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REVIEW

Chronic kidney disease for the primary care clinician

MR Davids, MY Chothia

Division of Nephrology, Stellenbosch University and Tygerberg Hospital, Cape Town, South Africa
Corresponding author, email: mrd@sun.ac.za

An epidemic of chronic kidney disease (CKD) is being experienced in South Africa. This is driven by a heavy burden of infections, non-communicable diseases, pregnancy-related diseases and injuries. The serious long-term complications of CKD include end-stage renal disease, heart disease and stroke. Competing priorities such as the high burden of HIV, tuberculosis and other infections, unemployment and poverty result in serious constraints to providing comprehensive renal care, especially in the public healthcare sector. The prevention and early detection of CKD by primary care practitioners is therefore of utmost importance. Annual screening is recommended for patients at high risk of developing CKD. This involves checking blood pressure, urine dipstick testing for albuminuria or proteinuria and estimating the glomerular filtration rate from serum creatinine concentrations. In patients with established CKD, renoprotective measures are indicated to arrest or slow down the loss of renal function. These patients are at high risk of cardiovascular disease and close attention should be paid to optimally managing their risk factors.

Introduction

There is a global epidemic of chronic kidney disease (CKD), with approximately one in ten adults affected.[1] A systematic review of the CKD burden in sub-Saharan Africa by Stanifer et al. estimated the prevalence at 13.9%.[2] Like most other countries, South Africa is also experiencing an increasing disease burden. Two studies from Cape Town have provided data on the population prevalence of CKD. Matsha et al.[3] reported a prevalence of 17.3% in a geographical cohort, while Adeniyi et al.[4] reported a prevalence of 6.4% in a cohort of teachers. In their review on the burden of non-communicable diseases (NCDs) in South Africa, Mayosi et al.[5] reported a 67% increase in deaths from kidney disease from 1999 to 2006.

Definition, diagnosis and staging of CKD

CKD is defined as abnormalities of kidney structure or function, present for three or more months, with implications for health and is classified based on the cause, glomerular filtration rate (GFR) category, and degree of albuminuria (Figure 1).[6] Kidney damage may be detected by the presence of abnormalities of blood (e.g. high creatinine concentrations indicating low GFR) or urine (e.g. proteinuria or albuminuria), or by the presence of abnormalities on renal imaging (e.g. polycystic kidneys).

The accurate estimation of GFR is critically important in the diagnosis and staging of CKD. In routine clinical practice, GFR is usually estimated from measurements of creatinine

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-300 mg/g 3-30 mg/mmol	>300 mg/g >30 mg/mmol
GFP categories (ml/min/ 1.73m²) 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			

Figure 1. Diagnosis and classification of CKD by GFR and degree of albuminuria. Patients at low or moderate risk for disease progression (green/yellow) should be followed up at least yearly, those at high risk (orange) twice-yearly, and those at very high risk (red) should be seen three or more times per year, as required. CKD—chronic kidney disease, GFR—glomerular filtration rate, KDIGO—Kidney Disease: Improving Global Outcomes. Reproduced from the KDIGO CKD guideline, with permission.[7]

Table I. The relationship between the categories for albuminuria and proteinuria. Adapted from Eknoyan et al.[6]

	Normal or mildly increased (A1)	Moderately increased (A2)	Severely increased (A3)	Nephrotic range
Albumin excretion mg/24h	< 30	30–300	> 300	> 2200
ACR mg/mmol	< 3	3–30	> 30	> 220
ACR mg/g	< 30	30–300	> 300	> 2200
Protein excretion g/24h	< 0.150	0.150–0.500	> 0.500	> 3.50
PCR g/mmol	< 0.015	0.015–0.050	> 0.050	> 0.35
PCR g/g	< 0.150	0.150–0.500	> 0.500	> 3.50

concentrations in blood, using various prediction equations. The Modification of Diet in Renal Disease (MDRD) study and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are the most commonly used formulae in adults. Current international guidelines recommend using the CKD-EPI equation unless another equation has superior accuracy in a specific population.[6]

Tests to assess proteinuria may be more readily available and less expensive than those for albuminuria, and are an acceptable alternative (Table I).

Screening for CKD

Individuals at increased risk for CKD should be screened annually.[8] These include individuals with the following risk factors:

- Diabetes mellitus
- HIV infection
- Hypertension
- Cardiovascular, cerebrovascular or peripheral vascular disease
- Obesity
- Autoimmune diseases
- Prior acute kidney injury
- Prior pre-eclampsia, eclampsia or HELLP syndrome
- Age > 60 years
- Family history of kidney disease

Screening should involve blood pressure measurement, urine dipstick testing and estimation of GFR. If proteinuria is found on dipstick testing then it should be quantified by measuring the protein/creatinine ratio or albumin/creatinine ratio on a random urine sample. A 24-hour urine sample is not required. The preferred method of estimating GFR is the CKD-EPI equation.

Once a diagnosis of CKD is made, renal function should be monitored more frequently, especially in patients with GFR < 60 ml/min/1.73 m^2, rapid GFR decline or risk factors for rapid GFR decline such as the use of nonsteroidal anti-inflammatory drugs or other potentially nephrotoxic medication and radiocontrast media.

Consequences of CKD

The obvious concern in a patient with CKD is progressive loss of renal function and the development of end-stage renal disease (ESRD) with the need for life-saving chronic dialysis or kidney transplantation. However, even those patients who do not progress to ESRD have an increased risk of death from cardiovascular and cerebrovascular disease.[9] In fact, a patient with early stage CKD is far more likely to succumb to cardiovascular disease than to progress to ESRD. The presence of CKD is now recognised as an independent risk factor for cardiovascular disease.[10,11] Cardiovascular mortality is 10 to 30 times higher than in the general population, after adjusting for factors such as sex, ethnicity and the presence of diabetes. The large burden of cardiovascular disease is attributed to the frequent presence of traditional factors, such as hypertension and dyslipidaemia, combined with the presence of non-traditional factors such as anaemia, chronic fluid overload, hyperphosphataemia, soft tissue and vascular calcification, chronic inflammation, malnutrition and hyperhomocysteinaemia. Patients with CKD are therefore a high-risk group and require optimal control of risk factors, such as aiming for lower blood pressure targets and treatment with specific agents.[11]

Drivers and common causes of CKD

Increases in NCDs, pregnancy-related disorders, injuries and the high burden of infectious diseases all contribute to the epidemic of CKD being experienced in South Africa. CKD is a frequent complication of NCDs like diabetes mellitus and hypertension and may also follow on from acute kidney injury which has developed in the setting of infectious disease, complicated pregnancies, or injuries related to violence or road traffic accidents.

In many cases of CKD, a specific diagnosis is never established because patients often present late, with poor renal function and shrunken kidneys, precluding a diagnostic kidney biopsy. In South African patients on renal replacement therapy (RRT), the most common reported renal diagnoses are hypertensive renal disease (34.7%), ESRD where the cause is unknown (32.4%), diabetic nephropathy (15.2%) and glomerular disease (9.9%).[12] In renal biopsy series, however, the most common diagnosis by far is glomerular disease.[13] This reflects the indications for performing renal biopsies. For example, diabetic patients with a typical clinical picture of diabetic nephropathy are usually not biopsied.

Diabetic nephropathy

Worldwide, the most common cause of ESRD is diabetic nephropathy. It remains a clinical diagnosis (Table II) and only patients with atypical features should be referred for a kidney biopsy. Many of these patients will have a renal pathology other

than diabetic nephropathy or will have diabetic nephropathy together with another renal disease.[14] During the early stages of diabetic nephropathy, moderate albuminuria (previously referred to as microalbuminuria) may be found. This is defined as albuminuria of 30–300 mg/24 h, or 30–300 mg/g creatinine, in at least two out of three spot urine samples.[15] The presence of moderate albuminuria increases the risk of progression to overt diabetic nephropathy by approximately 40%[16] and confers increased risk for a cardiovascular event such as stroke or myocardial infarction.[17] Optimisation of cardiovascular risk factors is particularly important in this group.

Table II. Criteria for the diagnosis of overt diabetic nephropathy[18,19]

1. In type 1 diabetics, a history of diabetes mellitus of >10 years. In type 2 diabetics, nephropathy may be present at the time of diagnosis.
2. Hypertension is usually present.
3. Persistent albuminuria/proteinuria. This tends to increase over time, eventually reaching the nephrotic range.
4. Diabetic retinopathy, especially in type 1 diabetics.
5. Progressive and sustained reduction in GFR to < 60 ml/min/1.73 m^2.

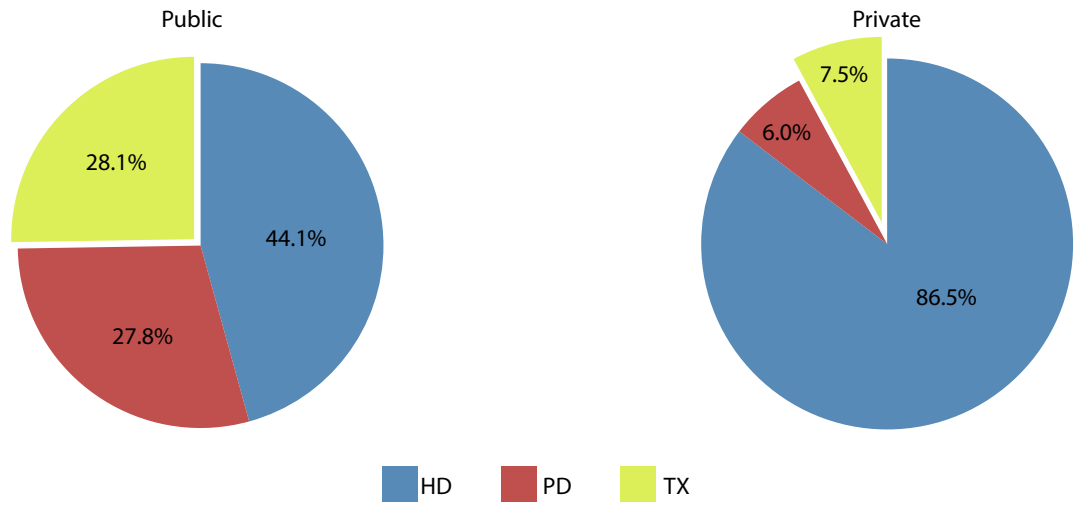
The South African Renal Registry has reported that nearly 40% of patients receiving RRT are diabetic, while diabetic nephropathy is the primary renal diagnosis in 15.2%.[12] Two studies have provided useful data on the long-term outcomes in South African patients with diabetes. Keeton et al.[20] found that renal failure was a major cause of death in patients with type 2 diabetes. By the end of their 12-year study, 80% of the patients had died and of these deaths, 29% were due to ESRD. Gill et al.[21] followed up type 1 diabetic patients for 20 years and reported a crude mortality rate of 43%, with 43% of these deaths due to renal failure.

Glomerulonephritis

Renal biopsy series indicate that mesangiocapillary glomerulonephritis (GN) is the most common primary glomerular disease encountered in the Cape Town area,[13,22] while focal segmental glomerulosclerosis is the most common in the north of the country.[23,24] Lupus nephritis is the most common secondary glomerular disease throughout the country. HIVAN, the most commonly identified renal pathology in HIV-positive patients, and diabetic nephropathy are the other common secondary forms of glomerular disease. Postinfectious glomerulonephritis, which is now rare in high-income countries, remains a significant problem in South Africa.

HIV infection

HIV-infected patients may develop CKD due to HIV-associated nephropathy (HIVAN), HIV-related immune complex disease, or following acute kidney injury related to infections or drug toxicity. The first report of HIVAN from South Africa was published by Bates et al. in 1994.[25] Despite having advanced kidney disease and nephrotic-range proteinuria, patients with HIVAN frequently do not have hypertension or significant peripheral oedema. The condition occurs especially in the absence of antiretroviral therapy and in patients with markedly reduced CD4 counts and elevated viral loads.[26] Individuals of African descent have a genetic susceptibility that is related to polymorphisms in the apolipoprotein L1 (APOL1) gene.[27] Two South African studies[28,29] have demonstrated the benefit of ART on renal outcomes in both HIVAN and HIV-related immune complex disease.



Treatment modality	Public sector		Private sector	
	Patients	%	Patients	%
Haemodialysis	1 401	44.1	6 124	86.5
Peritoneal dialysis	881	27.8	426	6.0
Transplant	893	28.1	532	7.5

Figure 2. Renal replacement therapy in South Africa, by treatment modality and healthcare sector.[12]

Hypertensive renal disease

In our registry data, hypertension has been reported as the aetiology of ESRD in 34.7% of patients.[12] However, in the largest South African renal biopsy series,[13] hypertensive renal disease was diagnosed in only 2.7% of cases despite approximately half of the patients being hypertensive. Many patients labelled as having "hypertensive renal disease" probably have primary glomerular disease and secondarily elevated blood pressure.[30] Hypertension should be recorded as the renal diagnosis only when the following criteria are met: hypertension known to precede renal dysfunction, left ventricular hypertrophy, proteinuria < 2 g/day, and no evidence of other renal diseases.[31,32]

CKD in children

Infants commonly suffer from congenital abnormalities of the kidney and urinary tract (CAKUT).[33] In older children, post-infectious glomerulonephritis is a common cause of acute nephritis. This usually resolves completely but a small proportion of children go on to develop CKD. Minimal change disease remains the predominant cause of childhood nephrotic syndrome. This mostly responds to steroids during early childhood and goes into remission after adolescence. HIV-associated renal disease is now rare since the implementation of the Maternal-to-Child-Transmission Prevention programmes and the availability of ART[34] and hepatitis B-related nephrotic syndrome has virtually disappeared since the introduction of routine hepatitis B immunisation in 1995.[35,36]

Renal replacement therapy

In December 2016, the number of patients who were treated with chronic dialysis or kidney transplantation stood at 10 257, a prevalence of 183 per million population (pmp).[12] The treatment modality was haemodialysis in 73.4%, peritoneal dialysis in 12.7% and transplantation in 13.9%. This is very different from the situation two decades ago when RRT was mainly delivered by government-funded public sector facilities and more than half of all patients had functioning kidney transplants.[37]

There has been a steady increase in the number of patients accessing haemodialysis in the private healthcare sector, where the treatment of ESRD is a "prescribed minimum benefit" for patients who are beneficiaries of medical aid schemes. The prevalence of treated ESRD in the private sector is on par with that of many high-income countries (798 pmp), whereas, in the public sector, the prevalence (68 pmp) has fallen below the level reported for 1994. This rate of treatment is well below that of countries with similar or lesser GNIPC. There are also large disparities in access to RRT between ethnic groups and between different provinces, with Blacks being the most under-served group and with two provinces (Limpopo and Mpumalanga) having no public sector dialysis centres at all.[12]

Because of resource constraints, national guidelines mandate that only patients who are transplantable can be accepted onto public sector dialysis programmes. In the Western Cape, guidelines for selecting patients for RRT have been developed after extensive consultation with stakeholders, including patient representatives and ethics experts.[38]

The survival of South African patients on RRT compares well with survival rates reported from better-resourced countries.[39] One-year survival in incident patients is 90.4%, and 90.1% in prevalent patients. There were no differences between public and private healthcare sectors.

Renal transplants are performed in six public sector and nine private sector centres.[12] Moosa[40] recently reviewed 25 years of transplantation in South Africa. During the period 1991–2015, 7 191 kidney transplants were performed, the majority (58.3%) derived from deceased donors. Hospitals in Cape Town and Johannesburg performed over 75% of these transplants. The trend has been towards a decline in the annual number of kidney transplants performed (Figure 3). Poor consent rates for kidney donation have been linked to education, religious beliefs, cultural traditions and a lack of transplant coordinators speaking the different local languages.[40,41]

Management of CKD and referral to a nephrologist

Patients with renal disease should be referred to a nephrologist when there is doubt about the diagnosis, such as in the case of unexplained acute kidney injury, nephrotic syndrome or nephritis as part of a systemic disease. These patients warrant a renal biopsy and may require specific therapy. Typical cases of post-infectious nephritis or diabetic nephropathy do not usually require a biopsy.

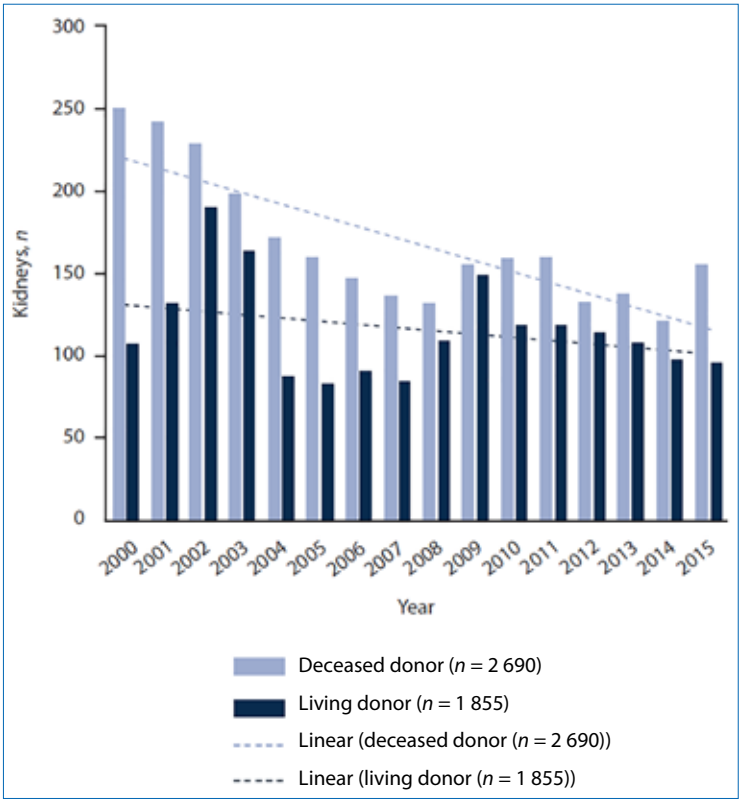


Figure 3. Numbers of deceased and living donor kidney transplants in South Africa, 2000–2015.[40]

The management of patients with established CKD revolves around the effective control of the underlying disease (e.g. immunosuppression in lupus nephritis), and strategies to arrest or slow the progressive loss of renal function through renoprotective measures. These include the following:

- Avoidance of nephrotoxic agents
- Prompt treatment of urinary tract infections
- Stopping smoking
- Low salt diet
- Good blood pressure control
- The use of angiotensin converting enzyme inhibitors or angiotensin receptor blockers, especially in patients with proteinuria
- Good blood glucose control in diabetics (as GFR declines, patients will be prone to hypoglycaemia and medications may have to be reduced or stopped)

The two most important measures to halt or slow down the progression of CKD to ESRD, regardless of the cause, are controlling blood pressure and reducing proteinuria. The most important anti-hypertensive drug class that addresses both of these factors is the renin-angiotensin-aldosterone system inhibitors (RAASi), including the angiotensin-converting enzyme inhibitors and the angiotensin receptor blockers. Other than systemic hypertension, patients with CKD also have intraglomerular hypertension. RAASi reduces intraglomerular pressure by dilating the glomerular efferent arteriole, thus decreasing both glomerular filtration pressure and proteinuria. The net result is increased nephron longevity. However, these agents may impair renal potassium excretion and patients should be monitored for hyperkalaemia since the CKD population is already at risk of developing this complication.

In addition, patients with CKD have so-called salt-sensitive or volume-dependent hypertension and therefore a low-salt diet and diuretic use are important in improving blood pressure control in this population. A salt-restricted diet of less than 6 g/day (a level teaspoon) is recommended.[42] High salt intake negates the effects of RAASi and diuretics. Thiazide diuretics, such as hydrochlorothiazide, are effective when GFR is greater than 30 ml/min/1.73 m^2. Once GFR falls below this level, it should be substituted with a loop diuretic such as furosemide.[43] The international KDIGO guidelines recommend a blood pressure target of less than or equal to 130/80 mmHg for all patients with CKD and proteinuria greater than 150 mg/day, regardless of diabetic status.[6]

If the CKD progresses despite these measures, patients should be referred for consideration of RRT, especially once the GFR approaches 30 ml/min/1.73 m^2. Timeous referral allows for the different options for renal replacement to be discussed and for preparations such as the screening of potential kidney donors or the creation of an arteriovenous fistula for chronic haemodialysis.

Conclusions

Like many African countries, South Africa faces an epidemic of chronic kidney disease. There are many competing health priorities, resulting in serious resource constraints to providing comprehensive renal care, especially in the public healthcare sector. The prevention and early detection of CKD by primary care practitioners is therefore of utmost importance. In patients with established CKD, renoprotective measures may arrest or slow down the loss of renal function. These patients are at high risk of cardiovascular disease and close attention should be paid to optimally managing their risk factors.

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