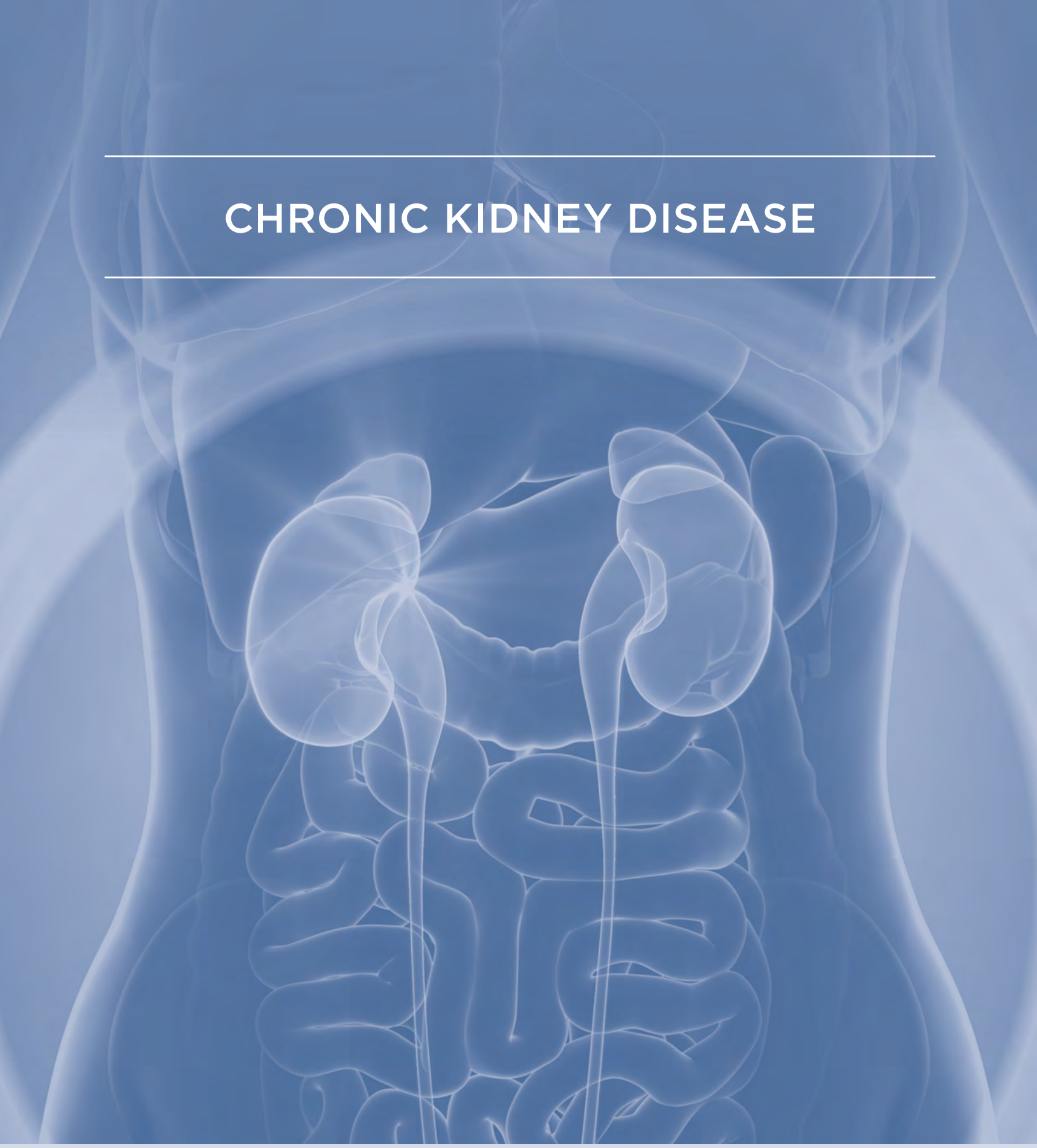
CHRONIC KIDNEY DISEASE



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CREATING A HEALTHIER HAWAIʻI

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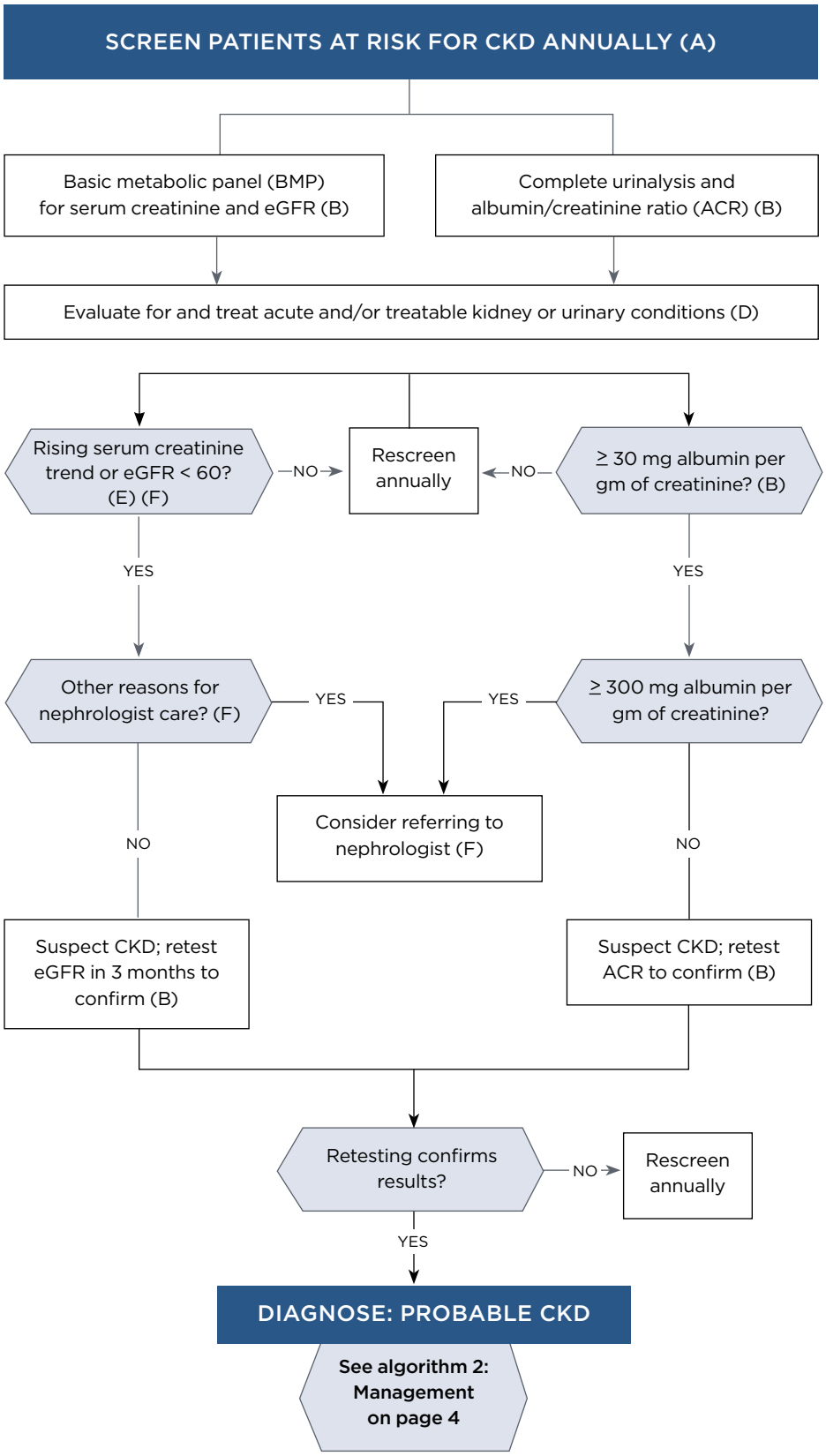


Algorithm 1: Screening

(A) Risk factors for CKD	
Screen patients who have ANY of these risk factors. [KDIGO]	
Chronic conditions	• Diabetes Type 1 (begin screening for CKD 5 years after diagnosis) • Diabetes Type 2 (begin screening for CKD at the time of diagnosis) • Hypertension • Cardiovascular disease (CVD), cerebrovascular and peripheral vascular disease • Systemic illness affecting kidneys (HIV, lupus, vasculitis, rheumatoid arthritis, hyperuricemia, multiple myeloma) • Orthostatic proteinuria
History	• Family history of kidney disease (dialysis, renal failure) • History of acute kidney injury • S/P NICU admission
Urologic problems	• Urinary obstruction, structural renal tract disease, urinary diversion surgery or reflux nephropathy • Recurrent urinary tract infections (UTIs) (> 3 in 1 year) • Kidney stones
Meds	• High dose or chronic treatment with nephrotoxic medication including NSAIDs • Chemotherapy
(B) Annual screening for CKD	
These are the primary screening tests for CKD. [KDIGO] **A morning spot urine sample is preferred for complete urinalysis.**	
BMP — For patients with risk factors	• Check eGFR (estimated glomerular filtration rate and trend of serum creatinine from baseline, especially if eGFR > 60). • If eGFR < 60, evaluate whether the patient needs nephrology care (see note [f]). • Use eGFR and ACR to help establish risk and severity if CKD is diagnosed. • The MDRD equation is the primary equation used for estimating eGFR. • If urgent care is not needed, retest in 1-2 weeks to determine if stable or rapidly progressing, • if stable, retest in 3 months to confirm CKD.
Albumin-creatinine ratio (ACR) — For patients with risk factors	• If 30–300 mg of albumin/gm creatinine, retest within 3 months. Two abnormal specimens are required before diagnosing CKD. • Collect first morning void. • **Note:** Vigorous exercise before the test, infection, fever, congestive heart failure (CHF), marked hyperglycemia, marked hypertension or menses may elevate ACR.
Complete urinalysis	• Check for active sediment (e.g., RBCs, WBCs and/or cellular casts). • If RBC without proteinuria or active sediment, refer to urology.

(C) CKD INDICATORS	
The following conditions provide evidence of kidney damage:	• Persistent albuminuria • Structural kidney abnormalities • Persistent hematuria of renal origin • Biopsy-proven kidney disease (e.g., glomerulonephritis or interstitial nephritis)
(D) FACTORS THAT AFFECT KIDNEY FUNCTION	
Patients with a recent decrease in renal function may be suffering from an underlying reversible process, which, if identified and corrected, may result in the recovery of function. In addition, certain drugs and substances affect kidney function or interfere with creatinine secretion. If eGFR is detected abnormal and thought to be due to one of the below, monitor for stability and possible improvement. If worsening continues despite correction of the below, consider referring to nephrology.	
Urinary tract obstruction or urinary tract infection (UTI)	
Decreased renal perfusion, caused by:	• Drugs that lower eGFR, such as NSAIDs and ACE inhibitors (ACEIs)/ARB • Hypovolemia, due to vomiting, diarrhea, diuretic use, bleeding, etc. • Hypotension, due to myocardial dysfunction, excessive antihypertensive medications or pericardial disease • Infection, such as pneumonia
Nephrotoxic drugs and substances, including:	• NSAIDs, COX-2 • Radiographic contrast material, particularly in diabetes patients • Aminoglycoside antibiotics, particularly with unadjusted doses
False elevation of serum creatinine (SCr). Certain drugs and supplements interfere with creatinine secretion or with the assay used to measure SCr. With these drugs, SCr will be affected but there will be no change in eGFR; a clue that this is the case is the absence of an elevated blood urea nitrogen (BUN). Examples of medications with this effect:	• Cimetidine • Trimethoprim • Cefoxitin • Flucytosine • Fenofibrates (ex: Tricor) • Creatine supplements • Ranexa
(E) FACTORS THAT MAY AFFECT THE INTERPRETATION OF eGRF	
• Pregnancy • If age > 80, eGFR < 60 may be due to loss of up to 1% eGFR per year after age 40 from natural aging • Unusual muscle mass	• Near-normal serum creatinine • Rapidly changing serum creatinine • Cirrhosis, nephrotic syndrome or past transplant • Medications listed in Table (D) above
(F) REASONS TO CONSIDER NEPHROLOGY REFERRAL	
• Uncertain etiology of rising serum creatinine, declining eGFR or abnormal urine ACR • Acute kidney injury or abrupt sustained fall in eGFR • eGFR: 45 (GFR categories G3b–G5)—see Algorithm 2 on page 4 • Rapid progression of CKD (see table on page 6)	• Active urine sediment to include unexplained urine RBCs, WBCs and cellular casts especially if albuminuria. RBC > 20 per high power field sustained and not readily explained (that does not clear with repeat testing) • CKD and hypertension refractory to treatment with 4 or more antihypertensive agents • Persistent abnormalities of serum potassium

STEP 1A: DETERMINE LIKELY CAUSE OF CKD OR REFER IF UNCLEAR

STEP 1B: IDENTIFY RISK LEVEL BASED ON GFR AND ALBUMINURIA[1]

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased < 30 mg/g < 3 mg/mmol	Moderately Increased 30-300 mg/g 3-30 mg/mmol	Severely Increased > 300 mg/g > 30 mg/mmol
GFR categories (ml/min/1.73²) Description and range	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			

Low risk (if no other markers of kidney disease, no CKD)

Moderately increased risk

High risk

Very high risk

STEP 2: CONSIDER RECOMMENDATIONS FOR RISK LEVEL

Recommendation	Low	Moderate	High	Very High
Lifestyle modification, cardiovascular risk management, blood pressure (BP) and blood sugar (BS) goals (see list on next page)	X	X	X	X
Kidney Disease Education for all, especially if GFR <60 or albuminuria	X	X	X	X
Imaging study modifications[1] • Avoid high osmolar agents if GFR ≤ 60 • Avoid gadolinium-containing contrast media once GFR ~ 15 • Avoid phosphate-containing bowel prep if GFR < 60			X	X
Preserve arm veins if dialysis an option; use hand veins for IVs, labs				X
Pneumonia vaccine[2] if GFR < 30: 1 dose PCV13; 1-2 dose PPSV23 Hepatitis B vaccine[2] if GFR < 30 and willing to dialyze				X
Prepare for transition: • Dialysis – Access surgery planning GFR ~ 20 • Transplant – Refer to transplant clinic GFR ~ 30 • Natural life – Consider palliative program support				X

[1] KDIGO (Kidney Disease Improving Global Outcomes) 2012 Clinical Practice Guidelines for the Evaluation and Management of Chronic Kidney Disease, Kidney International 3 (1) January 2013; 1-163.

[2] Advisory Committee on Immunization Practices (ACIP) Recommended Immunization Schedules for Persons Aged 0 Through 18 Years and Adults Aged 19 Years and Older – United States, 2013 Supplements, February 1, 2013/62(01); 1-1.

(A) CKD STAGING	
	• CKD is classified based on CGA – Cause, eGFR category and albuminuria[KDIGO] • The Stages "G1–G5" roughly equate to the previous Stages 1-5, but the new staging system also accounts for albuminuria and cause. For example, Stage G2/A1 is low risk if there are no other markers of kidney disease; Stage G3a/A2 is high risk.
(B) PATIENT EDUCATION	
	At diagnosis, patients need education on kidney function, expectations for CKD, treatment and self-management to slow CKD progression. All CKD patients, inclusive of those with low or no risk, should be offered education, especially if other markers of CKD are present: • Aloha Kidney: alohakidney.com; phone: 808-585-8404
(C) ALBUMINURIA AND HYPERTENSION MANAGEMENT	
	Albuminuria, hypertension and hypoperfusion are risk factors for CVD and can speed CKD progression. An ACE inhibitor (ACEI) is the best management agent for most patients; carefully monitor creatinine and potassium during titration (see pages 9-10). If an ACEI is not tolerated (usually due to a dry cough), switch to an ARB (combining an ACEI and ARB is not recommended). Other medications may also be needed.
(D) LIPID MANAGEMENT	
	Because dyslipidemias are prevalent in CKD and CKD patients are in the highest CVD risk category, lipid management is a key element of treatment. CKD patients can benefit from dietary counseling and statins depending on their age, disease stage and comorbidities. See pages 11–12 for information on unique aspects of dyslipidemia in CKD, a treatment algorithm and medication tables.
(E) DIABETES MANAGEMENT	
	In CKD patients with diabetes, a strong focus should be placed on glycemic control (HbA1c < 7%), albuminuria management (with an ACEI/ARB), and robust blood pressure control (BP < 140/90, or in some cases even as low as 130/80). See pages 13-14 for risk factors that can speed the decline of renal function in these patients, tips on determining whether CKD is the result of diabetes or another cause, and key resources for diabetes management. **Caution: As CKD progresses, there can be higher risk for hypoglycemia. HbA1c of 7-8% may be reasonable if patient at high risk for hypoglycemia.**
(F) AVOIDANCE AND/OR DOSE ADJUSTMENTS OF NEPHROTOXIC MEDICATIONS AND SUBSTANCES	
	These include NSAIDs, radiographic contrast (especially with diabetes patients) and aminoglycoside antibiotics (particularly with unadjusted doses).
(G) PRESERVATION OF VENOUS ACCESS	
	If willing to consider dialysis, patients with eGFR < 30 should use hand veins, to save arm with best arteries and veins for future fistula. Avoid PICC lines and subclavian catheters to prevent subsequent stenosis/thrombosis.

(H) DIETARY MANAGEMENT		
	All patients should reduce their intake of sodium, unless salt wasting nephropathy or problems with dehydration and hypotension, and all patients should reduce their intake of phosphorus and potassium additives. Depending on the patient's status, dietary management may also include management of potassium, phosphorus, calcium and protein. (Note: a very low protein diet is not recommended.) Referral to a registered dietitian (preferably with an interest in CKD is recommended.	
(I) CKD PROGRESSION DEFINED		
	• Progression: Decline in eGFR category – a drop in eGFR category OR a > 25% drop from baseline or rising trend in serum creatinine. • Rapid Progression: A sustained decline in eGFR.	
(J) MONITORING AND MANAGING OTHER COMORBIDITIES		
Hyper-kalemia	**Test for potassium:** • To prevent pseudohyperkalemia, remind patients to keep hand open, avoid vein tapping, slapping and rubbing during vein puncture. • At regular followup appointments. • For ACEI or ARB: within 2 weeks of any dose change. • For aldosterone receptor antagonist (ARA): At 4-7 days after adding or increasing dose if patient on ACEI or ARB; between 7-10 days after adding or increasing dose if patient not on ACEI or ARB. • If patient has hyperkalemia symptoms.	**Manage/treat based on potassium (mmol/L):** • Always ask about and d/c any K supplements including salt substitutes. • Limit dietary potassium if necessary after d/c any K supplements. • At 5.1 to 5.5: see above bullets. • At 5.5 to 6.0: see above; check for other causes; consider daily potassium lowering Rx and/or NaBC Rx, and/or refer to nephrologist if needed. • At > 6.0: consider urgent ER confirmation and management indicated.
Metabolic acidosis	Test for metabolic acidosis annually for moderately increased-risk patients, every 6 months for high-risk patients and every 3 months for very high-risk patients.	• Check for and address non-CKD causes. • Treat with sodium bicarbonate if serum bicarb levels < 23.
Anemia	• If anemia is present, screen for other causes; consider using RBC indices to guide workup. R/O GI bleeding if iron deficient. • If eGFR < 50, you can assume EPO is deficient.	• Begin with a 3-month trial of oral iron therapy if iron deficient. • WITH EXTREME CAUTION, consider IV iron supplements if iron stores remain low. • A nephrologist or hematologist should manage treatment with erythropoietin-stimulating agents (ESAs). There are risks of ESA for those with history of cancer or DVT/PE. ESAs can be used with informed consent.
Volume overload/ edema	• Monitor weight and check for symptoms at every visit. • Evaluate CVD risk; if eGFR > 30, volume overload often has a cardiac cause. • Evaluate for CHF and metabolic concerns, and reevaluate medications.	• Restrict dietary sodium to < 2,000 mg per day. • Treat with diuretics, preferably loop diuretics, adjusting dose/frequency based on patient response. Add a thiazide diuretic if necessary.
Metabolic bone disease	• Do a baseline measurement of iPTH, phosphorus, calcium, and calcium phosphate product at Stage G3 with followup testing based on baseline measures and stage	• Reduce phosphate additives for all with CKD • Consider phosphate binders if progressive rise in iPTH or s. phosphorus in spite of dietary counseling • Restrict calcium based binders or supplements if vascular/valvular calcification, hypercalcemia and low iPTH

Definition of CKD

Chronic kidney disease (CKD) can be defined as abnormalities of kidney structure or function, present for more than 3 months, with implications for health.

Predicting progression of CKD

Understanding the risk for CKD progression supports clinical decisions about testing, treatment and referral, as it supports shared decision making. It is important to explain to the patient that the goal is to slow disease progression and take measures to prevent or delay the need for ESRD and renal replacement therapy. KDIGO defines progression as follows:

- **Progression:** Decline in eGFR category – a drop in eGFR category OR a ≥ 25% drop in eGFR from baseline
- **Rapid Progression:** A sustained decline in eGFR of > 5 ml/year

In people with CKD progression, review current management, examine for reversible causes of progression, and consider referral to a specialist.[KDIGO]

Controversy regarding overdiagnosis

There has been some debate about whether relying on eGFR and albuminuria leads to overdiagnosis and overly aggressive treatment of CKD. Based on KDIGO guidelines, diagnosis of CKD has increased significantly (from approximately 1.7% of the population before KDIGO to 14% of the population after). This, combined with low rates of total kidney failure, suggest that many of those diagnosed will never progress to symptomatic forms of kidney disease.[BMJ]

We recommend monitoring change over time to determine treatment and progression risk.

Diagnostic Criteria And Staging

The 2012 Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guidelines for CKD clarify the definition and diagnosis of chronic kidney disease (CKD). Based on these guidelines, this section includes a best-practice definition of CKD (see sidebar), diagnostic criteria, and staging and progression guidelines.

Diagnostic criteria

The table below is adapted from the KDIGO guidelines. A patient should be diagnosed with CKD if markers of kidney disease (especially albuminuria) or decreased estimated glomerular filtration rate (eGFR) is present.

TABLE 1: DIAGNOSTIC CRITERIA FOR CKD

Either of the following present for > 3 months [KDIGO]	
Markers of kidney damage (1 or more)	• Albuminuria: ACR ≥ 30 mg/g • Urine sediment abnormalities • Electrolyte and other abnormalities due to tubular disorders • Abnormalities detected by histology • Structural abnormalities detected by imaging • History of kidney transplantation
Decreased eGFR	• eGFR < 60 ml/min/1.73 m2 (eGFR categories G3a–G5; see Step 1 on page 4

Staging of CKD

KDIGO stages are based on CGA — Cause, eGFR category and albuminuria category.

Assign cause based on the presence or absence of systemic disease and the location (observed or presumed) within the kidney (see table 2 on next page).[KDIGO]

Patients with eGFR > 45 and without albuminuria are generally at lower risk for progressive kidney failure. However, those with mild impairment in renal function but with albuminuria are at higher risk.[TON, LEV2]

See the management algorithm on page 4 for eGFR and albuminuria category.

TABLE 2: CLASSIFICATION OF CKD BASED ON CAUSE[KDIGO]		
	Examples of systemic diseases affecting the kidney	**Examples of primary kidney diseases (absence of systemic diseases affecting the kidney)**
Glomerular Diseases	Diabetes, systemic autoimmune diseases, systemic infections, drugs, neoplasia (including amyloidosis)	Diffuse, focal, or crescentic proliferative glomerulonephritis (GN), focal and segmental glomerulosclerosis, membranous nephropathy, minimal change disease
Tubulointerstitial Diseases	Systemic infections, autoimmune diseases, sarcoidosis, drugs, urate, environmental toxins (lead, aristolochic acid), neoplasia (myeloma)	Urinary tract infections, stones, obstruction
Vascular diseases	Atherosclerosis, hypertension, ischemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, systemic sclerosis	Antineutrophil cytoplasmic antibody (ANCA)-associated renal limited vasculitis, fibromuscular dysplasia
Cystic/congenital diseases	Polycystic kidney disease, Alport syndrome, Fabry disease	Renal dysplasia, medullary cystic disease, podocytopathies

KEY RECOMMENDATIONS

- **Screening:** Get an accurate blood pressure at every visit. Obtain home blood pressure readings if elevated. Check ACR as noted on page 2.
- **Management (see algorithm 4):**
  - Counsel lifestyle changes
  - Prescribe ACEI; If ACEI not tolerated, switch to ARB.
  - If ACEI or ARB not effective, add other meds based on guidance in hypertension management (pages 9-10).

ALBUMINURIA AND HYPERTENSION

Albuminuria is a marker of kidney damage as well as an important prognostic finding. A high level of albumin is associated with all-cause and cardiovascular mortality, independent of cardiovascular risk factors.[VAN]

Hypertension, a common complication of CKD, is also a risk factor for faster CKD progression and for cardiovascular disease (CVD).[NKF1] Reaching a target blood pressure goal is the key to managing albuminuria. Though all antihypertensive agents can be used to lower blood pressure in CKD, some agents (such as ACEIs and ARBs) also slow the progression of kidney disease by blocking the renin-angiotensin-aldosterone system (RAAS) (see sidebar on page 10). When setting a blood pressure goal, individualize targets and agents according to age, proteinuria status, CVD, comorbidities, risk of progression, retinopathy and tolerance to treatment.

Algorithm 4: Albuminuria/Hypertension Management

Abbreviations used in this algorithm: ACR = albumin-creatinine ratio; SBP = systolic blood pressure; ARA = aldosterone receptor antagonist; BB = beta blocker; CCB = calcium channel blocker

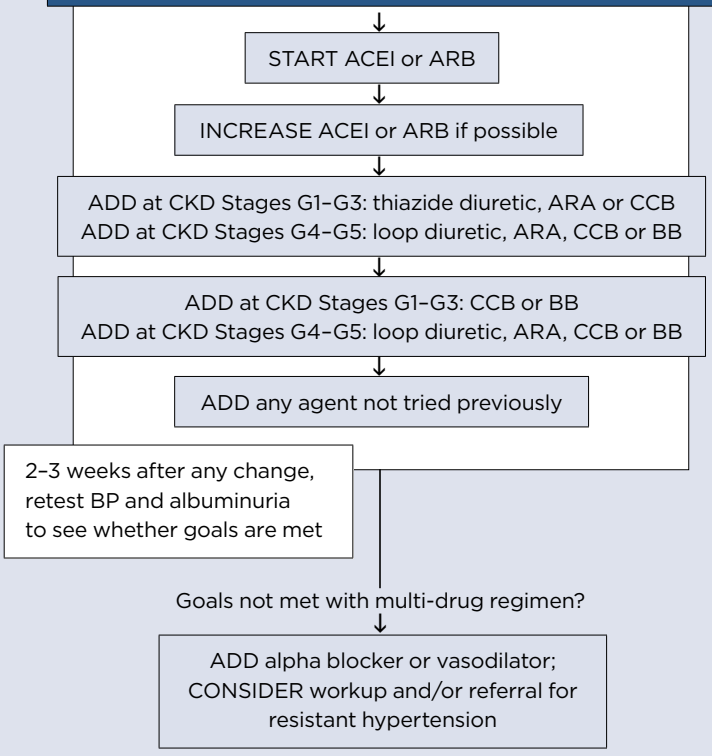
MANAGEMENT GOALS	
Albuminuria:	• Patients with moderately increased albuminuria (ACR 30–300): Eliminate detectable albumin. • Patients with severely increased albuminuria (ACR > 300): Reduce to 60% of baseline, or lower to ACR< 300 in high-risk CKD.
Hypertension:	• Patients without albuminuria: ≤ 140/90; patients with ACR > 300: ≤ 130/80

Goals not met?

THERAPEUTIC LIFESTYLE CHANGE (TLC)			
↑ Activity	Increase regular aerobic activity to at least 30 minutes 5 days a week (expected SBP reduction: 4-9 mm Hg).	**↓ Weight**	If overweight, lose weight: Maintain BMI of 18.5-24.9 (expected SBP reduction: 5-20 mm Hg per 10 kg weight loss).
↓ Dietary Sodium	Reduce dietary sodium to less than 1,500 mg/day (expected SBP reduction: 208 mm Hg). The DASH diet can be helpful at CKD Stage G1-G2; at Stage G3-G5, potassium in DASH diet is too high.	**↓ Alcohol**	Reduce alcohol to no more than 2 drinks per day for most men; no more than 1 drink per day for women and lighter weight men (expected SBP reduction: 2-4 mm Hg).

Goals not met?

INITIATE MEDICATION (WITH SPECIAL CONSIDERATION OF ALBUMINURIA) IN THE ORDER BELOW; IF THE GOAL IS NOT MET, MOVE TO THE NEXT MEDICATION STEP



Test serum creatinine (SCr) within 2 weeks of starting an ACEI or ARB or any dose change:

- If SCr is increased by < 15% compared to baseline, increase dose if needed.
- If SCr is increased by 15% to 25% from baseline, retest in 2 weeks. If retesting shows no further worsening, maintain dose.
- If SCr is increased > 25% from baseline, reduce dose by 50% or stop ACEI/ARB. Switch to the next-line agent. Retest in 2 weeks to ensure that the problem is resolved.

Test potassium: Within 4-7 days when adding an ARA or increasing dose (if patient is on ACEI or ARB) or between 7-10 days (if patient is not on ACEI or ARB).

- If potassium is > 5.5 mmol/L, reduce dose or stop therapy. Switch to the next-line agent. Suggest that patient reduce dietary potassium.

Notes:

- Monitor for signs of orthostasis, especially after change in medical therapy and with elderly or compromised patients.
- In patients with hypertension, many nephrologists encourage starting with an ACEI or an ARB even if the ACR is normal (even though the benefit for preventing future albuminuria has not been proven).

ACEI/ARB side effects

- **Decrease in eGFR:** A rise in serum creatinine usually begins a few days after starting or increasing ACEI/ARB dose. Check SCr and/or eGFR within 2 weeks of initiation or dose change.
- **Hypotension:** If patient is volume depleted, avoid startng an ACEI or ARB (which has higher rates of hypotensive symptoms). Start the ACEI or ARB at a low dose to minimize first-dose hypotension.
- **Hyperkalemia:** If a patient's initial potassium is > 5, reduce dietary potassium, start ACEI/ARB at a low dose, and monitor carefully (also if increasing dose). Discontinue ACEI/ARB if potassium is > 5.5 despite treatment. Refer patient to a dietitian.
- **Cough (dry, hacking):** Occurs in 5-20% of patients treated with an ACEI. Cough (much less common with ARBs) usually resolves a few days afer stopping therapy, but resolution can take up to 4 weeks. Cough generally recurs with rechallenge with any ACEI.
- **Angioedema (causes swelling of mouth, tongue, pharynx and eyelids):** A rare but potentially fatal complication (0.1-0.7% of ACEI-treated patients). Discontinue ACEI or ARB (although these have lower rates of complication); symptoms usually resolve within 24-48 hours. Protect the airway; tongue swelling can cause asphyxiation.

Managing low blood pressure (BP) and CKD

Decreased renal perfusion due to low blood pressure can be much more serious in CKD patients and increase risk of acute kidney injury and subsequent worsening of CKD.

There is no evidence that "lower is better" for a BP target. Once BP is controlled below a target goal, there is no benefit to increasing medication further to reach an even lower BP.

Be especially aware of symptoms of low blood pressure in patients with CKD. Consider titrating BP medications as indicated to allow the blood pressure to rise (while still remaining below recommended targets) if symptoms (such as lightheadedness, fainting, increasing fatigue or exercise intolerance) suggest low blood pressure. Also check for orthostatic changes in blood pressure.

ACEIs and ARBs

- **An ACE inhibitor (ACEI)** is the drug class of choice for hypertension and albuminuria management. Better outcomes are associated with agents that address the RAAS system and lower both albuminuria and blood pressure. ACEI or ARB therapy can result in a 35%-45% reduction in urinary proteins, with a dose-related effect.
- **Begin with an ACEI,** and if the patient doesn't tolerate ACEI treatment, switch to an ARB. Recent evidence suggests that increased adverse events may outweigh any benefits of combining an ACEI and ARB.[YUS] Begin at a low dose and titrate to the maximum tolerated dose (see the High Blood Pressure CPM) while monitoring and managing side effects (see algorithm on the previous page and the sidebar at right).
- **Contraindications —** Do NOT prescribe ACEIs or ARBs with:
  - Pregnancy (contraception is recommended with ACEI/ARB therapy for women of reproductive age; these drugs can cause problems in the second and third trimesters)
  - Bilateral renal artery stenosis

Other medications

Multi-drug regimens are necessary in many CKD patients. This summary recommends the following medications

- **Diuretics:** Thiazide diuretics are useful when added to an ACEI or ARB for albuminuria and hypertension management. Loop diuretics are preferred in patients with Stage G4–G5 CKD (eGFR < 30).
- **Aldosterone receptor antagonists (ARAs):** ARAs have been found effective for patients with refractory hypertension.
- **Calcium channel blockers (CCBs):** Either type of CCB — dihydropyridine (e.g., amlodipine) or nondihydropyridine (e.g., verapamil and diltiazem) can be used to manage albuminuria, but the nondihydropyridine CCBs have demonstrated more significant and consistent reductions in albuminuria. Avoid combining nondihydropyridine CCBs with beta blockers, due to the risk of bradycardia.

  NOTE: Avoid combining CCBs and beta blockers. Nondihydropyridine CCBs combined with beta blockers can lead to severe bradycardia, especially when used with digoxin.
- **Beta blockers (BBs):** Beta blockers can be part of combination therapy for most patients as a third- or fourth-line agent. Carvedilol may be one of the best choices due to its favorable effects on lipids, renal albumin excretion, and insulin sensitivity. Once a patient's heart rate is < 80 bpm, increasing BB dosage will have limited effectiveness; add other medications instead.
- **Alpha blockers, vasodilators:** These drugs should not be used unless previous therapies have been exhausted, and should not be used alone, due to a higher incidence of side effects (leg edema, orthostasis) and a lack of outcome data.
- **Direct renin inhibitors (DRIs):** Aliskiren (Tekturna) is not recommended with an ACEI or an ARB.

CVD risk, dyslipidemia and CKD

CKD patients have unique factors that lead to a higher risk for developing CVD. While many CKD patients have the traditional CVD risk factors (hypertension, diabetes and dyslipdemia) several other factdors increase the risk of developing CVD: [NOG]

- Inflammation
- Oxidative stress
- Volume overload
- Malnutrition
- Anemia
- Albuminura

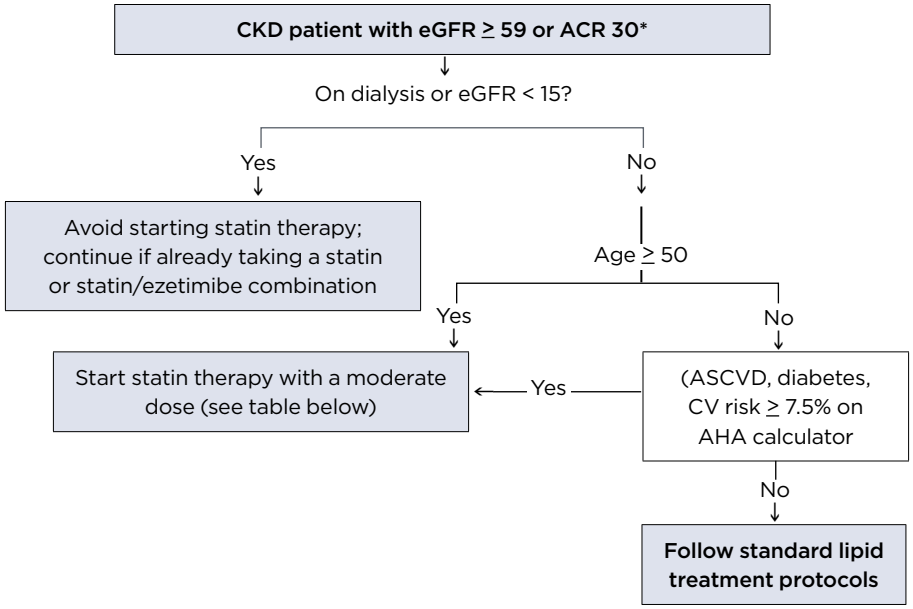
Lifestyle weight management and therapeutic lifestyle change (TLC)

For all CKD patients, management of dyslipidemia should include recommending lifestyle weight management and therapeutic lifestyle changes. Counsel patients to:

- See a registered dietitian (RD) for nutrition counseling to manage lipids. Tailored nutrition therapy can be very effective for lowering LDL and triglycerides but has little influence on HDL.
- Increase regular aerobic activity to > 150 minutes a week. A recent study found that with an exercise therapy program, HDL levels increased and triglyceride levels decreased, and that these changes are correlated significantly with an improvement in eGFR.[TOY]
- If overweight, lose weight: Maintain BMI of 18.5-24.9 (expected SBP reduction: 5-20 mm Hg per 10 kg weight loss).
- Reduce alcohol to < 2 drinks a day for most men; < 1 drink a day for women and lighter-weight men; abstain if high triglycerides.

DYSLIPIDEMIA MANAGEMENT

Triglyceride measurement is based on a fasting lipid profile. Very high (> 500 mg/dL) fasting triglycerides are unusual in CKD Stage G1 to G3, but are more common in Stages G4 to G5 or dialysis. If not corrected by removing a secondary cause, treatment to reduce the risk of pancreatitis takes precedence over treatment of LDL cholesterol. There are no LDL treatment goals for patients with CKD, and followup blood tests are not generally recommended, except to evaluate compliance.



Algorithm adapted from KDOQI clinical practice guidelines for dyslipidemia management in patients with CKD.[NKF4]

(A) RECOMMENDED DOSES (MG/D) OF STATINS IN ADULTS WITH CKD (STAGES 3–5)

Moderate doses from Intermountain's *Cardiovascular Risk and Cholesterol Guidelines*

MEDICATION	DOSE (MG/D)
atorvastatin	**10**
simvastatin[1]	**20–40**
pravastatin	**40**
fluvastatin	40 bid
pitavastatin	2–4
rosuvastatin	10

1. Combined simvastatin/ezetimibe also has been shown to be effective in reducing CV risk in patients with CKD, but has not been found to be superior to statins alone; dose: 20/10 mg/d.
2. **Bold type** indicates preferred medications; lovastatin omitted as generally not used in stages 3–5 due to lack of studies.

KEY RECOMMENDATIONS

- Recommend therapeutic lifestyle change/weight management for all patients (particularly those with elevated triglycerides only), and select medication based on the criteria described in the table on page 11.
- For patients who are treated for elevated LDL, only retest LDL if it would change treatment.
- Evaluate patients for secondary causes of dyslipidemia. Conditions include nephrotic syndrome, hypothyroidism, excessive alcohol ingestion and chronic liver disease. Medications include anticonvulsants, highly active antiretroviral therapy, beta blockers, diuretics, androgens/anabolic steroids, oral contraceptives, corticosteroids, cyclosporine, sitolimus and 13-cis-retinoacid.

Aspirin risk

Balance risk for atherosclerotic events and risk for bleeding when prescribing aspirin to CKD patients.

Lipid Management

Cardiovascular disease (CVD) is one of the most common comorbidities of CKD, and CKD patients should be considered in the high CVD risk category, similar to patients with coronary artery disease. CVD is the major cause of mortality in CKD;[WEI] patients with early CKD are more likely to die of cardiovascular disease than progress to Stage G5 CKD.[NOG] In addition, dyslipidemias may contribute directly to CKD progression.[NKF4] Lower serum HDL cholesterol is an independent predictor of a faster decline in eGFR.[BAK]

Prevalence and profile of dyslipidemia in patients with CKD. Dyslipidemias are prevalent in CKD due to a variety of factors, including changes in proteinuria, eGFR and CKD treatments. Following are typical findings in CKD patients; however, this profile may differ, reflecting the pattern seen with comorbidities such as diabetes and nephrotic syndrome, or with use of steroids and cyclosporine:

- Triglycerides, VLDL, LDL, Lipoprotein (a) and apoprotein B are often elevated.
- As CKD progresses, especially into Stage G5, total cholesterol, HDL, and LDL may decline (see below). Despite this decline, coronary risk remains high.
- LDL decreases in hemodialysis, but increases in peritoneal dialysis.

Use of lipid-lowering drugs (LLDs) in patients with CKD. Because those with lower levels of CKD have a higher risk from elevated lipids, start statins as early as recommended by guidelines. Despite the issues complicating the picture of dyslipidemia and CVD risk in patients with CKD, major guidelines[NKF2] and a review of LLD trials with CKD patients[NOG] advise the following:

- Only statins (or statins with ezetimibe) have evidence for improved clinical outcomes. (See management guidelines on page 11.) Multiple LLD trials have been reassuring on the risk of statins used in CKD.
- Recent trials of lipid-lowering drugs have shown benefit with the use of statins in Stages G1 to G4 CKD.[NOG] Multiple trials showed that statins used in Stages G1 to G4 reduced vascular events. These include the Pravastatin Pooling Project, Heart Protection study (simvastatin), ASCOT LLA (atorvastatin), and SHARP (ezetimibe + simvastatin).
- Statins have not been proven to improve morbidity and mortality in CKD Stage G5 or end-stage renal failure.[NOG] Deciding whether to use statins in these patients should be based on consultation with a nephrologist. The SHARP and 4D trials showed questionable benefit from statins in Stage G5 and dialysis; the ALERT trial showed no measurable benefit from statins in transplant patients. However, in patients with coronary artery disease or peripheral vascular disease, statins may still be indicated.

KEY RECOMMENDATIONS

Screening

Screen diabetes patients annually for CKD, with the following distinctions based on DM type:

- With type I DM, screening should begin 5 years after diagnosis.
- With type II DM, screening should begin at diagnosis.

Management

Focus is shifting to individualized care for blood pressure and glycemic control. Emphasis on treating high blood pressure and ASCVD prevention with lipid management may be especially helpful in reducing mortality among diabetes patients with CKD.

General guidelines:

- Glycemic control: HbA1c < 7% for most patients.
- ACEI or ARB if ACR ≥ 30: Most effective way to reduce albuminuria; see page 10. (Avoid dual use of ACEI and ARB.)
- BP control: BP goal < 140/90 for patients with diabetes and CKD unless ACR > 300; then goal < 130/80.

Diabetes Management

CKD is common in patients who have been diagnosed with diabetes mellitus (DM). Approximately 40% of patients with type I DM and 20% to 40% of patients with type II DM will develop chronic kidney disease. Diabetes is the most common cause of end-stage renal disease, accounting for 45% of patients on dialysis. For patients with comorbid diabetes and CKD, mortality risk is 2 times greater and nonfatal complications (such as CHF, nonfatal MI, nonfatal stroke) occur 1.5 to 3 times more frequently than for those with diabetes alone.[PAP]

CKD risk factors for patients with diabetes

The National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for CKD evaluation and classification identify key risk factors shown to cause early or more rapid worsening of renal function in patients with diabetes:[NKF2]

- Genetics — patients with a sibling or parent with diabetes and CKD
- Elevated blood pressure
- Glomerular hyperfiltration
- High/elevated HbA1c
- Race — African Americans, Hispanics, Pima Indians
- High BMI
- Tobacco use
- Diabetic retinopathy

CKD can usually be attributed to diabetes if albuminuria is either severely increased (ACR > 300 mg/g) OR moderately increased (ACR 30 to 300 mg/g) in a patient with DM retinopathy or type I DM of > 10 years duration.

In a patient with diabetes, consider another cause for CKD and resulting treatment decisions if any of these factors are present:

- Absence of diabetic retinopathy
- Low or rapidly decreasing eGFR
- Rapidly increasing albuminuria or nephrotic syndrome
- Refractory hypertension
- Presence of an active urinary sediment
- Signs or symptoms of another systemic disease
- Type I DM of less than 10 years duration

Management focus

Focus is shifting to individualized care for managing patients with diabetes and CKD. Follow these general guidelines:

- **Glycemic control.** Keeping HbA1c at 7.0% or lower in DM patients reduces the risk of developing albuminuria. While there are no large, long-term trials on the effect of glycemic control on established CKD progression, most experts recommend a 7.0% HbA1c goal for most patients with diabetes and CKD. Individualization is recommended as indicated clinically.
- **Use of an ACEI or ARB.** Albuminuria (ACR > 30 mg/g) is an early marker for renal dysfunction in diabetes patients and a strong risk factor for CVD. ACEI/ARB medications have been shown to be the most effective in DM patients to reduce albuminuria — even in DM patients with normal blood pressure. (Based on current evidence, dual use of an ACEI and ARB should be avoided.) See page 10.
- **Blood pressure control.** To reduce mortality risk, focus on meeting blood pressure goals in patients with albuminuria (ACR > 300 mg/g) of BP < 130/80 and BP < 140/90 for those without albuminuria.

Insulin therapy

For insulin, the evidence doesn't support specific dosage changes, but careful monitoring is required. As renal function declines, the effect of insulin is prolonged and risk for hypoglycemia increases.

Metformin use in high-risk patients

KDIGO recommends that metformin be continued in people with eGFR ≥ 45 (eGFR categories G1–G3a); its use should be reviewed in those with GFR 30–44 (eGFR category G3b); and it should be discontinued in people with eGFR < 30 (eGFR categories G4–G5).[KDIGO]

Glycemic control goal

We recommend individualized therapy with a goal of 7% HbA1c. For example, the target may be extended above 7% for patients with comorbidities or limited life expectancy and risk of hypoglycemia.

TABLE 11: MEDICATIONS USED TO TREAT DIABETES

(Apply dosage adjustments below to guidance in the Adult Diabetes Mellitus CPM)

Class	Medication	Stage G3a	Stage G3b	Stage G4	Stage G5	Notes
Biguanides	metformin* (Glucophage)	No change	No change	AVOID	AVOID	• Risk of lactic acidosis
Sulfonylureas	glimepiride (Amaryl)	↓ 50%	↓ 50%	↓ 50%	↓ 50%	• Start type 2 DM patients with CKD on 1 mg per day; adjust dose based on fasting blood glucose after that • Some risk of hypoglycemia
	glipizide XL (Glucotrol XL)	No change	No change	No change	No change	• The preferred sulfonylurea in CKD • Some risk of hypoglycemia
Thiazolidine-diones	pioglitazone (Actos)	No change	No change	No change	No change	• Can promote fluid retention and precipitate CHF • Avoid in patients with NYHA class III or IV cardiac status
DPP-4 Inhibitors	alogliptin (Nesina)	↓ 50%	↓ 50%	↓ 75%	↓ 75%	
	linagliptin* (Tradjenta)	No change	No change	No change	No change	
	saxagliptin* Onglyza	↓ 50%	↓ 50%	↓ 50%	↓ 50%	
	sitagliptin phosphate* (Januvia)	No change	↓ 50%	↓ 75%	↓ 75%	• Decreased medication clearance when creatinine clearance < 50 ml/min
GLP-1 receptor agonists**	exenatide (Byetta)	See note	See note	AVOID	AVOID	• Use caution when initiating or when increasing dose from 5 mcg to 10 mcg in Stage G3
	exenatide ER (Bydureon)	No change	No change	AVOID	AVOID	
	liraglutide (Victoza)	No change	No change	No change	No change	
	albiglutide (Tanzeum)	No change	No change	No change	No change	
	dulaglutide (Trulicity)	No change	No change	No change	No change	
Amylin mimetic	pramlintide acetate (Symlin)	No change	No change	No change	AVOID	• Should only be used for patients on insulin and only by providers with significant knowledge of its properties • Moderate risk of hypoglycemia
SGLT2 Inhibitors	canagliflozin (Invokana)	No change	No change	AVOID	AVOID	• Maximum dose is 100 mg once daily • Use not recommended at Stage G3b
	dapagliflozin (Farxiga)	AVOID	AVOID	AVOID	AVOID	
	empagliflozin (Jardiance)	No change	AVOID	AVOID	AVOID	

* For medication combinations (such as sitagliptin, saxagliptin, or linagliptin combined with metformin):
  - Follow dose recommendations for individual drug components as listed above.
  - If recommendations differ for the 2 combined drugs (e.g., no change for one and reduce 50% for the other), follow the more conservative recommendation.

** Use caution during treatment initiation and dose increases. Advise patients to report nausea, vomiting and dehydration symptoms that may complicate underlying renal disease. These medications are not recommended as monotherapy.

KEY RECOMMENDATIONS

- Educate patients at high risk for hyperkalemia to watch for severe muscle weakness or fatigue and contact your office if it occurs.
- Educate all CKD patients on potassium and their diet. See page 22. Consider referral to a registered dietitian.
- Test for potassium:
  - Within 2 weeks of any ACEI/ARB dose change.
  - Within 4-7 days (if patient is on ACEI or ARB) when adding an ARA or increasing dose (between 7 and 10 days if patient not on ACEI or ARB).
  - If the patient has any symptoms of hyperkalemia and at regular CKD followup appintments.
  - If you identify hyperkalemia, redraw blood and retest to rule out hemolysis or a lab error.
  - If results are confirmed, follow the guidance on the next page for management based on the severity of hyperkalemia.

More on potassium and CKD

- **How potassium is excreted.** In healthy patients, an increased potassium load is typically excreted, without complications, in a process that depends in part on aldosterone, insulin, beta-2 adrenergic receptos and Na-K-ATPase activity in cell membranes.[MOU2]
- **How CKD complicates potassium.** Both CKD and medications used to treat DKD (see list at right) impair the excretion process in multiple ways. CKD comorbidities, such as metabolic acidosis can also affect potassium clearance.
- **Why it matters.** Because potassium is involved in cellular membrane potential and conduction, hyperkalemia interferes with all electrically active cells neurons, voluntary muscles and involuntary muscles. The most prominent effect is on myocardial cell conduction which is why hyperkalemia can cause fatal arrhythmias.

Other Comorbidities

Hyperkalemia

Hyperkalemia is defined as a serum potassium level greater than 5 mmol/L. Since the kidneys are responsible for excreting potassium, impaired renal function is a major cause of hyperkalemia.[K AH,ROS2] In fact, impaired renal function was present in up to 83% of patients requiring hospitalization due to hyperkalemia.[MOO]

Why is it important?

Hyperkalemia may result in muscle weakness, paralysis, cardiac conduction abnormalities or dysrhythmias. If hyperkalemia is not recognized and treated early, it can lead to fatal cardiac arrhythmias.[EVA] Patients requiring hospitalization from hyperkalemia have a mortality rate up to 41%.[MOO]

What causes it?

- Medications should always be looked at first as the underlying cause in patients with CKD. With the following commonly prescribed medicines, consider either dosage reduction or elimination to improve hyperkalemia:[PER1]
  - ACEIs, ARBs, or direct renin inhibitors (see page 9 for algorithm with guidance on ACEI/ARB dosage reductions)
  - Potassium supplements
  - Potassium-sparing diuretics such as spironolactone, eplerenone, triamterene and amiloride
  - NSAIDs, including OTC preparations
  - Bactrim (trimethoprim/sulfa)
  - Digoxin
  - Nonselective beta blockers (such as atenolol and propranolol)
  - Cyclosporine and tacrolimus
  - Heparin
  - OTC herbal supplements and vitamins such as alfalfa, dandelion, horsetail, nettle or multivitamins containing potassium
- **Other causes.** Once medications have been eliminated, consider other causes of hyperkalemia: [EVA]
  - Lab error or hemolysis during the blood drawing process (recheck results) or pseudohyperkalemia in the setting of marked WBC elevation (CML, etc.).
  - Increased potassium release from cells and/or decreased tissue uptake: Metabolic acidosis, insulin deficiency, hyperglycemia, hyperosmolality, increased tissue catabolism (rhabdomyolysis, major surgery, radiation therapy).
  - Reduced urinary excretion: Hypoaldosteronism (most common in diabetics), renal failure, low urine flow, decreased effective circulating volume depletion, obstruction.
  - Dietary potassium in patients with renal insufficiency: CKD patients should control their potassium intake; see the sidebar at left and the dietary section on page 22.

Management Approach

Management should be based on the patient's potassium level. Eliminating medications and OTC substances that increase potassium, along with tighter restrictions on dietary potassium, often resolves the condition if K+ is 5.1 to 6.0. If K+ is > 6.0, emergency/urgent treatment is required. Management advice based on expert consensus of the CKD CPM at Intermountain Health Care is summarized in the table below.

TABLE 12: HYPERKALEMIA PREVENTION AND MANAGEMENT APPROACH

K^+ Level	Physician Management	Patient Education "Zone"
3.5 to 5.0 mmol/L	• No management needed; provide general education about potassium.	**SAFETY ZONE** In the safety zone, patients should limit high potassium foods to keep potassium from getting too high.
5.1 to 5.5 mmol/L	• Review the patient's use of over-the-counter substances that may be causing the problem (see previous page). Consider tighter limits on dietary potassium. See the dietary advice on page 22. • Retest potassium within 2 weeks to see if the problem is resolved.	**CAUTION ZONE** Managing potassium in this zone involves stricter dietary limits and may mean medication changes or medical treatments.
5.5 to 6.0 mmol/L	• Along with the steps above, review and adjust the dose of prescribed medications. Begin with mediations other than ACEI/ARB therapy. Retest potassium within 2 weeks after any change in therapy. • Reduce or stop ACEI/ARB therapy if other medications are not present and ACEI/ARB therapy is the likely cause. See page 10. • Look for other causes if mediations are reduced/stopped without positive results. • Refer the patient to a nephrologist if hyperkalemia persists despite your efforts to manage it.	
> 6.0 mmol/L	• Consider hospitalization or make an emergency referral for cardiac monitoring and urgent treatment. • If the patient can't or won't go for emergency treatment, use all the measures described above and consider the following treatment options: – **Loop diuretics** (or increasing the dose if they are already used). For dosing of diuretics, see the sidebar on page 19. – **Sodium polystyrene sulfonate (Kayexalate)**. Sodium polystyrene sulfonate is generally dosed at 15 to 30 grams orally, with subsequent doses given every 4 to 6 hours as needed to lower potassium levels.[MOU1] Use caution with sodium polystyrene sulfonate, especially postoperatively, as bowel necrosis has been reported in post-op patients using this medication.[GRUY] – **Fludrocortisone (Florinef)**. The usual fludrocortisone dosage is 0.1 mg daily, although more will be needed in some patients. Primary side effects are hypertension and fluid retention, which may respond to an added diuretic.[HOL] – **Insulin with glucose**. Administer insulin therapy with glucose if the patient is diabetic. A common regimen is 10 units of regluar insulin in 500 mL of 10% dextrose, given over 60 minutes. Another regimen is a bolus injection of 10 units of regular insulin, followed immediately by 50 ml of 50% dextrose (25g glucose).[MOU1]	**DANGER ZONE** This zone means urgent treatment and may require hospital stay to get potassium levels back to normal.

KEY RECOMMENDATIONS

- Screen BMP at the following intervals, based on CKD stage:
  - Every 12 Months at Stages G1 and G2.
  - Every 6 months at Stage G3.
  - Every 3-4 months at Stages G4 and G5.
- Manage. Treat to maintain bicarb > 22 mEq/L by giving sodium bicarbonate or baking soda.
- Consider other causes. Treating the cause may help prevent further problems.

Other causes of acidosis

- It is helpful to know whether acidosis is non-anion gap or anion gap. An anion-gap calculator is available at: **mdcal.com/anion-gap**
- Other causes of non-anion gap acidosis:
  - Diarrhea
  - Renal tubular acidosis
  - Medications: acetazolamide, spironolactone
- Causes of anion gap acidosis:
  - Medications: Isoniazid, salicylates, paraldehyde
  - Alcohol or methanol poisoning
  - Diabetic or alcoholic ketoacidosis
  - Lactic acidosis
  - Rhabdomyolysis and/or uremia with renal failure

Metabolic Acidosis

Metabolic acidosis (serum bicarbonate < 22 mEq/L) is common in patients with CKD — particularly patients with diabetes — and can become apparent when the patient's eGFR drops below 50. Metabolic acidosis in CKD is typically non-anion gap acidosis and is chronic and mild.

How CKD causes metabolic acidosis

The kidneys maintain acid-base balance by excreting hydrogen ions, reabsorbing filtered bicarbonate from tubular fluid, and ammoniagenesis. When eGFR is below 50, ammonium (NH4 +) excretion per nephron is 3 to 4 times higher than normal rates. Despite this compensation, CKD leads to progressive retention of hydrogen ions and the development of metabolic acidosis.

Why treat metabolic acidosis?

- Metabolic acidosis can cause significant problems. Chronic metabolic acidosis can lead to muscle wasting and weakness, impaired albumin synthesis, and loss of bone minerals. It can also exacerbate hyperkalemia. If severe, metabolic acidosis can result in coma and death.
- Treatment can slow CKD progression. New studies suggest that correction of metabolic acidosis may also slow the progression of CKD.[DEB,MAH]
- Treatment is inexpensive and effective. Treatment with sodium bicarbonate is an easy OTC solution. Sodium bicarbonate does not aggravate hypertension or require diuretics.

Evaluation and monitoring

Metabolic acidosis is evaluated by a basic metabolic panel.

Management

KDOQI guidelines NK F3 recommend maintaining serum bicarbonate levels above 22 mEq/L by giving sodium bicarbonate. Sodium bicarbonate is preferred over sodium citrate (with the exception of patients with kidney stones), due to the potential for increased passive absorption of aluminum with sodium citrate.

Sodium bicarbonate supplementation has not been shown to aggravate hypertension or lead a patient to need diuretics, despite the increased sodium load. Usual daily dosing is 0.5 mEq (42 mg bicarbonate) per kg. Usual dosing of sodium bicarbonate tablets is 1,300 mg, twice daily — begin with 650 mg twice daily and titrate the dose as needed. However, baking soda is an inexpensive option:

- For a 150 lb patient, 1 teaspoon of baking soda daily
- For a 200 lb patient, 1.25 teaspoons of baking soda daily

KEY RECOMMENDATIONS

- Regularly monitor iron stores (ferritin and/or transferrin saturation) based on CKD stage.
- Begin with a 3-month trial of oral iron therapy.
- If the patient does not tolerate oral iron or iron stores remain low after 3 months, consider IV iron therapy.
- Use ESAs for low EPO only if absolutely necessary.

Use of erythropoietin stimulating agents (ESAs)

There is no clear recommended target Hgb level for ESA therapy and ESAs should not be administered in an attempt to normalize Hgb.

Recent evidence on use of ESAs suggests no clear benefit and possible increased risk for adverse events, including stroke. Studies have shown increased risk for adverse events if target Hgb > 11.5. ESA therapy is best managed by a nephrologist or hematologist.

The 2012 KDIGO guidelines for using ESAs (e.g., Procrit, Epogen or Aanesp) to treat anemia in patients with CKD recommend:

- Initiating only for patients not on dialysis with severe anemia (Hgb < 10 g/dL).
- Starting therapy for patients in CKD stage 5 (not on dialysis) when Hgb is between 9 and 10.
- Only using to prevent the need for blood transfusion.
- Determining appropriateness based on rate of fall of Hgb concentration, prior response to iron therapy, risks of needing a transfusion and related to ESA therapy and symptoms that can be attributed to anemia.

ANEMIA

Anemia is a common complication of CKD as a consequence of the loss of erythropoietin (EPO) production by the impaired kidneys. The risk for anemia increases as eGFR drops below 60; more than 80% of patients with Stage G4 CKD will have some degree of anemia. Patients with diabetes may develop EPO deficiency at earlier stages of CKD. (Note: Polycystic kidney disease patients tend to retain EPO production and not become anemic, in spite of marked reduction in eGFR.)

Diagnosis and monitoring

Diagnose anemia in adults and children over 15 with CKD when the Hb concentration is 13.0 g/dL (130 g/L) in males and 12.0 g/dL (120 g/L) in females.[KDIGO] While iron deficiency is common in CKD, rule out other causes of anemia such as GI bleeding.

If serum creatinine (SCr) is < 1.5 mg/dL, check the EPO level. If renal function is impaired (SCr > 1.5 mg/dL or eGFR < 45 mL/min), checking EPO is unnecessary, as EPO deficiency can be assumed.

Monitor CKD Stages 3–5 patients with and without comorbid anemia as follows:

TABLE 13: ANNUAL MONITORING FOR ANEMIA (MORE OFTEN WHEN CLINICALLY INDICATED)

CKD Stage	3	4 (no dialysis)	5 (dialysis)
CKD patients WITHOUT anemia			
Recommended Hgb testing frequency	≥ 1/year	≥ 2/year	≥ 4/year
CKD patients WITH anemia (not treated with an ESA – see info on ESAs at left)			
Recommended Hgb testing frequency	≥ 4/year	≥ 4/year	≥ 12/year

Management

Consider iron supplementation (see table below) for relative iron deficiency, beginning with a 1 to 3-month trial of oral iron therapy. Do not supplement with iron if ferritin > 800 ng/mL, due to the possibility of iron overload. Consider IV iron therapy if patient does not tolerate oral iron or if patient is compliant, but iron stores remain low after 3 months.

TABLE 14: RECOMMENDATIONS FOR IRON SUPPLMENTATION THERAPY

Oral (initial 3-month trial recommended)	IV* – Only when oral therapy unsuccessful and patient not on dialysis or ESA therapy
Usual dosing: 65 mg elemental iron, 3 times daily. Take only on empty stomach. Do not take within 2 hours of consuming: • Bran, fiber, grains, nuts, soy, vegetables • Tea, coffee, caffeine • Red grape juice, wine • Dairy, egg • Thyroid medications, phosphate binders, carbonate antacids, copper supplements	Usual dosing: 1 gram IV iron sucrose (Venofer) in divided doses as follows: • 200 mg IV injected undiluted over 2 to 5 minutes • Injected on 5 different occasions within a 14-day period • Total cumulative dose of 1,000 mg

* To protect the patient's venous access, minimize the number of transfusions if possible and avoid the nondominant arm.

KEY RECOMMENDATIONS

- Screen at every visit. Check for weight change and other signs, such as shortness of breath, refractory hypertension or peripheral edema.
- Evaluate cardiac risk, especially if eGFR > 30; edema may have a cardiac cause.
- Manage volume overload.
  - Discontinue or reduce medications that can cause edema.
  - Restrict dietary sodium to 1,500 mg per day.
  - Prescribe diuretics, starting with a loop diuretic.

Educate patients to avoid overhydration

Patients newly diagnosed with kidney disease may hold to the myth that they should drink large amounts of water daily to "flush the kidneys." As this behavior can cause volume overload, it's important to correct this misconception during discussions about kidney disease with patients at Stage G3b or later.

Adjusting loop diuretics

Loop diuretics have a dose-responsive curve. You may need to increase the dose beyond the typical maximum to treat volume overload. To decide whether to adjust the dose or the frequency of a loop diuretic, ask the patient whether the current dose prompts urination.

- If a single dose does not prompt urination, increase the dose rather than giving the same dose twice daily. For example, if a patient doesn't respond to 40 mg of furosemide (Lasix), the single dose may need to increase to 80 mg.
- If a single dose prompts urination, increase the frequency of that dose to twice daily.

Volume Overload and Edema

Volume overload is a frequent complication of CKD at Stages G4 and G5, or with severe nephrotic syndrome at any CKD stage. The kidneys typically balance sodium and intravascular volume until eGFR falls below 15. However, even at earlier CKD stages (eGFR below 40), the kidneys are less able to respond to sodium, and these patients can be prone to volume overload.

Evaluation and monitoring

- Monitor patients regularly for signs and symptoms of volume overload:
  - Check a patient's weight at every visit. An increase in weight may be a sign of salt and water retention. Educate patients to weigh themselves routinely and schedule an appointment if they experience a weight gain of 5 lbs or more in less than 1 week.
  - Check for other signs, including refractory hypertension, shortness of breath, or peripheral edema. (Please note that peripheral edema does not always indicate volume overload.) Patients with volume overload may also have jugular venous distension, hepatojugular reflux, pulmonary crackles, chest discomfort, and progressive decrease in exercise tolerance.
- In patients with signs or symptoms, evaluate CV risk and check for cardiac causes. In patients with eGFR > 30, volume overload is often caused by a cardiac condition such as heart failure. If eGFR < 30, CKD is more likely to be the cause.

Management

- Discontinue or reduce the dose of medications that can cause edema:
  - NSAIDs
  - Thiazolidinediones (e.g., rosiglitazone/Avandia, pioglitazone/Actos)
  - Calcium channel blockers
  - Direct vasodilators (e.g., minoxidil/Loniten, hydralazine/Apresoline)
  - GABA analogues (e.g., gabapentin/Neurontin and pregabalin/Lyrica)
  - Pramipexole (Mirapex)
  - Corticosteroids
  - Estrogens
- Restrict dietary sodium to 1,500 mg per day. Dietary sodium is a contributor to volume overload and edema.
- If volume overload persists, prescribe diuretics.
  - Begin with a loop diuretic. See High Blood Pressure on page 9.
  - If volume overload does not respond, adjust the loop diuretic dose or frequency. See the sidebar for tips on adjusting loop diuretic therapy.
  - If volume overload still does not respond, try a different loop diuretic. For example, if oral absorption is impaired (such as in bowel edema), switching from furosemide (Lasix) to another loop diuretic such as torsemide (Demadex) may be helpful.
  - If volume overload does not respond with a loop diuretic alone, consider adding a thiazide diuretic. Follow up to monitor the patient for hypokalemia or prerenal azotemia. See page 10.

If these measures are not effective, refer the patient to a nephrologist.

KEY RECOMMENDATIONS

- Monitor. Annually measure serum levels based on CKD stage (see table 15).
- Reduce phosphate; regulate calcum and vitamin D.

Osteoporosis and bisphosphonates

- Diagnosis of osteoporosis in patients in CKD Stages 3b-5 becomes increasingly challenging. Rule out other forms of osteodystrophy before treating with bisphosphonates.
- In CKD Stage 4-5 patients, bisphosphonates safety and efficacy has not been well-studied in CKD populations and IV bisphosphonates have been implicated in nephrotoxicity. KDIGO

Vitamin D

Evaluate patients with levels of iPTH above the upper normal limit of the assay for vitamin D deficiency.

Metabolic Bone Disease

Early in the course of CKD, changes in bone mineral metabolism and calcium and phosphate homeostasis occur (resulting in renal osteodystrophy, extraskeletal calcifications, etc.). These changes progress as kidney function declines.KDIGO

Controversy exists about treatment targets for serum concentrations of calcium, phosphate, and intact parathyroid hormone (iPTH), and the impact of vitamin D on these mineral metabolites. Recent research on the role of fibroblast growth factor 23 (FGF-23) (an important molecule in phosphate, iPTH and vitamin D homeostasis) has caused many to question the previous focus on iPTH. The optimal iPTH value for patients in CKD Stages 3b-5 is unknown.

Evaluation and monitoring

KDIGO monitoring and evaluation guidelines for CKD Stages 3b-5 recommend:KDIGO

- Measuring serum levels of calcium, phosphate, iPTH, and alkaline phosphatase for baseline values and subsequent retesting as indicated in table 15 below.
- Not performing bone mineral density (DEXA) testing routinely — the information may be misleading or unhelpful because DEXAs neither assess bone quality nor help predict fractures.

TABLE 15: MONITORING FREQUENCY FOR METABOLIC BONE DISEASE KDIGO

CKD Stage	Annual testing frequency**			
	Serum calcium	Phosphorus	iPTH	Alkaline phosphatase activity
3	1–2	1–2	1–2	Based on baseline level and CKD progression
4	2–4	2–4	1–2	≥ 1*
5	4–12	4–12	2–4	≥ 1*

* For Stages 4-5D, retest more frequently in presence of elevated iPTH
** The frequency of testing is determined by severity of disease, the rate of progression and current treatment

Management

TABLE 16: MANAGEMENT OF METABOLIC BONE DISEASE—GOALS AND RECOMMENDATIONS

Goals	Recommendations (serum calcium < 9.5)	Recommendations (serum calcium > 9.5)
• Reduce phosphate levels unless phosphate is already low. Target: Within age-appropriate limits. (Maintain serum phosphate concentreation in the normal range based on local laboratory reference values.) • Regulate calcium. Target: 8.4 to 9.5 mg/dL • Regulate vitamin D. Target: 30 to 50 mg/mL	**Limit dietary phosphorus to 800 to 1,000 mg daily.**	
	Consider calcium phosphate binders as initial therapy. Follow patient's calcium levels and do not exceed 2,000 mg per day of total elemental calcium. Products include: • Calcium carbonate antacids such as Tums or Rolaids. Tablet weight is 40% elemental calcium; some patients need 1 to 3 tablets with each meal • Calcium acetate (PhosLo) by prescription	**Consider noncalcium phosphate binders.** These are more expensive than calcium-based medications and can cause GI upset. Product choice depends on preferred formulation: • Sevelamer (RenaGel or Renvela): available in tablet or powder to be sprinkled on food. Usual dosing is 0.8 or 1.6 grams, 3 times daily with meals • Lanthanum (Fosrenol): available as large tablet (chewable or crushed to sprinkle on food). Initial dose is 1,500 mg per day, with doses up to 4,500 mg per day • See page 23 for information about dietary management of phosphorus, calcium and vitamin D

KEY RECOMMENDATIONS

- Referral to a registered dietitian (RD) is recommended to tailor diet information to fit a particular patient's disease stage and status.
- In the early stages of CKD, primary dietary management should focus on diet related to diabetes, hypertension, lipid managment and obesity. These conditions will accelerate loss of kidney function.
- As CKD progresses, loss of appetite and taste aversions are common, along with the development of malnurition.

  Malnutrition must be avoided because it increases the patient's risk of mortality. Dietary restrictions should be liberalized if malnutrition is present.
- Use of the DASH diet is appropriate in the early stages of CKD, but is generally high in potassium and phosphorus and its use may need to be reassessed in the later stages.

Vegetarians and protein

- A vegetarian diet is fine for CKD patients, but diet counseling would be appropriate. To get the necessary amino acids, vegetarians must combine proteins from multiple sources, including:
  - Milk or eggs, for lacto-ovo vegetarians
  - Soy (tofu, soy milk, etc.)
  - Beans, lentils, peas, other legumes
  - Nuts, seeds
  - Whole grains (wheat, oats, rice, etc.)
- To get the necessary amino acids, vegetarians may need to consume more protein than these guidelines recommend. However, a vegetarian diet may bring other health benefits that slow CKD progression. If a potassium restriction is indicated, it may become very difficult to meet protein needs on a vegetarian diet, as most vegetarian sources of protein are high in potassium.

DIETARY MANAGEMENT

In patients with CKD, nutritional needs and interventions change based on the stage and progression of the disease. Nutritional goals must be individualized to maintain the best health possible of each patient and maintain serum blood levels within appropriate levels. **Referral to a dietitian is suggested.** Dietary strategies are helpful in managing sodium, potassium, phosphorus, calcium and protein. However, the need for diet restrictions should be assessed regularly, and the patient should be provided with the most liberal diet possible – imposing only those restrictions necessary based on the patient's current condition.

TABLE 17: DIETARY MANAGEMENT OF CKD

Goals	Recommendations and tips
Malnutrition	Guidelines from the Academy of Nutrition and Dietetics and the American Society of Parental and Enteral Nutrition (ASPEN) have defined updated clinical criteria for malnutrition, listed below.[SKI] Refer a patient to a registered dietitian (RD) for nutritional management if two or more of these criteria are present: • Weight loss: – > 5% in 1 month – > 7.5% in 3 months – > 10% in 6 months – > 20% in 1 year • Reduced dietary intake for ≥ 1 month • Muscle loss • Fluid accumulation • Loss of subcutaneous fat • Reduced grip strength Note: While serum albumin may help in screening for malnutrition, it is not diagnostic because of multiple limitations. However, reduced serum albumin is a predictor of mortality in CKD.
Protein intake	• Recommend a moderate protein intake of 0.8 to 1 g per kg of weight daily. A very low protein diet (< 0.6 g protein per kg of weight daily) to preserve kidney function is not recommended. It's important to discourage excessive protein intake (e.g., the Atkins diet and similar high-protein diets). However, very little evidence exists to support the traditional wisdom that tightly restricting dietary protein is important in CKD. • Tips: Encourage patients to focus on high biologic value proteins (main animal proteins). These provide all of the essential amino acids and allow patients to consume less total protein while still meeting their amino acid needs. – 1 ounce of meat contains 7 grams high biologic value protein – The protein of 1 egg or 1 cup of milk = approximately 1 ounce of meat – 3 ounces of meat is about the size of a deck of cards • Examples of a 0.8 g/kg protein diet with about 50% of protein from high biologic value sources: – For a man with an ideal weight of 180 pounds: 65 grams of protein daily, with about 35 grams being high biologic value (5 ounces of meat) and the other 30 grams from protein in other foods (breads, vegetables, etc.). – For a woman with an ideal weight of 140 pounds: 50 grams of protein daily, with 28 grams being high biologic value (4 ounces of meat) and the rest from protein in other foods.

Promoting positive change

While limits on specific nutrients can be important for CKD patients, they can also be challenging. Imposing strict dietary limits—with no room for compromise—is an approach that may backfire. Some patients react by concluding that the goal can't be met and it's not worth the effort to try managing their diet.

Remember that any positive change in a patient's diet is worthwhile.

If your patient needs to manage one or more nutrients, explain why, provide resources to help (see the list below), provide encouragement to keep working toward the goal, and refer the patient to a registered dietitian nutritionist (RDN).

National Kidney Foundation resources

The NKF has produced a variety of patient education resources, available in an A to Z index at **kidney.org/atoz**

Topics covered include general nutrition for CKD patients and topics on nutrition for dialysis or transplantation (look under N), plus specific nutrients including carbohydrates, cholesterol, potassium, phosphorus and sodium (look under the appropriate letter).

TABLE 17: DIETARY MANAGEMENT OF CKD (CONT.)

Dietary concern	Recommendations and tips
Sodium Sodium is an extracellular electrolyte involved in fluid balance. Increased sodium intake can cause increased intravascular volume; this increases the workload for the kidneys and the heart. A high-sodium diet can also impede ACEI/ARB therapy. Decreased sodium intake may help slow CKD progression by lowering intraglomerular pressure. Hyponatremia may not indicate a need for additional salt in the diet, but may be related to overhydration, hyperglycemia or starvation.	• **Recommendation:** KDIGO guidelines recommend that CKD patients limit sodium to 2,000 mg daily (or 1,500 mg daily if edema/fluid retention).[KDIGO] This goal may be difficult for many patients to meet, and requires overall dietary changes that will take time to achieve. • **Tips for limiting sodium intake:** – Make foods from scratch; restaurant meals and packaged foods are often high in sodium. Use NO salt in cooking (just herbs and spices), and don't add salt after food is prepared. – Limit salted snacks like chips and pretzels. – Avoid convenience food, packaged seasonings and cured meats. Avoid frozen meals; even those labeled "healthy" often have high levels of sodium. Avoid canned foods and/or rinse canned foods before use. – Use herbal blends (such as Mrs. Dash), pepper, garlic, lemon or lime juice and vinegar to season foods; check the labels and avoid those that contain salt. Check the labels of salt substitutes and avoid those with potassium.
Potassium Potassium is an intracellular electrolyte with key function invoved in muscle contraction. When a patient with renal disease can maintain both aldosterone secretions and distal flow, potassium excretion is usually maintained with normal limits. Hyperkalemia usually becomes apprent if the patient has low output, hypoaldosteronism, or increased tissue breakdown. If an ACEI is prescribed, dietary potassium will likely need to be limited.	• **Recommendation:** If patient's serum potassium level increases to more than 5 mEq/L, dietary potassium should be restricted to 2,000 to 4,000 mg daily, depending on the patient's level of hyperkalemia. The need for potassium restriction can change rapidly. (Note: Patients on diuretics may require a high-potassium diet with additional potassium supplementation.) • **Tips for limiting potassium intake:** – Significantly limit potatoes, tomatoes and tomato-based sauces, bananas, oranges and orange juice, prunes and prune juice, cooked spinach and chard, winter squash and avocados. – Avoid multiple high-potassium foods in 1 meal or 1 day. – Limit dairy products to 1 serving daily. – Avoid salt substitutes – they often are high in potassium. – Avoid noni juice, alfafa, dandelion, horsetail and nettle (and combination supplements containing them).
Phosphorus As eGFR falls, phosphorus retention can begin, and high phosphorus levels contribute to CKD progression.	• **Recommendation:** Phosphorus management targets depend on the stage of CKD: – At Stage G3 and G4, serum phosphate should be kept to normal limits: < 4.6 mg/dL. – At Stage G5 CKD, serum phosphate should be kept at < 5.5 mg/dL. • **Tips for managing phosphorus:** – Limit dietary phosphorus to 800 to 1,000 mg daily when a patient's serum phosphate is above the levels listed above. Patients can limit phosphorus by decreasing intake of legumes, nuts, organ meats, dairy products, colas, and chocolate (or taking a phosphorus binder when these foods are consumed). – Consider phosphorus binder therapy when hyperphosphatemia exists at the above levels or once eGFR falls below 30. Tums is generally the first-line phosphorus binder. Other options include calcium acetate (PhosLo), sevelamer (Renvela), and lanthanum (Fosrenol).

Referral to a registered dietitian nutritionist (RDN)

Patients should be referred to a registered dietitian nutritionist (RDN) when any new diet restriction is ordered or when lack of diet understanding is apparent. Combining these restrictions can be frustrating for patients, as they sometimes seem to contradict each other.

An RDN can help tailor diet information to fit a particular patient, helping the patient get the most benefit from these restrictions while still finding some joy in eating. See the list below for contact information. Many insurers cover consultations with RDNs for patients with CKD and/or diabetes; patients should check with their health plans.

RDN resources

Patients can be referred to see an outpatient registered dietitian at the facilities listed below. Note that some medical group regions have dietitians employed by the medical group.

- Aloha Kidney
  For more information:
  alohakidney.com
  To register, call
  808-585-8404
- Pali Momi Medical Center
  Health Management
  98-1079 Moanalua Rd.
  ʻAiea, HI 96701
  808-535-7733
- Straub Medical Center
  Health Management
  1100 Ward Avenue
  Suite 940
  Honolulu, HI 96813
  For an appointment call:
  808-522-4325
- Wilcox Medical Center
  Health Management
  3-3420 Kūhiō Hwy
  Līhuʻe, HI 96766
  808-246-1380

TABLE 17: DIETARY MANAGEMENT OF CKD (CONT.)

Dietary concern	Recommendations and tips
Calcium Calcium levels are often low in patients with CKD. Changes in vitamin D, metabolism elevated phospho-rus and limiting high calcium foods (e.g. limiting dairy productions on low potassium and low phosphorus diets) can result in hypo-calcemia.	• **Recommendation:** Normal serum calcium is 8.5 to 10.2 mg/dL; assess calcium status concurrently with vitamin D deficiency and phosphorus. Note: For patients with hypoalbuminemia, the calcium measurement needs to be corrected using this formula: Corrected calcium = measured serum calcium + [0.8 x (4.5 – serum albumin)] • **Tips:** – The use of calcium supplements may be indicated. Patients should be supplemented with 1,200 to 1,500 mg elemental calcium daily, in divided doses. The total elemental calcium of supplements and calcium-based phosphorus binders should not exceed 2,000 mg. – Calcium supplements should be taken in between meals on an empty stomach and should not be taken with iron supplements. – Calcium carbonate contains 40% elemental calcium and is the recommended calcium source. – Calcium citrate is not recommended in CKD because it may increase risk of aluminum toxicity.
Supplements and herbal remedies Many supplements and herbal rem-edies are touted to improve kidney function, while some may actually be harmful to the kidneys or worsen other areas of concern with CKD.	• Educate CKD patients to use caution with all complementary and alternative medicine (CAM) supplements. Patients should avoid supplements that may harm the kidneys, as well as supplements that are erroneously touted by the CAM community to improve kidney function. • Strongly discourage the following supplements, as they may be nephrotoxic or worsen other areas of concern in CKD: herbs containing aristolochic acid (in some weight loss supplements), high-dose capsicum (cayenne, pepper sauces such as Tabasco, chili pepper), chromium nicotinate, comfrey, creatine, lobelia, L-Lysine, noni juice or extract, pennyroyal, piracetam, sarsaparilla, uva-ursi and yohimbe. (This list is not all-inclusive.) • Caution patients about use of black licorice to treat hyperkalemia. Though black licorice is touted as a natural treatment for hyperkale-mia in the CAM community, no level of intake has been studied. • Caution patients about CAM remedies often used for urinary problems. Patients may believe that some CAM remedies used to treat upper urinary tract problems, particularly cranberry extract, can be transferred to kidney disease. Caution patients that these CAM remedies do not apply to kidney disease and that high amounts of these supplements will not improve kidney function.
Iron	• Recommendation: A high iron diet is generally not recommended to help treat anemia in CKD patients due to poor dietary absorption, medication interactions, and the complexity of existing diet restrictions.
Vitamin D	For those at risk for vitamin D deficiency, dietary intake is typically insufficient.

NOTES:

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