CKD: Management and Prognosis

6

Adeera Levin and Magdalena Madero

Clinical Scenario

You are caring for a 63 year old man with a history of diabetes mellitus, hypertension and gout, with one remote episode of Kidney stones. His eGFR 38 mL/min, urine albumin creatinine ratio (uACR) 48 mg/mmol; Hb 115 g/L; Transferrin saturation 0.20%; his electrolytes are normal apart from a slightly elevated potassium 5.1 mol/L. His HbA1C 7.9%, and his blood pressure is 138/85 mmHg. With a 24 h ambulatory BP monitor, you note that he does not have a nocturnal dip. He is currently on an ARB (Losartan), a diuretic (Chlorthalidone), lipid lowering agent (simvastatin), metformin and insulin.

Introduction

The prognosis of CKD is predicated on both underlying cause of the kidney disease, the GFR and the albuminuria levels, (CGA classification, KDIGO) [1]. This classification system helps to identify those at high risk of progression, and of other complications (cardiovascular events, hospitalization, infection, death, and AKI).

The management of CKD is then focused on addressing modifiable risk factors to improve patient outcomes, and reduce the incidence of events or delay progression of CKD and attendant CV and other system complications.

Epidemiology and Causes

The epidemiology of CKD is well described in multiple publications. The estimated prevalence around the world is approximately 10% in the adult population, with variability in estimates due to data capture, ability to obtain blood and urine samples, and regional differences in true prevalence. The causes of CKD may differ in different parts of the world, driven by local exposures and conditions. That being said, diabetes and hypertension remain the leading causes of CKD worldwide, as the incidence of these conditions rises, so will CKD. In addition, recurrent AKI episodes due to infections, malnutrition, diarrheal illness, heat stress or combinations thereof is well recognized in specific regions of the world. Kidney diseases may be classified according to cause, or into categories associated with anatomic locations (e.g. prerenal, intrinsic and post renal). Any sustained kidney injury, regardless off the etiology, could translate into CKD. As many conditions may coexist, or accrue over time within an individual, the

A. Levin (✉)
Division of Nephrology, University of British Columbia, Vancouver, BC, Canada
e-mail: ALevin@providencehealth.bc.ca

M. Madero
Division of Nephrology, Instituto Nacional de Cardiologia Ignacio Chavez, Ciudad de México, Mexico

D. Banerjee et al. (eds.), *Management of Kidney Diseases*,
https://doi.org/10.1007/978-3-031-09131-5_6

etiology of CKD is often multifactorial. Major categories of CKD include Congenital or Acquired conditions. Congenital conditions often include malformations of the genito-urinary system, which lead to a reduction in nephron mass or dysfunctional glomerular and tubular function, all of which culminate in progressive kidney decline. Inherited diseases contribute to approximately 4% of CKD worldwide, and include conditions such as APCKD, Alport's Syndrome, Fabry' disease amongst others. Acquired conditions include glomerulonephritidies, diabetes, stone disease, tubulointerstial diseases, due to drugs, toxins and environmental pollutants. It is beyond the scope of this chapter to delineate all the causes of CKD, but the reader is referred to Table 6.1.

Table 6.1 Causes of chronic kidney disease

Cause	Example
Tubulointerstitial nephritis	Acute or chronic due to analgesic medications (NSAIDS),antibiotics, toxins, heavy metals, herbal medications
Glomerulonephritis (primary)	IgA nephropathy, membranoproliferative glomerulopenprhitis, focal segmental glomerulosclerosis, membranous nephropathy
Glomerular disease (due to systemic illness)	Vasculitis, systemic lupus Erithematoso, amyloidosis, diabetes mellitis, trombotic microangiopathy
Hereditary diseases	Polycystic kidney disease, Alport syndrome, medullary cystic disease, Fabrys disease
Hypertension	Nephroangioesclerosis
Obstructive	Benign prostatic hyperplasia, posterior urethral valves, ureteral obstruction (litiasis, malignancy, congenital), vesicoureteral reflux
Large renal vascular disease	Renal artery stenosis (atherosclerosis or fibromuscular displasia)

Investigations

Chronic Kidney Disease is often under recognized and therefore not treated. Investigations that help to both prognosticate and manage CKD are listed in Fig. 6.1. The classification of CKD is based on eGFR and albuminuria determination. Staging patients with CKD according to cause, eGFR, and albuminuria enhances risk stratification for the major complications of CKD [1].

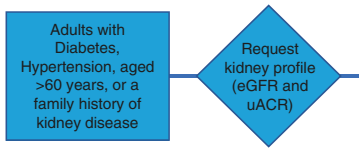
If available, imaging techniques (such as ultrasound) are important to assess size, symmetry and space occupying lesions intrinsic or extrinsic to the kidney.

Urinalysis in addition to urine albumin or protein determinations may add additional information. For example, red cells, white cells or casts may contribute to further diagnostic investigations (e.g., biopsy) or signal new or additional processes contributing to CKD progression.

CKD screening however is not recommended in the general population, screening should be done in high-risk populations such as age > 60 years, diabetes, hypertension, family history of kidney disease, history of kidney stones etc.

Note that regular monitoring of various parameters will help to determine responsiveness to therapy, and serve as excellent feedback for patients and the health care providers.

The regularity of monitoring depends on health care system resources as well as specifics of the patient. Recommendations in the table below presume access to resources for 'average' individuals, and would not apply to those whose other comorbidities (e.g. terminal cancers or advance heart failure), or advanced age, or both which would limit interventions or utility.



CKD is classified on the basis of: Cause (C) GFR (G) Albuminuria (A)				Albuminuria categories Description & range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories by eGFR (ml/min/1.73m²) Description & range	G1	Normal or high	>90	1	1	2
	G2	Mildly decreased	60-89	1	1	2
	G3A	Mildly to moderately decreased	45-59	1	2	3
	G3B	Moderately to severely decreased	30-45	2	3	3
	G4	Severely decreased	15-29	3	3	4+
	G5	Kidney failure	<15	4+	4+	4+

Fig. 6.1 Risk of CKD Progression and Frequency of Assessment: Summary of recommendation statement (according to estimated glomerular filtration rate (eGFR) and albuminuria)

- The GFR and albuminuria grid depicts the risk of progression, morbidity and mortality by colour, from lowest to highest (green, yellow, orange, red, deep red)
- The numbers in the boxes are a guide to the frequency of assessment annually.
  - Green annual assessment for those at risk (Green can reflect CKD with normal eGFR and albumin-to-creatinine ratio (ACR) only in the presence of other markers of kidney damage, such as imaging showing Polycystic kidney disease or kidney biopsy abnormalities)
  - Yellow suggests assessment at least once per year
  - Orange suggests assessment twice per year
  - Red suggests assessment three times annually
  - Deep red suggests assessment four times annually
- These are general parameters only, based on expert opinion and must take into account underlying comorbid conditions and disease state, as well as the likelihood of impacting a change in management for any individual patient

(Kidney International 2013; 3 (Suppl):5 [1]. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39 (Suppl 1):S1 [2])

Management

The general management of the patient with CKD involves the following issues.

- Treatment of reversible causes of kidney dysfunction (e.g. obstruction, underperfusion).
- Preventing or slowing the progression of kidney disease.
- Treatment of the complications of kidney disease.
- Adjusting drug doses (or discontinuing) when appropriate for the level of estimated glomerular filtration rate (eGFR).
- Identification and adequate preparation of the patient in whom kidney replacement therapy will be required.

Treatment of Reversible Causes of Kidney Failure

hypovolemia, hypotension, nephrotoxic drugs (NSAIDS, Ace Inhibitors, antibiotics), Intravenous contrast material, obstruction, sepsis are common causes of reversible kidney injury and should always be assessed as an initial approach to kidney function deterioration.

Slowing the Progression of Kidney Disease

Treatment of the underlying cause of kidney disease should be targeted, i.e. APDKD, diabetes, glomerular disease, viral infections, liver disease, cardiac disease, malignancy etc. In those conditions there may be treatments or strategies that are suggested by the specificity of the diagnosis. Note that is some cases there may be more than one cause of CKD.

In addition, there are treatments that are universal for CKD patients: blood pressure control and proteinuria reduction. Blood pressure should be controlled to less than 120/80 mmHg using standardized office blood pressure measurement [2]. More intensive versus less intensive blood pressure control reduces the risk of end-stage renal disease (ESRD) in patients with proteinuric chronic kidney disease (CKD), but not in patients with nonproteinuric CKD. However, more intensive blood pressure lowering may reduce mortality in patients with CKD (whether they have proteinuria or not), even though there is no benefit on kidney endpoints among patients without proteinuria. The mortality benefit from aggressive blood pressure lowering noted in the Systolic Pressure Intervention Trial (SPRINT) [3].

The preferred antiypertensive agents in subjects with proteinuria are ACE inhibitors, ARB and mineralocorticoid receptor antagonists.

ACE inhibitors generally reduce protein excretion by approximately 30–35% in patients with nondiabetic or diabetic CKD. Similar results have been demonstrated with ARB [4]. The antiproteinuric effect is most prominent in patients who are on a low-sodium diet or who are treated with diuretics and it is dose dependent. Clinical trials have demonstrated a benefit of antihypertensive therapy with renin-angiotensin system (RAS) inhibitors, mostly angiotensin-converting enzyme (ACE) inhibitors, in patients with proteinuric nondiabetic chronic kidney disease (CKD). The renoprotective effect of angiotensin II receptor blockers (ARBs) has been best demonstrated in patients with diabetic nephropathy. It seems likely that they have a similar renoprotective effect as ACE inhibitors in nondiabetic CKD but supportive data are limited. ACE inhibitors or ARB should be given to proteinuric patients, with a recommendation of titrating either to maximal dose, however the combination of ACE and ARB has not been superior to individual treatment for CKD progression and has been associated with hyperkalemia and acute kidney injury [5].

Other Treatments

Patients who have proteinuric CKD (with or without diabetes) can benefit from treatment with SGLT2 inhibitors. Most of the trials including SGLT2 inhibitors have been performed in proteinuric patients although there is evidence to suggest that the benefit may be extended to non proteinuric CKD [6].

More recently newer non selective mineralocorticoid inhibitors such as finerenone reduced CKD progression in proteinuric diabetic kidney disease. More studies with these types if agents are required to confirm these findings [7].

Other targets for halting kidney disease progression should may protein restriction (0.8 g/kg/day), smoking cessation, weight management, glycemic control, healthy diet and physical activity.

Treatment of CKD Complications

The complications of kidney function include volume management, anemia, mineral bone disease, metabolic acidosis, hyperkalemia and malnutrition. These have been covered extensively in other chapters of this book, and are not dealt with here.

Drug Dosing and Adjustments in CKD

There are drugs which are nephrotoxic and should be avoided in CKD pts. (e.g. aminoglycosides, NSAIDs, some chemotherapeutic agents), or at least used with extreme caution.

There are other medications which require dose modification in CKD, and other which should be stopped at different GFR thresholds. A full list is beyond the remit of this chapter, but the reader is encouraged to review patient drug profiles, and before commencing new medications, to review the indications and potential side effects.

Drugs may impact kidney function through direct tubular or interstitial toxicity (e.g. Lithium, tenofovir, aminoglycosides); or promote progression fibrosis through multiple mechanisms (e.g. proton pump inhibitors, calceniurin inhibitors). Some drugs lead to a change in serum creatinine through interfering with creatinine secretion which is often confused with 'kidney damage': these changes are reversible with cessation of the drug (e.g. cotrimoxazole, cimetidine, fenofibrate).

Drugs that are excreted by the kidney require dose adjustments or cessation with advanced CKD (e.g. digoxin, novel anticoagulants e.g., apixiban).

Identification and Adequate Preparation of the Patient in Whom Kidney Replacement Therapy Will Be Required

Management of patients with CKD requires prognostication and anticipation of the need for Kidney replacement therapy in those who are eligible for it, or in whom it is appropriate. Use of the KFRE (kidney failure risk equation https://kidneyfailurerisk.com) [8] may help to identify those at highest risk for kidney failure within 2 years, and might help with planning of discussions.

The role of clinicians and clinical team members working with patients and families is to identify appropriate time points and educational materials which will help with decision making. There are data to suggest that decision making about complex choices (such type of dialysis, transplantation etc.) requires time, multiple interactions and appropriate tools to enhance understanding, Those who choose hemodialysis would ideally require placement of arteriovenous fistula at least 3–6 months prior to anticipated commencement of dialysis; those who choose peritoneal dialysis require catheter placement at least 2–4 weeks prior to commencement; and if living pre-emptive transplantation is required this process often takes between 6 and 9 months of preparation for donors and recipients. Thus, overall, best practices would suggest that discussions about kidney replacement therapy should commence at least 18 months in advance of anticipated need if possible, to optimize decision making and allow adequate time for discussion and procedures/processes to be put in place.

Conservative management options for those who either choose not to have KRT, or in whom it is not appropriate due to significant morbidity or futility should be offered. These include ongoing supportive care, symptom management and provision for palliative care services [9].

Health care system resources will vary around the world, and within jurisdictions. Not all countries or regions can offer KRT to individuals, and thus conservative care strategies should be clearly articulated and offered when KRT is not available [10].

Clinicians and their teams should have a good understanding of resources available in their jurisdiction, and how to access them to aid in appropriate timing for individuals patients.

Practice Points

Management of progressive CKD involves:

- Treatment of reversible causes of kidney dysfunction
- Prevention/slowing the progression ofCKD with BP control use of RAASi and SGLT2i
- Treatment of the complications of kidney disease, anaemia, CKD-MBD, hyperkalaemia
- Adjusting drug doses (or discontinuing) when appropriate for the level of eGFR
- Identification and adequate preparation of the patient for KRT

Conclusions

The 63 year old man has chronic kidney disease related to diabetes and may benefit from tighter blood pressure control. A calcium channel blocker may be started once the ARB and diuretic dose are maximised. Despite mild anemia treatment with iron or erythropoietin is perhaps not necessary at this stage. Tighter blood sugar control may not help but a SGLT2i may prevent progression of CKD and CV events.

Questions

1. What is the CKD stage on this patient?
   A. G3b A2
   B. G3A A1
   C. G1 A2
   D. G2 A2
   E. G4 A3

Answer: the correct answer is A, the patient has a GFR of 38 mL/min (stage G3B) and ACR of 48 g/g (stage A2).
EASY.

2. Based on his risk factors, how often does he need medical attention?
   A. Once a year
   B. Twice a year
   C. Three times/year
   D. Four times/year

EASY, Answer: based on the expert recommendations this patient risk is high for progression and cardiovascular events and should be monitored twice a year.

3. His target blood pressure should be:
   A. <120/80
   B. <130/80
   C. <140/90
   D. <110/70
   E. Between 130/80 and 140/90

Easy: The correct answer is A, based on data from SPRINT, CKD patients benefit from strict BP control. Current KDIGO guidelines recommend BP <120/80 in all CKD patients with and without albuminuria.

4. Based on his blood pressure, what would be the next step
   A. No change in management
   B. Increase losartan dose to a maximal dose
   C. Add an ACE inhibitor
   D. Start MRA
   E. Initiate SGLT2i

Easy; the correct answer is B, ARB dose should be maximized before adding another agent. The patient BP should be targeted to <130/80. Adding an ACE inhibitor to an ARB in DKD is no longer recommended. Mineralocorticoid receptor antagonists or SGLT2 inhibitors could be initiated once the patient is on maximal doses of ARB or ACE inhibitors.

5. Lowering blood pressure in this patient would:
   A. Delay the progression to ESKD
   B. Reduce cardiovascular complications
   C. Reduce all cause mortality
   D. No benefit
   E. B and C

Difficult; the correct answer is E, data from SPRInt showed BP reduction in CKD patients with small amounts of albuminuria benefit from cardiovascular and all cause mortality but does not halt CKD progression.

6. Adding SGLT2 inhibitor in this patient would result in:
   A. Delay in CKD progression
   B. Increase the risk of acute kidney injury
   C. Increase the risk for cardiovascular events
   D. Substantial glycemic control

The correct answer is A, SGLT2 inhibitors delay CKD progression even in normoalbuminuric (<30 mg/g), moderately increased albuminuria (30–299 mg/g) or large albuminuria (>300 mg/g), although the risk reduction is higher with higher ACR. SGLT2 inhibitors do not increase the risk of AKI (CREDENCE), are associated with a decrease in CV events. The glycemic control obtained from SGLT2 inhibitors is poor and the benefit is independent from glycemic control.

7. The estimated GFR calculations should not be used in the which of the following populations (Check all that apply)
   A. Amputees
   B. People at extremes of weight and height
   C. People of African descent
   D. People of Asian descent
   E. A and B

The correct answer is E, as the eGFR calculations are based on populations means, presuming height and weight distributions for age norms, and were never tested in those with severe cachexia or very high BMI, nor in those with amputations. Thus they should be used in caution with those individuals, or interpreted corrected for BSA.

8. Based on the new blood pressure guidelines, target BP should be established based on what type of blood pressure readings?
   A. Standardized Office Blood Pressure
   B. Manual Office Blood Pressure
   C. Home Blood Pressure readings
   D. Ambulatory Blood Pressure Measurements

The correct answer is A: standardized office BP measurement is recommended in preference to routine office BP measurement for the management of high BP in adults.

9. The recommended sodium intake in a patient with CKD and hypertension is:
   A. <1 g of sodium per day or <45 mmol per day or <2.5 g of sodium chloride per day
   B. <2 g of sodium per day (or <90 mmol of sodium per day), or <5 g of sodium chloride per day
   C. <4 g of sodium per day (or <180 mmol of sodium per day) or <8 g of sodium chloride per day
   D. Sodium restriction is not recommended if patients already of SGLT2 inhibitor

The correct answer is B. Targeting a sodium intake <2 g of sodium per day (or <90 mmol of sodium per day, or <5 g of sodium chloride per day) in patients with high BP and CKD is recommended.

10. Which of the following statements is correct:
    A. An AVF should be placed between 3 and 6 months before starting hemodialysis
    B. an AV graft could be placed within 2 weeks of hemodyalisis initiation and is the preferred choice
    C. a catheter can be placed for urgent hemodialysis initiation in those patients without mature AV fistula
    D. AV Fistulas are contraindicated in diabetic patients due to small vessel size
    E. A catheter should always be placed prior to starting RRT, regardless of other access planning

The correct answers are A and C. Although an AVgraft can be placed 2 weeks before hemodialysis initiation, it is not the preferred choice. Diabetic patients are suitable for AV fistulas although sometimes vessels are not ideal for fistula creation. If a patient already has an AVF or AVgraft, these can be used to start hemodialysis and catheters should be avoided.

Test your learning and check your understanding of this book's contents: use the "Springer Nature Flashcards" app to access questions using https://sn.pub/cz9Cok. To use the app, please follow the instructions in Chap. 1.

References

1. KDIGO. Summary of recommendation statements. Kidney Int. 2013;3 (Suppl):5.
2. Improving Global Outcomes (KDIGO) Blood Pressure Work Group. KDIGO 2021 clinical practice guideline for the management of blood pressure in chronic kidney disease. Kidney Int. 2021;99(3S):S1–S87.
3. SPRINT Research Group, Wright JT Jr, Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC Jr, Fine LJ, Cutler JA, Cushman WC, Cheung AK, Ambrosius WT. A randomized trial of intensive versus standard blood-pressure control. N Engl J Med. 2015;373(22):2103–16.

4. Kunz R, Friedrich C, Wolbers M, Mann JF. Meta-analysis: effect of monotherapy and combination therapy with inhibitors of the renin angiotensin system on proteinuria in renal disease. Ann Intern Med. 2008;148(1):30–48.
5. Fried LF, Emanuele N, Zhang JH, Brophy M, Conner TA, Duckworth W, Leehey DJ, McCullough PA, O'Connor T, Palevsky PM, Reilly RF, Seliger SL, Warren SR, Watnick S, Peduzzi P, Guarino P, VA NEPHRON-D Investigators. Combined angiotensin inhibition for the treatment of diabetic nephropathy. N Engl J Med. 2013;369(20):1892–903.
6. Heerspink HJL, Kosiborod M, Inzucchi SE, Cherney DZI. Renoprotective effects of sodium-glucose cotransporter-2 inhibitors. Kidney Int. 2018;94(1):26–39.
7. Bakris GL, Agarwal R, Anker SD, Pitt B, Ruilope LM, Rossing P, Kolkhof P, Nowack C, Schloemer P, Joseph A, Filippatos G, FIDELIO-DKD Investigators. Effect of Finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219–29.
8. Tangri N, Stevens LA, Griffith J, et al. A predictive model for progression of chronic kidney disease to kidney failure. JAMA. 2011;305(15):1553–9.
9. Davison SN, Levin A, Moss AH, Jha V, Brown EA, Brennan F, Murtagh FE, Naicker S, Germain MJ, O'Donoghue DJ, Morton RL, Obrador GT, Kidney Disease: Improving Global Outcomes. Executive summary of the KDIGO controversies conference on supportive care in chronic kidney disease: developing a roadmap to improving quality care. Kidney Int. 2015;88(3):447–59.
10. Harris DCH, Davies SJ, Finkelstein FO, Jha V, Bello AK, Brown M, Caskey FJ, Donner JA, Liew A, Muller E, Naicker S, O'Connell PJ, Filho RP, Vachharajani T, Strategic Plan Working Groups. Strategic plan for integrated care of patients with kidney failure. Kidney Int. 2020;98(5S):S117–34.