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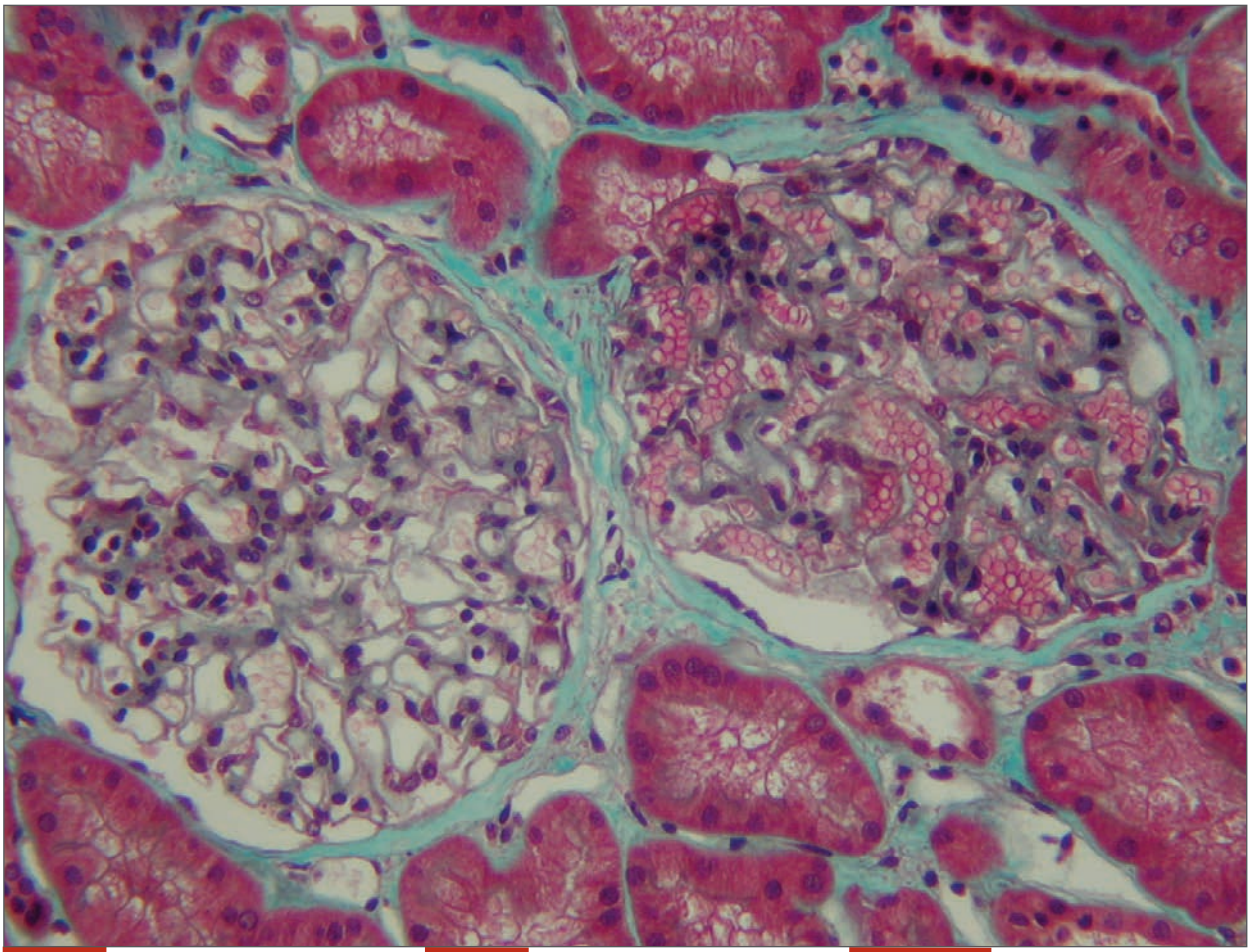


FIGURE
Histology specimen from a renal biopsy showing two abnormal glomeruli

How is chronic kidney disease classified?

CHRONIC KIDNEY DISEASE (CKD) IS A SIGNIFICANT HEALTH PROBLEM WITH UP TO 10% of adults having evidence of underlying CKD[1] or risk factors for its development. Recent national surveys[2] reported the prevalence of albuminuria to be 8% and CKD 5% in adults in England. (CKD was defined in the surveys as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2). The total annual CKD cost to NHS England is estimated to be £1.45 billion.[3]

Despite being so common, CKD frequently goes unrecognised as individuals with kidney disease often lack specific symptoms. Advanced CKD is associated with an increased risk of acute kidney injury (AKI), falls, frailty and mortality.[4] Earlier recognition and treatment may delay or prevent progression of CKD to end-stage renal disease (ESRD) and reduce these complications.[5] A late diagnosis of advanced CKD is associated with increased morbidity and mortality.

Although many of the CKD indicators will no longer be included in the Quality and Outcomes Framework (QOF) in 2015-16[6] the majority of individuals with CKD will still be covered by other QOF indicators (e.g. hypertension, diabetes and cardiovascular disease).

CKD CLASSIFICATION

CKD is defined as either a reduction in measured kidney function (eGFR), the presence of urinary abnormalities (haematuria/proteinuria), or a combination of both, for more than three months.

CKD can be further classified according to eGFR and the urinary albumin: creatinine ratio (ACR). CKD has previously been categorised into five stages based on eGFR measurements. »

In the most recent NICE guidelines for CKD, published in July 2014,[7] the various CKD stages 1-5 are now represented by G (for GFR) categories (G1-5) which have the same eGFR thresholds as previous CKD guidelines. The ACR category is denoted as A (for albuminuria) with three categories: A1, A2 and A3,[7,8] see table 1, below.

Table 1

Classification of CKD

GFR category	GFR (ml/min/1.73m²)
G1	> 90
G2	60-89
G3a	45-59
G3b	30-44
G4	15-29
G5	< 15

ACR category	ACR (mg/mmol)
A1	< 3
A2	3-30
A3	> 30

Table 2

Urological and nephrological evaluation of haematuria

Urological evaluation including renal imaging and cystoscopy is required in all patients with significant haematuria as defined by:

Visible haematuria (macroscopic or gross haematuria) at any age

Non-visible haematuria (microscopic or dipstick-positive haematuria) if:

- Symptomatic at any age (hesitancy, frequency, urgency, dysuria)
- Persistent (defined as 2 out of 3 dipsticks positive) and aged > 40 years

If a urological cause is excluded, a nephrology referral should be considered **if the patient meets any of the CKD criteria for referral or has:**

Significant proteinuria (ACR ≥ 30 mg/mmol or PCR ≥ 50 mg/mmol = 0.5 g/24hr)

Evidence of progressive CKD

- A sustained decrease in eGFR ≥ 25% and a change in GFR category within 12 months or
- A sustained decrease in eGFR > 15 ml/min/1.73m² per year

Stage 4 or 5 CKD (eGFR < 30 ml/min/1.73m²)

Isolated haematuria (i.e. in the absence of significant proteinuria) with hypertension in those aged < 40 years

Visible haematuria coinciding with intercurrent (usually upper respiratory tract) infection

The ACR category has been introduced to emphasise that patients with higher levels of albuminuria (in any eGFR stage) have an increased risk of progression to ESRD and other adverse outcomes, including higher risks of cardiovascular events and all cause mortality.

CAUSES

Common causes of CKD include conditions such as diabetes, atheromatous renal vascular disease, glomerulonephritis (see *Timely diagnosis and treatment essential in glomerulonephritis*, p13),[9] pyelonephritis and polycystic kidney disease.

Most cases of CKD in the elderly are caused by the cumulative effect of other disease states, especially hypertension and atherosclerosis. The CKD classification system will identify many elderly patients with a low eGFR but without progressive kidney failure. It is important not to alarm these individuals unduly with a misplaced diagnosis of advanced kidney failure.

SCREENING

Testing for CKD using eGFR and ACR should be offered to patients with the following risk factors:[7]

- Diabetes
- Hypertension
- Cardiovascular disease (ischaemic heart disease, chronic heart failure, peripheral vascular disease or cerebral vascular disease)
- Structural renal tract disease, recurrent renal calculi or prostatic hypertrophy
- Multisystem diseases that may impact on kidney function (i.e. systemic lupus erythematosus, rheumatoid arthritis, sarcoidosis)
- Family history of ESRD or hereditary kidney disease
- Two to three years post acute kidney injury (AKI), even if serum creatinine had returned to baseline
- Opportunistic detection of haematuria

eGFR should be monitored at least annually in patients prescribed drugs known to be nephrotoxic such as calcineurin inhibitors (ciclosporin or tacrolimus), lithium and NSAIDs.[7] CKD may be identified in many patients during follow-up of diabetes, heart failure or ischaemic heart disease under current QOF indicators.

'Advanced CKD is associated with an increased risk of AKI, falls, frailty and mortality'

BASELINE INVESTIGATIONS

For individuals with newly identified reduced eGFR the first step is to exclude AKI. Review of previous serum creatinine (and eGFR) tests may confirm CKD. If no previous renal function tests are available then the patient should have a repeat serum creatinine and eGFR within one week to exclude AKI with rapid loss of renal function.

In all newly identified CKD patients the following parameters should be checked at the earliest opportunity:

- Blood pressure
- Dipstick urinalysis
- Random urine ACR or urine protein:creatinine ratio (PCR)
- Glucose, cholesterol and full blood count

An ultrasound scan should be offered to certain individuals with CKD,[7] see box 1, below. In patients with a family history of inherited kidney disease the implications of an abnormal result should be discussed before imaging is arranged.

TESTING FOR PROTEINURIA

Cardiovascular events and progression of CKD are more common if albuminuria or proteinuria is present.[8,10] NICE guidance suggests that reagent strips for dipstick urinalysis provide a simple screening

Box 1

Indications for an ultrasound scan of kidneys and renal tract in patients with CKD

- Symptoms of urinary tract obstruction
- Visible haematuria, or persistent non-visible haematuria if > 40 years old
- eGFR categories G4 or G5 (eGFR < 30 ml/min/1.73m²)
- Accelerated progression of CKD
- Family history of polycystic kidney disease

Table 3

Suggested monitoring of CKD in general practice

STAGE	G1	G2	G3a	G3b	G4	G5
U&E and ACR (times per year)	A1-3: once		A1-2: once	A1-2: once A3: twice	A1-2: twice A3: three times	Four times or more
Treatment	● Treat BP to a target < 140/90 mmHg (130/80 if urine ACR ≥ 70 mmol/mol) ● ACEi or ARB if -ACR ≥ 3 mg/mmol + diabetes -ACR ≥ 30 mg/mmol + BP ≥ 140/90 mmHg -ACR ≥ 70 mg/mmol ● Consider a statin + aspirin 75 mg for secondary prevention ● Advise lifestyle changes as appropriate					
Referral	Progressive CKD Decrease in GFR ≥ 15 ml/min/1.73m² ± urine ACR ≥ 70 mg/mmol ± systolic BP ≥ 160 mmHg (despite treatment with multiple agents)				Discussion with or referral to renal unit is usual	Usually automatic (Unless not for active treatment based on comorbidity)

test but are not an accurate method of quantifying proteinuria. ACR should be used to detect albuminuria in patients with diabetes and all individuals with reduced eGFR.

Urine ACR:

- < 3 mg/mmol is normal
- 3-70 mg/mmol should be confirmed by an early morning urine sample
- > 70 mg/mmol equates to proteinuria (a confirmatory sample is not required)

Urine ACR has a greater sensitivity for low levels of proteinuria than PCR. For quantification and monitoring of very high levels of proteinuria, PCR can be used as an alternative.

HAEMATURIA

Asymptomatic non-visible haematuria is very common in general practice. It often has a urological cause such as kidney or urinary tract malignancy, stones, inflammation, infection or hyperplasia of prostate or bladder.

Box 2

Risk factors (in addition to proteinuria) for CKD progression

- Cardiovascular disease
- Hypertension
- Diabetes
- Smoking
- Acute kidney injury
- Persistent urinary outflow tract obstruction
- African, African-Caribbean or Asian ethnic origin
- Chronic NSAID use

'Patients with higher levels of albuminuria (in any eGFR stage) have an increased risk of progression to ESRD and other adverse outcomes'

In young adults haematuria is often transient and may be of no consequence. Brief clinical guidelines have been published by the British Association of Urological Surgeons and the Renal Association on assessment of haematuria.[11]

Initial assessment should include:

- **History:** symptoms of infection, obstruction or systemic illness
- **Examination:** blood pressure, bladder or prostate
- **Investigations:**

Blood - serum creatinine and eGFR, bone profile

Urine - urine ACR, urinalysis and MSU (exclude UTI)

Indications for referral to nephrology and urology in patients with haematuria are listed in table 2, p20.

IDENTIFYING PATIENTS AT RISK

Once identified CKD can then be classified according to eGFR and urine ACR categories (see table 1, p20). Decreased eGFR and increased ACR are both associated with adverse outcomes (such as CKD progression, AKI, cardiovascular events and all cause mortality). An individual's risk of adverse outcomes may be assessed using their eGFR and urine ACR results, along with the other factors that make progression of CKD more likely, see box 2, below.

REFERRAL

The decision to make a nephrology referral for an individual patient with CKD should be based on assessments of kidney function (eGFR), the severity of proteinuria (urine ACR), concerns about poorly controlled blood pressure, or suspected inherited renal disease.

When considering referral to renal services the patient's comorbidities and wishes should be taken into account. Consider discussing management issues with a nephrologist (virtual referral) where it may not be necessary for a patient to attend for hospital-based assessment.

1. Based on eGFR

- **New G5** (eGFR < 15 ml/min/1.73m²): discuss immediately
- **New G4** (eGFR 15-29 ml/min/1.73m²): refer or discuss
- **Progressive CKD** on repeat testing (a sustained decrease > 25% in eGFR or a change in eGFR category within 12 months or a fall in eGFR > 15 ml/min/1.73m² per year): refer routinely

2. Based on proteinuria (ACR):

- > 300 mg/mmol and or nephrotic syndrome: refer urgently
- 100 mg/mmol: refer routinely
- 30-100 mg/mmol and haematuria: refer routinely

3. Based on blood pressure

- Poorly controlled hypertension despite the use of at least three antihypertensive drugs at optimal dosage: refer routinely
- eGFR < 60 ml/min/1.73m² and inadequately controlled blood pressure despite two to three antihypertensive agents: refer routinely
- Suspected renal artery stenosis: e.g. > 25% rise in serum creatinine after ACE inhibitor (ACEi) or angiotensin receptor blocker (ARB) »

key points

SELECTED BY
Dr Peter Saul
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Chronic kidney disease (CKD) is defined as either a reduction in measured kidney function (eGFR) or urinary abnormalities (haematuria/proteinuria) or a combination of both, present for more than 3 months. In the most recent NICE guidelines the various CKD stages 1-5 are now represented by G (for GFR) categories (G1-5) which have the same eGFR thresholds as previous CKD guidelines. The ACR category is denoted as A (for albuminuria) with three categories: A1, A2 or A3. The ACR category has been introduced to emphasise that patients with higher levels of albuminuria have an increased risk of progression to end-stage renal disease.

Most cases of CKD in the elderly are caused by the cumulative effect of other disease states, especially hypertension and atherosclerosis. The CKD classification system will identify many elderly patients with a low eGFR but without progressive kidney failure. It is important not to alarm these individuals unduly with a misplaced diagnosis of advanced kidney failure.

Individuals with newly identified reduced eGFR should have AKI excluded. All newly identified CKD patients should have blood pressure (BP), dipstick urinalysis, random urine ACR or urine protein:creatinine ratio (PCR), glucose, cholesterol and full blood count checked at the earliest opportunity. An ultrasound scan should be offered to individuals with increased risk.

Cardiovascular events and progression of CKD are more common if albuminuria or proteinuria is present. Urine ACR has a greater sensitivity for low levels of proteinuria in comparison with PCR. Referral for patients with CKD should be based on assessment of kidney function (eGFR), the severity of proteinuria (urine ACR), concerns about poorly controlled BP, or suspected inherited renal disease.

BP should be treated ideally to < 140/90 mmHg, if ACR > 70 mg/mmol treat BP ideally to < 130/80 mmHg with ACEi or ARBs as first-choice therapy. Caution must be exercised when reducing BP in elderly patients with widespread vascular disease, as kidney perfusion may be compromised by a fall in BP leading to acute kidney injury.

ACEi or ARB therapy should be offered to patients with CKD to reduce proteinuria, a statin should be offered to those with CKD, and an antiplatelet agent considered for secondary prevention of cardiovascular disease. Medication should be reviewed, NSAIDs stopped and doses of medication adjusted according to eGFR.

administration in patients with widespread atherosclerotic vascular disease: refer routinely

4. Known or suspected rare or genetic cause of CKD

TREATMENT

Blood pressure

Treat blood pressure ideally to < 140/90 mmHg with multiple agents if necessary.[7] If ACR > 70 mg/mmol treat blood pressure ideally to < 130/80 mmHg with ACEi or ARBs as first-choice therapy.[7] However caution must be exercised when reducing blood pressure in elderly patients with widespread vascular disease, as kidney perfusion may be compromised by a fall in blood pressure leading to AKI. Serum creatinine, eGFR and potassium should be checked 7-10 days after commencing treatment or changing dosages of ACEi or ARB.

Proteinuria

ACEi or ARB therapy should be offered to patients with CKD to reduce proteinuria. Treatment should be offered to patients with CKD and:

- Diabetes with an ACR > 3 mg/mmol
- Hypertension with an ACR > 30 mg/mmol
- An ACR > 70 mg/mmol[7]

'Patients should have access to their medical data to encourage self-management'

Cardiovascular risk

A statin should be offered to patients with CKD, and an antiplatelet agent considered for secondary prevention of cardiovascular disease.

Other

Medications should be reviewed, NSAIDs stopped and doses of medications adjusted according to eGFR. Lifestyle modification such as smoking cessation, reduction of obesity, increased exercise and reduction in dietary salt intake are recommended. Patients should be offered education regarding their condition and have access to their medical data to encourage self-management of their CKD.

MONITORING

The majority of patients with CKD may be managed in primary care. The amended QOF CKD indicator recommends that a CKD register be established and maintained for CKD G3a to G5 (previously stages 3 to 5).[6] This can also include patients with milder proteinuria (ACR 30-100 mg/mmol), isolated non-visible haematuria and stable CKD stages G3 and G4, see table 3, p21.

The frequency of eGFR monitoring should be tailored to changes to the patient's treatment (such as change in dose of ACEi/ARBs, diuretics, NSAIDs) intercurrent illness and whether they have chosen conservative management of their CKD.

Large rises in serum creatinine (> 30%) and a commensurate fall in eGFR are generally associated with underlying renal vascular disease, heart failure treatment and concomitant acute illness. A falling eGFR will require closer monitoring and a sustained fall should be confirmed by repeating serum creatinine and eGFR within one month. Suggestions for management include:

- Temporary cessation of ACEi or ARBs if the patient is at risk of dehydration (should not be stopped indefinitely if these drugs are prescribed for vascular or renal protection indications)
- Stop NSAIDs
- Drugs containing trimethoprim can cause a marked increase in serum creatinine and serum potassium: repeat sample 48 hours after medication complete

CONCLUSION

Although CKD is common, it is frequently underrecognised resulting in late diagnosis and increased risk of progression. An individual's risk of adverse outcomes may be assessed using their eGFR and urine ACR results. Effective monitoring and management of CKD patients within primary care should allow timely onward referral, thus reducing the increased morbidity and mortality risks associated with late referral.

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Useful information

NICE
CG182. Chronic kidney disease: early identification and management of chronic kidney disease in adults in primary and secondary care
www.nice.org.uk/guidance/cg182

GAIN
Guidelines for adults with chronic kidney disease
www.gain-ni.org

Renal Association
Rapid access to information about eGFR and CKD stages with links to management
www.renal.org/eGFR

Edinburgh Renal Unit
Articles on kidney disease that are suitable for both healthcare professionals and patients
http://renux.demed.ed.ac.uk/EdREN/index.html

Think Kidneys
NHS campaign to improve the care of people at risk of, or with, acute kidney injury. It highlights links between acute kidney injury and subsequent development of CKD. A combination of patient information and education links
www.thinkkidneys.nhs.uk/

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