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Clinical management of chronic kidney disease

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Chronic kidney disease (CKD) is a major public health problem which commonly presents to primary and secondary care. Reporting of estimated glomerular filtration rate (eGFR) has markedly increased identification of these patients. Prevalence may be genuinely rising, perhaps as a consequence of diabetes mellitus and obesity.[1] CKD is primarily a marker of cardiovascular risk: stage 3 CKD carries a 40–100% increased risk of cardiovascular events.[2] For the minority at risk of progressive decline in kidney function, prompt identification is necessary to allow early intervention and prevent complications.

Classification

The CKD classification system originated in the USA and was quickly adopted internationally.[3] The modified version used by UK guidelines is shown in Table 1.[4,5] It is based on the GFR and the presence or absence of kidney damage. The latter is loosely defined as the persistent presence of proteinuria (including microalbuminuria), haematuria or structural disease of the kidney (whether defined with imaging or histology). The reduced GFR and/or damage must be present for more than 90 days to establish chronicity. (Note that stages 1 and 2 require the presence of kidney damage whereas a reduced GFR alone is sufficient for stages 3–5.)

Identification and staging

CKD is generally asymptomatic until stage 4, so most patients are identified because of routine blood and urine tests. Structural abnormalities may be identified on imaging performed for other reasons.

Estimated glomerular filtration rate

Although serum creatinine (SCr) is a good marker of change in GFR in an individual patient, it is a poor measure of absolute GFR.[6] One major flaw is that in addition to correlating inversely with GFR, SCr also correlates with muscle mass. eGFR is a calculated value derived from SCr, age, gender and race[6] in which these three parameters essentially provide a correction for muscle mass (commonly used equations are given in Table 2). If muscle mass differs substantially from the average for age, race and gender, the eGFR will be less accurate. Common examples include amputees and the malnourished. In such patients, a 24-hour urinary creatinine clearance may still be of value. eGFR has been validated in whites and black Americans but its reliability is unproven in other races. eGFR should not be used in children, in pregnancy, the very elderly and those at both extremes of weight. It is unreliable in liver failure.

eGFR is increasingly inaccurate above 60 ml/min/1.73 m^2 and many laboratories do not report eGFR above that level. Higher changes in kidney function should be monitored using SCr, with a change of more than 10–15% likely to be significant. SCr is increased by the ingestion of cooked meat, so confirmatory samples are best taken after abstaining from meat for 12 hours. Like SCr, eGFR reflects GFR only in steady state, so both are unreliable when kidney function is changing rapidly (eg in acute kidney injury (AKI)). Having newly identified a reduced eGFR, it is important to exclude AKI with a further sample within 1–2 weeks. To establish the diagnosis of CKD requires a further sample at least 90 days later.

Proteinuria

Dipstick urinalysis performs poorly in the detection or exclusion of proteinuria as it measures urine protein concentration which depends on urine flow rate. Creatinine is excreted in urine at a relatively constant rate and can be used to adjust for dilution of the urine. Spot urine samples for total protein-creatinine ratio (TPCR) or albumin-creatinine ratio (ACR) perform at least as well as 24-hour urine samples in most circumstances and are far more convenient.[7] The first morning void is preferred but random samples are satisfactory.

ACR has a proven role in diabetic kidney disease and should be used to screen for and monitor this disease. Whether TPCR or ACR should be used in non-diabetic kidney disease is controversial, with guidelines making differing recommendations.[4,5] Most research on outcomes and interventions[7,8] is based on total proteinuria rather than albuminuria so the theoretical advantages of the more costly ACR remain unproven.

Haematuria

Non-visible haematuria may be detected on dipstick urinalysis. If persistent, and after urological causes have been excluded, it should be considered a marker of kidney damage.[9] It does not require confirmation with microscopy but warrants ongoing monitoring.

Investigations

Having identified CKD on the basis of an eGFR, a urine abnormality or imaging, an attempt should be made to establish the underlying diagnosis and prognosis. Accurate diagnosis may lead to specific therapies, in addition to general management (discussed below). Conversely, extensive investigation of asymptomatic patients with stable CKD stage 3, no proteinuria and no haematuria is unlikely to be rewarding. Most of these patients will have simple glomerulosclerosis. More attention is warranted, however, if vascular disease or risk factors are absent.

Basic investigations

History and physical examination may point to a specific diagnosis: for example, diabetes mellitus, a family history of

inherited nephritis, a recently started medication, palpable polycystic kidneys or a vasculitic rash. Blood pressure is key to treatment and should be measured and acted upon. Initial investigations for all patients with CKD should include:

- urea and electrolytes
- eGFR
- random blood glucose
- serum calcium and phosphate
- full blood count
- dipstick urine for hematuria
- urine ACR or TPCR.

Further investigation

Additional tests may be appropriate: for example, hypercalcaemia may prompt investigation for myeloma. It is unclear which patients benefit from urinary tract imaging. Nevertheless, lower urinary tract symptoms, a family history of polycystic kidney disease, deteriorating kidney function or CKD stages 4–5 should prompt a renal tract ultrasound.

Significant (TPCR ⩾100 mg/mmol) or more moderate proteinuria (TPCR ⩾50 mg/mmol), in combination with haematuria raises the likelihood of primary glomerular disease or vasculitis. These patients should be referred to a nephrologist, but renal ultrasound and serological screen for immunological disease would usually be appropriate. The screen should be tailored to the clinical presentation but would usually include antinuclear antibody, serum complement, serum immunoglobulins, serum and urine electrophoresis.

Table 1. The US National Kidney Foundation Kidney Disease Outcomes Quality Initiative classification of chronic kidney disease, as modified for use in the UK.

Stage	Definition	GFR (ml/min/1.73 m^2)	Population prevalence (%)
1	Presence of kidney damage with normal or raised GFR	⩾90	1.8
2	Presence of kidney damage with mildly reduced GFR	60–89	3.2
3A	Moderately reduced GFR	45–59	6.3
3B	Moderately reduced GFR	30–44	1.4
4	Severely reduced GFR	15–29	0.4
5	End-stage kidney disease	<15	0.2*

*If significant proteinuria is present the suffix p should be used.

Guidelines define significant proteinuria as a total protein-creatinine ratio ⩾100 mg/mmol[4] or ⩾50 mg/mmol.[5] If the patient is receiving dialysis, the suffix D will appear, and a functioning transplant will be denoted by the suffix T.

(Prevalence data are from Ref 1, with the split between stage 3A and 3B estimated from data in Ref 2.)

GFR = glomerular filtration rate.

Table 2. Formulae to predict glomerular filtration rate or creatinine clearance from serum creatinine.[6] The isotope dilution mass spectrometry (IDMS)-traceable formula is recommended in the UK. The UK National External Quality Assurance Service provides correction factors to correct SCr assays to an IDMS-traceable assay.

1	*Cockcroft-Gault equation*: eCC = [(140 − age) × weight]/(0.814 × SCr) × 0.85 (if female)
2	*6-variable MDRD formula*: eGFR = 170 × (0.011312 × SCr)$^{-0.999}$ × age$^{-0.176}$ × (2.8 × SU)$^{-0.170}$ × (0.1 × SAlb)$^{0.318}$ × 0.762 (if female) × 1.180 (if black)
3	*4-variable (or abbreviated) MDRD formula*: eGFR = 186.3 × (0.011312 × SCr)$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) × 1.212 (if black)
4	*IDMS-traceable MDRD formula*: eGFR = 175 × (0.011312 × SCr)$^{-1.154}$ × age$^{-0.203}$ × 0.742 (if female) × 1.212 (if black)

eCC = estimated creatinine clearance (ml/min); eGFR = estimated glomerular filtration rate (ml/min/1.73 m^2); SCr = serum creatinine (μmol/l); MDRD = modification of diet in renal disease; SAlb = serum albumin (g/l); SU = serum urea (mmol/l). Age is in years and weight in kg.

Management

The three main aims of treatment of CKD are to:

- slow deterioration of kidney function
- reduce cardiovascular risk, and
- address the complications of CKD.

Some renal diseases require specific therapies (eg immunosuppressive agents) but most will also benefit from these general measures.

Drug administration

Drugs may be contraindicated, ineffective or require dose adjustment in the presence of CKD. Available guidance is limited in value but should be consulted.[10] Dose should be based on the actual GFR (ml/min), whereas eGFR is reported adjusted for body surface area (ml/min/1.73 m^2). In practice, for most patients there is little difference between the two values. The actual GFR can be easily calculated using the Cockcroft-Gault equation (Table 2) or from eGFR (though there is less evidence to support this approach).

Hypertension and proteinuria

Blood pressure control. Hypertension is common in patients with CKD and associated with poorer outcomes.[8] Proteinuria is also associated with poorer cardiovascular and renal outcomes.[8,11] Tight blood pressure control slows progression of renal disease in proteinuric patients.[8] It is also assumed to be beneficial in reducing cardiovascular risk in both proteinuric and non-proteinuric CKD, although there is little direct evidence.

Guidelines recommend maintaining systolic blood pressure (SBP) at 120–139 mmHg and diastolic blood pressure (DBP) below 90 mmHg in all patients with CKD.[5] In patients with proteinuria (TPCR ⩾100 mg/mmol, ACR ⩾70 mg/mmol) and/or diabetes mellitus, SBP should be kept at 120–129 mmHg and DBP below 80 mmHg.[4,5] Reducing SBP below 100–110 mmHg may be detrimental.[8]

Drug treatment. Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin-2 receptor blockers (ARBs) confer additional benefit, independent of blood pressure, both in reducing proteinuria and slowing decline of kidney function.[12] They are the first-line agents in proteinuric patients (TPCR ⩾50 mg/mmol, ACR ⩾30 mg/mmol if hypertensive; TPCR ⩾100 mg/mmol, ACR ⩾70 mg/mmol if not hypertensive).[5] In patients with diabetes mellitus, ACEI and ARB are also indicated for microalbuminuria (ACR 2.5–30 mg/mmol in men, 3.5–30 mg/mmol in women) even if not hypertensive. A combination of ACEI and ARB may give additional benefits in proteinuric patients[13] but a recent large trial revealed worse renal outcomes in patients with minimal proteinuria[14] so caution is required. Monitoring of SCr and potassium is mandatory after commencing ACEI or ARB in CKD and these drugs should be discontinued if there is an unacceptable rise in SCr (>30%). The role of direct renin inhibitors and aldosterone antagonists, now under investigation, appears promising.

Diuretics are commonly used in the treatment of hypertension in CKD as volume expansion (even subclinical) is often a major contributor. As GFR declines, thiazide diuretics lose their efficacy and loop diuretics become the diuretic of choice.

Modification of other cardiovascular risk factors

In addition to treatment of hypertension, aggressive reduction of other cardiovascular risk factors is usually recommended. Treatment of dyslipidaemia with statins is supported by *post hoc* analyses in stage 3A CKD.[15] Large trials are currently investigating efficacy in more advanced CKD; to date, studies have been negative.[16–18] There is little available evidence to inform the use of antiplatelet therapy. Although there is an increased risk of bleeding in CKD with aspirin,[19] the increased cardiovascular risk weighs in favour of aspirin for most patients. Smoking cessation, weight reduction and an appropriate exercise regimen have minimal evidence to support them but are usually recommended.

Other complications of chronic kidney disease

Renal anaemia,[20] CKD mineral bone disease,[21] metabolic acidosis[22] and other complications of CKD typically arise in stage 4–5 CKD and are managed by nephrologists. The non-nephrologist should remain alert to their presence in less advanced CKD.

Referral

Most patients with CKD will be managed in primary care and do not require referral to a nephrologist. However, referral may be necessary for further investigation, counselling, more complex therapies or because of the likelihood of progression to dialysis or kidney transplantation (Table 3). Younger adults with CKD of any stage should be considered for referral because of the higher risk of reaching dialysis within their lifetime.

Table 3. Reasons for considering referral of a patient with chronic kidney disease (CKD) to a nephrologist.*

Patient group	Details
Significant proteinuria	Proteinuria ⩾1 g/day TPCR ⩾100 mg/mmol ACR ⩾70 mg/mmol
Proteinuria **and** haematuria	Proteinuria ⩾0.5 g/day TPCR ⩾50 mg/mmol ACR ⩾30 mg/mmol Haematuria ⩾1+
Deteriorating kidney function	A fall of >5 ml/min/year in 1 year A fall of >10 ml/min/year in 5 years
Severe CKD	CKD stage 4 or 5
Poorly controlled hypertension	Blood pressure ⩾140/90 mmHg despite at least four drugs
Suspicion of rare or genetic causes of CKD	

*Clinical judgement may suggest other patients should also be referred.

ACR = albumin-creatinine ratio; CKD = chronic kidney disease; TPCR = total protein-creatinine ratio.

Key Points

- **Chronic kidney disease (CKD) is defined by a reduced estimated glomerular filtration rate (eGFR), proteinuria, haematuria and/or structural abnormalities persistent for more than 90 days**
- **CKD is common affecting over 13% of the population**
- **Increased cardiovascular risk is the main consequence of mild to moderate CKD**
- **The most effective intervention is good blood pressure control, with angiotensin-converting enzyme inhibitors or angiotensin-2 receptor blockers preferred in proteinuric patients**

KEY WORDS: cardiovascular risk, chronic kidney disease, estimated glomerular filtration rate, haematuria, hypertension, proteinuria

Controversies in chronic kidney disease

1 Some argue that a reduced GFR is a natural consequence of ageing and that CKD medicalises old age. CKD is certainly common in the elderly, but the healthy elderly have relatively preserved GFR so CKD is not inevitable. Recent studies suggest that stage 3A carries little or no additional risk in the over 75s[23] so intervention may be unnecessary.
2 The CKD classification labels isolated microalbuminuria as stage 1. Some consider this is a further example of medicalisation, with limited evidence that it represents genuine kidney disease in non-diabetics.
3 It remains unclear what strategy should be used to screen for kidney disease. Better prediction of cardiovascular and renal risk[24] is required if interventions are to be targeted appropriately.
4 There is a dearth of intervention studies in this population, but extrapolation from other populations may not be appropriate.

Summary

CKD is common and its prevalence may be increasing. It carries with it a substantial cardiovascular risk but the vast majority of patients will never require dialysis. The minority requiring further investigation or complex management should be promptly identified and referred to a nephrologist. The remaining patients require lifelong monitoring in primary care and careful attention to their cardiovascular risk factors.

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