

ARTICLE

Clinical aspects of chronic kidney disease

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Any patient seeking any form of medical advice at any clinic or hospital, or from a doctor or other healthcare worker, should have their blood pressure recorded and a urine dipstick test done. The most useful indication of a diagnosis of any stage of chronic kidney disease, is the presence of either hypertension, urinary dipstick abnormality or both. Many practitioners frequently refer such patients to urologists, which must be discouraged. Referral should be to a nephrologist or specialist physician.

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Clinical course of chronic kidney disease

Although patients with kidney disease may present with symptoms such as oedema (nephritic or nephrotic syndrome) and changes in urine composition, histological and functional renal decompensation can often not be diagnosed owing to a lack of symptoms. Undetected loss of kidney function over an extended period of time can eventually lead to the symptomatic stage of kidney failure or even end-stage renal disease. The only indication of the presence of renal disease in an asymptomatic patient may be a raised blood pressure with or without urine abnormalities detectable on urine examination, such as microalbuminuria and proteinuria cells, and casts on urine microscopy.

General practitioners – not the nursing staff – should therefore perform urine dipstick tests for all their patients. Current trends where tests are not conducted by the examining medical professional but rather at a ‘test station’ should be discouraged as consistency and expertise in the interpretation of the results are very important in the examination process. If blood or protein is detected, a fresh specimen should be centrifuged and examined under the microscope.

General practitioners commonly mistake urine abnormalities for urinary tract infections and invariably refer patients to urologists. Factors that would necessitate referral to a nephrologist rather than a urologist are:

- degree of proteinuria – more protein, more likely glomerular disease
- presence of casts

- in addition, any of the following:
 - kidney failure
 - complicated hypertension
 - serological activity on blood tests (e.g. erythrocyte sedimentation rate and antinuclear factor).

When a reduced glomerular filtration rate (GFR) is present, comorbidities should always be managed in their own right, e.g. anaemia, hyperkalaemia, metabolic disorders (i.e. calcium and phosphorus disorders) and – very important in the South African (SA) context – primary hypertension, which is the main cause of chronic kidney disease (CKD).

The aetiology of CKD cannot always be easily determined and it is important to take a detailed history combined with a thorough clinical examination. It is often necessary to include examination of both structure (renal ultrasound) and function (estimated GFR (eGFR)) of the kidneys in the evaluation.

CKD often presents as a urinary abnormality in the face of normal renal function. Detecting such patients early may protect renal function and delay the need for dialysis by treating the underlying disease, reducing hyperfiltration and treating comorbidities. A complication of CKD is that patients have a higher risk

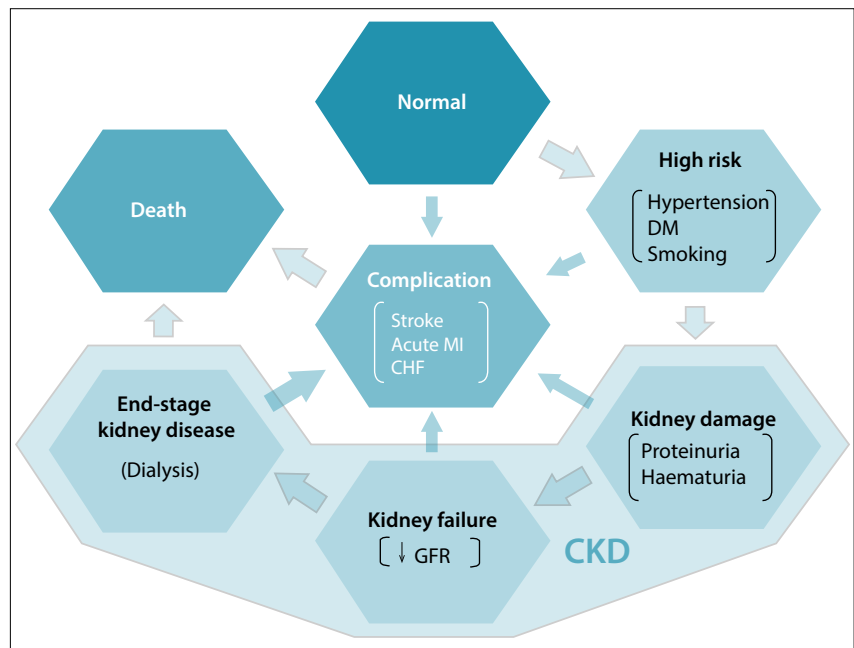


Fig. 1. Clinical course of chronic kidney disease (CKD). CKD progresses from stage 1 to stage 5. More patients may die of cardiovascular diseases than progress to a higher stage of CKD. (MI = myocardial infarction; CHF = congestive heart failure; GFR = glomerular filtration rate; DM = diabetes mellitus.)

of developing cardiovascular disorders (CVDs), e.g. stroke, acute myocardial infarction (MI) and congestive heart failure (CHF). This risk increases exponentially as CKD progresses towards end-stage kidney disease and patients sometimes die of this complication before they reach the final stage of CKD, when renal replacement therapy is required. This is indicated by wider arrows in Fig. 1.^[1]

The diagnosis of CKD is often accompanied by (i) microalbuminuria (earliest abnormality) or (ii) proteinuria on the urine dipstick test, even before any significant reduction in kidney function can be detected.

It may happen that CKD is only diagnosed when a complication such as anaemia or a bone mineral disorder occurs. These complications are more frequently found in stages 4 and 5 CKD, when kidney function is significantly reduced. This again shows the importance of early diagnosis in order to limit or prevent such complications.

Unfortunately, a large group of public sector patients in SA are referred to renal units for the first time when they present with end-stage renal failure (ESRF). This may be the result of insufficient access to adequate healthcare facilities and no regular follow-up visits, especially when abnormalities are detected in the earlier stages of CKD. Patients are often admitted for acute kidney failure, which could have been prevented with regular checkups.

Kidney disease as a result of drug toxicity is not always associated with urine dipstick test abnormalities. Furthermore, there may not be any evidence of previous risk factors for CKD. When prescribing drugs that are excreted via the kidney or that are nephrotoxic, one should evaluate and regularly monitor the eGFR.

Importantly, patients >45 years of age lose GFR by 1 mL/min/year, even though they may present with a 'normal' serum creatinine level. Consequently, many elderly people fall into stage 3 CKD (<60 mL/min/1.73 m²), despite an apparent normal creatinine level.

CKD and CVD: Cardiorenal association

The classic target organs in CVD (heart, brain and kidneys) may be associated with CKD. Specifically, patients with CKD (especially those on dialysis) often have a combination of chronic inflammation and chronic malnourishment that may contribute to the pathogenesis of accelerated atherosclerosis.

CKD and CVD share many common risk factors, which is evident in the increased morbidity and mortality rates for stroke, MI

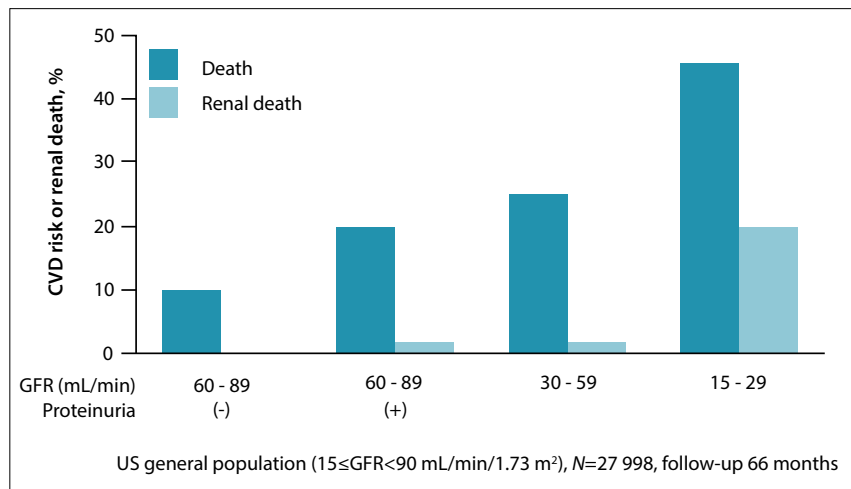


Fig. 2. Comparison of the rate of death prior to transplant/dialysis and renal replacement therapy. Data, with modification, from Keith et al.^[2]

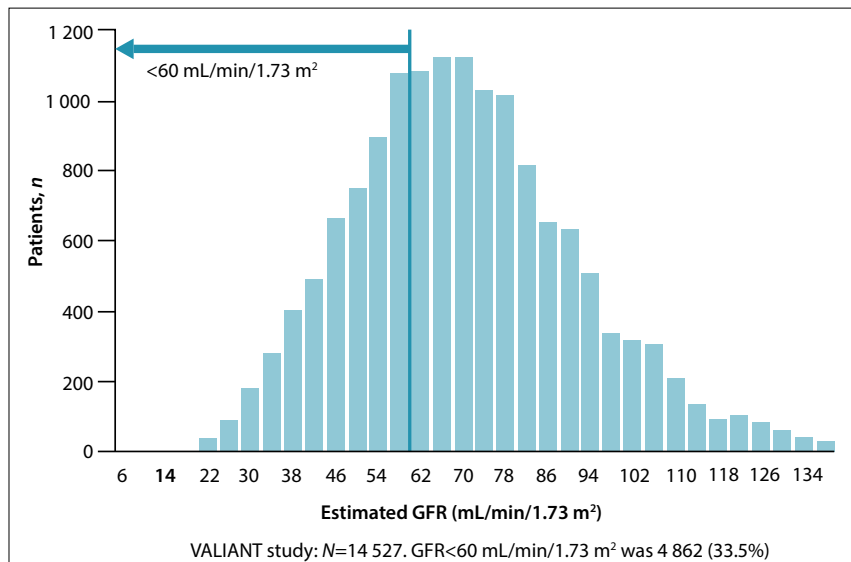


Fig. 3. Distribution of estimated glomerular filtration rate at baseline among 14 527 patients. Data, with modification, from Anavekar et al.^[3]

and CHF. It is therefore very important to establish the possible relationship between CKD and CVD for any patient with early signs of CVD.

Statistics show that CKD patients are more at risk of dying from CVD than ESRF. This is highlighted in Fig. 2,^[2] where CVD-related deaths and renal-related deaths in the US population are compared according to CKD function levels. In the earlier stages of CKD and even in the progressive stage 4 of CKD, patients are more likely to die from CVD than renal failure. Deaths from CVD in patients with proteinuria are more common than in those without proteinuria.

It has been reported in Europe, the USA and Japan that even a mild reduction in kidney function (stages 1 and 2) and/or the presence of proteinuria increases the risk of MI and stroke.

It has, however, also been shown that kidney function is affected by CVD. In this regard the data from Anavekar et al.^[3] show that one-third of patients who suffered from MI had kidney function related to stage 3 CKD (eGFR < 60 mL/min/1.73 m²) (Fig. 3).

From the same study^[3] the follow-up of MI sufferers within 3 years after the first attack showed that there is a correlation between increased risk of reinfarction and advanced stages of CKD. This can be seen in Fig. 4.

Common risk factors preceding either CKD, CVD or both include endothelial damage caused by fluid retention and hypervolaemia. Anaemia is a risk factor for the development of CVD. In patients with stages 3b - 5 CKD, anaemia is a risk factor in hastening progression to ESRF. Therefore, anaemia should be treated accordingly. In

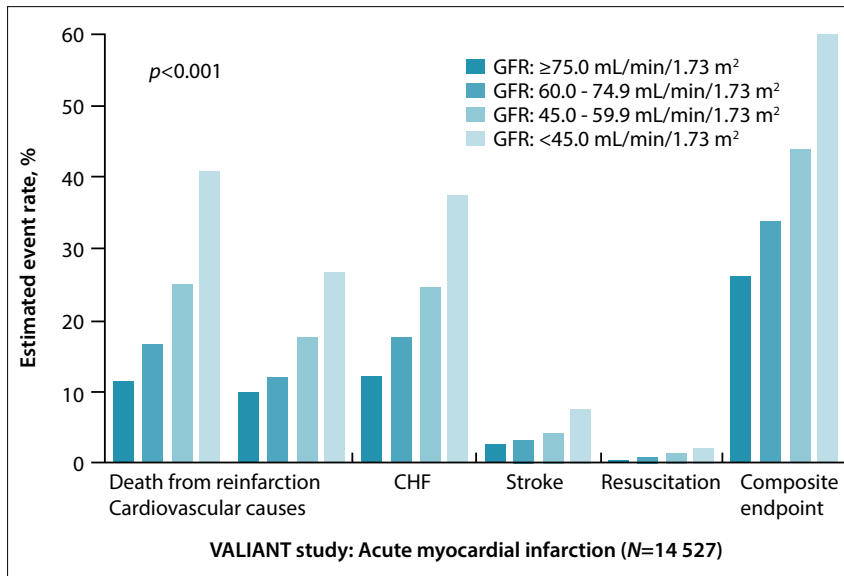


Fig. 4. Kaplan-Meier estimates of the rates of death at 3 years from cardiovascular disease causes reinfarction, congestive heart failure, stroke, resuscitation after cardiac arrest, and the composite endpoint, according to the estimated glomerular filtration rate at baseline. Data, with modification, from Anavekar et al.^[3]

Table 1. WHO clinical criteria for metabolic syndrome*

Insulin resistance, identified by one of the following:

- Type 2 diabetes
- Impaired fasting glucose
- Impaired glucose tolerance
- Or, for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinaemic, euglycaemic conditions

Plus any two of the following:

- Antihypertensive medication and/or high blood pressure (≥ 140 mmHg systolic or ≥ 90 mmHg diastolic)
- Plasma triglycerides ≥ 150 mg/dL (≥ 1.7 mmol/L)
- High-density lipoprotein cholesterol <35 mg/dL (<0.9 mmol/L) in men, or <39 mg/dL (1.0 mmol/L) in women
- BMI >30 kg/m² and/or waist:hip ratio >0.9 in men, or >0.85 in women
- Urinary albumin

BMI = body mass index.

*Derived from Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus: Provisional report of a WHO consultation. *Diabet Med* 1998;15:539-553.

addition, the following factors affect the function and structure of the kidneys and heart vasculature: hypertension, calcium, phosphate and parathyroid hormone abnormalities, inflammation, increased sympathetic tone, disturbances in the renin-angiotensin-aldosterone axis, oxidative stress, dyslipidaemia, smoking and an increase in the levels of asymmetric dimethylarginine.

NB: A recent and very important study was done on the role of increased plasma levels of trimethylamine N-oxide (TMAO)

in CKD, which is also associated with coronary artery disease pathogenesis. This study found that a gut microbial-dependent metabolite of dietary choline, lecithin (phosphatidylcholine) and L-carnitine occur early in patients with CKD. These serum levels increase with the severity of CKD. TMAO was found to cause more rapid renal functional deterioration, vascular endothelial damage, renal fibrosis, atheroma and CVD. These dietary amino acids are especially high in all red meats (including pork), but not in poultry or most fish.

Consequently, it might in future become advisable to place our earlier CKD patients (e.g. those with stages 3a or 3b CKD) on a fish/poultry/egg diet and omit red meat completely.^[4]

CKD and lifestyle-related diseases

Generally, lifestyle-related disease (LRD) is defined as a disorder affected by and normally related to aspects of diet and lifestyle. As communities progress from hunter gatherers/subsistence farmers, where food was less readily available and required physical effort to obtain, to a more affluent lifestyle with less exercise and ‘fast food’, this problem has increased worldwide. SA is no exception, and in future the impact on healthcare is expected to increase.

It needs to be acknowledged that there is also a genetic factor to LRDs, but the most common complications of metabolic syndrome (excessive or non-balanced eating and lack of exercise or movement, which causes fat accumulation even to the extent of morbid obesity) are hypertension, diabetes and dyslipidaemia. The similarities between insulin resistance (pre-diabetes) and metabolic syndrome often result in the interchangeability of the two terms, with the only distinction related to the symptomatic presentation for diagnosis. Table 1 provides a guideline for the diagnosis of metabolic syndrome.

The direct relationship between contributing factors of LRDs (e.g. smoking, lack of exercise and stress) and CKD has been well researched and can be caused by abdominal obesity accumulating in visceral fat, which may cause proteinuria or reduced kidney function. It is therefore of vital importance that early diagnosis of CKD should trigger changes in lifestyle and diet for the management and prevention of progression of CKD. This is even more important in the SA context, where healthcare is greatly affected by limited resources and funding.

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