iron deficiency in patients with CKD. Its management is outlined in detail in the Nephrology Clinical Guidelines: Management of Renal Anaemia In Fiji.

Key Points:

1. Exclude or address all correctable causes of anaemia including iron, vitamin B12 and folate deficiencies, occult blood loss, haemolysis and bone marrow disorders.
2. Iron therapy, ideally given intravenously, will usually raise the Hb successfully and should be trialled before erythropoeisis stimulating agents (ESA) are used.
3. ESA therapy should only be prescribed by a specialist and is reserved for those who have had an inadequate response to iron, have symptoms attributable to anaemia, would otherwise be considering a blood transfusion, and are likely to survive long enough for meaningful benefit.
4. When using ESAs, the target Hb is between 10-11g/dL. Higher targets are associated with increased risk of adverse events with no clinical benefit. During ESA therapy iron stores must be maintained, targeting Ferritin 500-700 mcg/L and TSAT 20-40%.

7.2. FLUID OVERLOAD

The capacity to excrete required volumes of urine usually remains adequate until advanced CKD, especially once the eGFR falls below 15ml/min/1.73m^2. If present, comorbidities such as cardiac or liver failure also contribute to the accumulation of fluid.

Key Points:

1. Salt restriction <5g/day
2. Fluid restriction
    a. This alone is often sufficient to maintain euvolaemia, and is prefered to escalating diuretic doses. Remember to consider all liquids in the diet (e.g. soups, juices, tea, milk).
    b. In general, the restriction should match the individual patient's urine output capacity. For example, a fluid restriction of 1 litre is required for someone who typically voids only 1 litre of urine per day.
3. Diuretics
    a. Frusemide can be used safely in all stages of CKD, including advanced CKD.
    b. Typical doses are 20-160mg/day, but higher doses up to 500mg/day may be required in those with stage 5 CKD.
    c. Hydrochlorothiazide can be an effective addition to frusemide if the fluid overload is resistant to frusemide alone.

4. Self-monitoring
    a. Patients who have a history of fluid overload should be educated to weigh and monitor themselves daily. An increase of >1kg in 24 hours, >3kg in a week, or worsening oedema is concerning for fluid accumulation.
    b. Provide the patient with an appropriate action plan to manage fluid accumulation themselves such as increasing frusemide doses and/or fluid restriction, and seeking medical attention if this is not successful.

7.3. HYPERKALAEMIA

Potassium levels consistently above 6.0 mmol/L are of concern and should be managed, while levels ≥6.5 mmol/L significantly predisposes to cardiac arrhythmias. When managing hyperkalaemia clinicians are advised to first try and identify contributing factors, particularly metabolic acidosis (HCO_3 < 22 mmol/L) before limiting dietary potassium intake, which has anti-hypertensive and other benefits. [24] Indeed, the effect of dietary potassium on the risk of hyperkalaemia is likely overinflated [23], whilst harm can occur by restricting fibre and micronutrient rich foods.

If dietary changes are to be pursued then it is recommended to refer to a dietician where available. After a dietary recall is conducted, the most nutritionally-poor, calorically-dense, high dietary source of potassium for the individual patient should be restricted first. [23] Advice to limit all fruit and vegetables can be dangerous and counter productive due to their alkali content. Instead, limiting very high potassium food sources such as juices, vegetable sauces, dried fruit, meats/fish, milk products (especially condensed milk), coconut products, avocado and mango is preferable. In addition, boiling root vegetables can reduce their potassium content.

Key Points:

1. First identify and correct contributing factors
    a. Metabolic acidosis – section 7.4
    b. Constipation – results in bowel potassium reabsorption
    c. Hypoinsulinaemic states – low carbohydrate diets, advanced diabetes
    d. ACEi/ARB use
2. Promote potassium excretion
    a. Potassium wasting diuretics (e.g. thiazides, frusemide) if fluid state allows
    b. Resonium in short-term courses only
3. Dietary changes as described above
4. Refer immediately to the closest emergency centre if K ≥ 6.5 mmol/L

7.4. METABOLIC ACIDOSIS

Metabolic acidosis in CKD, typically defined as serum HCO_3 < 22 mmol/L, occurs due to a reduced capacity to excrete the daily acid load from food and endogenous production. It has been shown to contribute to worsening kidney function, demineralization of bone, impaired cardiac function, hyperkalemia, and an increased risk of death. [29]

Key Points:

1. Dietary changes
    a. Increase vegetables and fruits – high sources of dietary alkali
    b. Decrease meats/fish and dairy – high sources of dietary acid
    c. These diet changes can be as effective as sodium bicarbonate therapy and should be

instituted first [30]

2. Oral sodium bicarbonate capsules
    a. Preferred to dietary changes if hyperkalemia is concurrently present, but to be used cautiously if the patient is already fluid overloaded because of its sodium content
    b. Serum HCO_3 18-22 mmol/L = start 840mg twice daily
    c. Serum HCO_3 <18 mmol/L = start 1680mg twice daily
    d. Target serum HCO_3 22-26 mmol/L. Therapy should be stopped if HCO_3 > 26mmol/L.

7.5. MINERAL DISORDERS

A range of mineral disorders can occur in advanced CKD due to changes in metabolism and renal excretion, the management of which can be complex and should occur with specialist advice. The key treatment steps are as follows. [31] Routine measurement of minerals when eGFR >30ml/min/m^2 is not necessary.

Hypocalcaemia

1. Consider treatment in adults if corrected serum calcium is persistently < 1.80 mmol/L, or if symptomatic. [32]
    a. Threshold to commence treatment may be lower in children and young adults
2. Oral calcium carbonate
    a. To be taken on empty stomach to avoid calcium binding to dietary phosphate and reducing absorption
    b. Starting dose of 500mg once daily and titrated to target corrected Ca 1.80 – 2.10 mmol/L
3. Oral calcitriol
    a. Increases absorption of dietary calcium. Only to be used under the supervision of a specialist for severe hypocalcaemia resistant to calcium carbonate alone
    b. Starting dose of 0.25mcg once daily and titrated to effect

Hyperphosphataemia

1. Dietary change
    a. Restrict animal products (meat, dairy, eggs) as their phosphate content is absorbed approximately twice as much compared to phosphate from plant foods.
    b. Avoid highly processed foods, especially sugary drinks, which often have phosphate additives.
2. Oral calcium carbonate
    a. Acts as a phosphate binder when taken with meals, thus reducing dietary phosphate absorption
    b. Only to be considered if dietary change is unsuccessful and serum phosphate levels are persistently > 1.80 mmol/L and rising, whilst corrected calcium is less than 2.4 mmol/L. [31]
    c. Starting dose of 500mg once or twice daily taken with largest meals of the day
    d. Monitor serum calcium and if hypercalcaemia develops therapy should be reduced.

Secondary Hyperparathyroidism

1. First ensure adequate treatment of hyperphosphataemia and hypocalcaemia as above.
2. If PTH is persistently and markedly elevated then specialist advice is required.

7.6. PRURITIS

Pruritis typically occurs in advanced CKD and can severely affect quality of life. The cause is multifactorial and includes uremia, hyperphosphataemia, hyperparathyroidism and nerve changes in the skin.

Key points

1. Exclude other skin conditions (e.g. scabies)
2. There is very little evidence to support the use of anti-histamine therapy
3. Topical treatments (e.g. QV intensive, menthol 0.05%) and Blackmore's evening primrose oil 1 capsule twice a day have both been shown to be effective for some patients
4. Gabapentin can be trialled for those who have persistent pruritis despite the above options
    a. eGFR 15-29 – start at 100mg nocte, titrate cautiously to max 300mg nocte
    b. eGFR < 15 – start at 100mg alternative nocte, titrate cautiously to max 300mg alternative nocte

7.7. HYPERURICAEMIA & GOUT

Lifestyle changes are an important step in the management of hyperuricaemia (section 5.4). Specifically, all patients with hyperuricaemia should be advised to reduce alcohol and sugar-sweetened drinks, reduce meat and seafood consumption, and achieve a healthy weight.

Drug treatment of asymptomatic hyperuricaemia is <u>not</u> currently recommended or approved. [32]

Indications for Allopurinol [33]

1. ≥2 gout flares per year
2. ≥1 more gouty tophi present
3. Radiological evidence of gouty arthritis
4. Recurrent kidney stones in the presence of hyperuricaemia

Allopurinol use in CKD [33]:

1. Target serum uric acid levels <360 micromol/L, or <300 micromol/L if tophi present
2. Start with low dose of 50-100mg daily
3. Increase the dose every 4 weeks until target achieved
4. The maximum dose of allopurinol depends on the eGFR [27]
    a. 20-50ml/min/1.73m^2; 300mg daily
    b. 10-20ml/min/1.73m^2; 200mg daily
    c. <10ml/min/1.73m^2; 100mg daily
5. When first initiating and up-titrating allopurinol it is recommended to prescribe flare prophylaxis with colchicine 0.5mg/day. This should be stopped by 6 months.

7.8. PAIN MANAGEMENT IN CKD

Somatic and neuropathic pain is very common in both the general community and in patients with CKD. As in the general population, the management of pain in patients with CKD should utilise adjunctive non-pharmacologic interventions such as massage, acupuncture, mindfulness-based stress reduction, thermal therapy and exercise programs.

When medications are used special considerations are required due to altered drug pharmacokinetics from reduced kidney function. Table 5 provides some general guidelines when prescribing for patients with advanced CKD (eGFR < 30ml/min/1.73m^2), but as the evidence base is limited caution should always be taken and physician discretion is advised.

Table 5. Analgesia dosing in patients with advanced CKD [27,34]

Drug	Dosing in CKD stage 4 & 5	Safe to use?
Paracetamol	No dose reduction required.	Safe in kidney failure
NSAIDs	Avoid unless on dialysis and already anuric.	Avoid
Codeine	Avoid as accumulation can cause significant opioid toxicity. If necessary limit to 120mg/day	Avoid
Tramadol	Avoid if possible. If necessary max 100mg bd in CKD stage 4, max 50mg bd in CKD stage 5	Avoid if possible
Oxycodone	Start at 50-75% of normal dose e.g. 2.5mg PO 4-6hrly/PRN and titrate cautiously. Consider increasing dose interval.	Use with caution
Morphine	Avoid if possible. If necessary reduce 25-50% of normal dose and increase dose interval. Avoid slow release preparations.	Avoid if possible
Fentanyl	Start at 25-50mcg subcutaneous or IV 2-4hrly/PRN	Safe in kidney failure
Amitriptyline	Start at low end of dose range, e.g. 10mg oral nocte. Titrate cautiously.	Use with caution
Gabapentin	Start at low end of dose range and titrate cautiously. CKD stage 4, max 300-600mg/day. CKD stage 5, max 100-300mg/day or alternative daily.	Use with caution
Pregabalin	Start at low end of dose range, 25mg nocte. CKD stage 4, max 150mg daily. CKD stage 5, max 75mg nocte.	Use with caution

ABBREVIATIONS

ACEi; angiotensin converting enzyme inhibitor
ACR; albumin to creatinine ratio
AKI; acute kidney injury
ARB; angiotensin receptor blocker
BP; blood pressure
CKD; chronic kidney disease
CVD; cardiovascular disease
ESA; erythropoietin stimulating agents
eGFR; estimated glomerular filtration rate
Hb; haemoglobin
IV; intravenous
KDIGO; Kidney Disease Improving Global Outcomes
MI; myocardial infarction
SBP; systolic blood pressure
SGLT2; Sodium-Glucose Co-transporter-2
SLE; systemic lupus erythematosus
TSAT; transferrin saturation

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REFERENCES

1. GBD Chronic Kidney Disease Collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2020; 395:709-33
2. Krishnan A, Chandra Y, Malani J et al. End-stage kidney disease in Fiji. Internal Medicine Journal 2019; 49:461-466
3. GBD Mortality and Causes of Death Collaborators. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1459–544.
4. Tonelli M, Muntner P, Lloyd A et al. Risk of coronary events in people with chronic kidney disease compared with those with diabetes: a population-level cohort study. Lancet 2012;380(9844):807-14.
5. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. Am J Kidney Dis 1998;32: S112-S119.
6. Johnson DW. Evidence-based guide to slowing the progression of early renal insufficiency. Intern Med J 2004 January;34(1-2):50-7.

7. Komenda P, Ferguson TW, Macdonald K et al. Cost-effectiveness of primary screening for CKD: A systematic review. Am J Kidney Dis. 63(5):789-797
8. KDIGO 2012 Clinical practice guideline for the evaluation and management of chronic kidney disease. Kidney International 2013; 3(1): S1-163
9. National Institutes of Health, USA. Explaining your kidney test results: A tool for clinical use. NIH publication 12-6220; 2012
10. World Health Organisation, Guideline for the pharmacological treatment of hypertension in adults 2021; License: CC BY-NC-SA 3.0 IGO
11. KDIGO 2021 Clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney International 2021; 99(3): S1-87
12. Cheung AK, Rahman M, Reboussin DM et al. Effects of Intensive BP Control in CKD. JASN 2017; 28(9) 2812:2823
13. McMahon EJ, Campbell KL, Bauer JD et al. Altered dietary salt intake for people with chronic kidney disease. Cochrane Database of Systematic Review 2021, Issue 6.
14. Juraschek SP, Miller ER, Weaver CM et al. Effects of sodium restriction and the DASH diet in relation to baseline blood pressure. J Am Coll Cardiol 2017; 70(23): 2841-2848
15. KDIGO 2020 Clinical practice guideline for diabetes management in chronic kidney disease. Kidney International 2020; 98(4): S1-115
16. Nuffield Department of Population Health Renal Studies Group; Impact of diabetes on the effects of sodium glucose co-transporter-2 inhibitors on kidney outcomes: collaborative meta-analysis of large placebo-controlled trials. Lancet . 2022 Nov 4;S0140-6736(22)02074-8
17. KDIGO 2022 Clinical practice guideline for diabetes management in chronic kidney disease. Kidney International 2022 Nov;102(5S):S1-S127
18. Lam D, Shaikh A. Real-Life Prescribing of SGLT2 Inhibitors: How to Handle the Other Medications, Including Glucose-Lowering Drugs and Diuretics. KIDNEY360 2: 742–746, 2021
19. Keith DS, Nichols GA, Gullion CM, Brown JB, Smith DH. Longitudinal follow-up and outcomes among a population with chronic kidney disease in a large managed care organization. Arch Intern Med 2004 March 22;164(6):659-63.
20. KDIGO 2013 Clinical practice guidelines for lipid management in chronic kidney disease. Kidney International 2013; 3(3): S1-56
21. Gregg PL, Hedeyati SS. Management of traditional cardiovascular risk factors in CKD: What are the data? Am J Kidney Disease 2018; 72(5):728-744
22. KDIGO 2012 Clinical practice guidelines for management of blood pressure in chronic kidney disease. Kidney International 2012; 2(5): S1-85
23. Carrero JJ, Gonzalez-Ortiz A, Avesani C et al. Plant-based diets to manage the risks and complications of chronic kidney disease. Nature Reviews Nephrology 2020; 16: 525-542
24. Quintela BC, Carioca AA, Ramalho de Oliveira JG et al. Dietary patterns and chronic kidney disease outcomes: A systematic review. Nephrology 2021; 26(7): 603-612
25. Joshi S, McMacken M, Kalantar-Zadeh K. Plant-Based Diets for Kidney Disease: A Guide for Clinicians. Am J Kidney Dis 2020; 77(2):287-296
26. Ikizler TA, Burrowes JD, Byham-Gray LD et al. KDOQI clinical practice guidelines for nutrition in CKD: 2020 update. Am J Kidney Dis 2020; 76(3):S1-107
27. Ashley C, Dunleavy A (ed), 2019, *The Renal Drug Handbook 5th Edition,* CRC Press, Boca Raton, Florida.
28. Jones C, Roderick P, Harris S et al. Decline in kidney function before and after nephrology referral and the effect on survival in moderate to advanced chronic kidney disease. Nephrol Dial Transplant 2006; 21: 2133–2143
29. Raphael KL. Metabolic acidosis in CKD: Core Curriculum 2019; Am J Kidney Dis 74(2):263-275
30. Goraya N, Munoz-Malonado Y, Simoni J, Wesson DE. Treatment of Chronic Kidney Disease-Related Metabolic Acidosis With Fruits and Vegetables Compared to NaHCO3 Yields More and Better Overall Health Outcomes and at Comparable Five-Year Cost. Am J Nephrol 2019;49(6):438-448
31. KDIGO 2017 Clinical practice guideline update for the diagnosis, evaluation, prevention and treatment of chronic kidney disease-mineral bone disorder (CKD-MBD). Kidney International

2017; 7: 1-59
32. Quarles LD, Berkoben M. UpToDate: Management of secondary hyperparathyroidism in adult dialysis patients. Topic last updated March 2021, accessed June 2021.
33. Richette P, et al. EULAR 2016 updated evidence-based recommendations for the management of gout. Ann Rheum Dis 2017; 76:29-42
34. The Royal Melbourne Hospital, Nephrology symptom management guidelines, accessed December 2021, <https://www.thermh.org.au/health-professionals/clinical-services/nephrology/chronic-kidney-disease/nephrology-symptom>