Epidemiology and causes of chronic kidney disease

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Abstract

Chronic kidney disease (CKD) is diagnosed when evidence of kidney damage (reduced glomerular filtration rate (GFR) or proteinuria) has been present for >3 months. It is divided into categories depending on GFR and urine albumin:creatinine ratio (UACR). CKD is common, affecting 13% of the adult population globally; the prevalence rises sharply with age. Recognition of CKD is important because it is associated with multiple adverse outcomes including increased risk of cardiovascular events, acute kidney injury (AKI) and progression to end-stage kidney disease (ESKD). Risk factors for CKD can be divided into initiating and perpetuating factors, and include genetic factors, ethnicity, socioeconomic factors and age. There are multiple causes of CKD, the most common being diabetes mellitus. Other causes include glomerulonephritis, genetic disorders, drugs, cardiovascular disease, multisystem diseases, urinary tract obstruction, infections and AKI. In order to reduce the burden of CKD, it is essential to recognize which patients are at most risk so they can be diagnosed and treated early to reduce the risk of progression to ESKD. Individuals with newly diagnosed hypertension, cardiovascular disease, diabetes mellitus, multisystem disorders, evidence of urinary obstruction or significant family history should be tested for CKD.

Keywords Causes; chronic kidney disease; chronic kidney failure; definition; end-stage kidney disease; prevalence; renal replacement therapy; risk factors

Key points

- Chronic kidney disease (CKD) is common, affecting around 13% of the adult population globally
- The prevalence of CKD rises sharply with increasing age
- CKD is important because it is associated with multiple adverse outcomes including increased risk of cardiovascular events, acute kidney injury and progression to end-stage kidney disease
- Risk factors for CKD include older age, male sex, African ancestry, lower socioeconomic status, genetic factors and hypertension
- There are many causes of CKD, including diabetes mellitus, glomerulonephritis, genetic disorders, cardiovascular disease, multisystem diseases, drugs, urological conditions, infections and acute kidney injury
- It is important to identify individuals at high risk of having CKD so they can undergo testing to facilitate early diagnosis and treatment to reduce cardiovascular risk and slow progression towards end-stage kidney disease

Introduction

Chronic kidney disease (CKD) is common and is associated with a significantly increased risk of multiple adverse health outcomes. The most obvious risk is progression to end-stage kidney disease (ESKD), which results in patients requiring dialysis and/or renal transplantation, together termed renal replacement therapy (RRT). However, in many populations the risk of ESKD is relatively low, and other risks including morbidity and death from cardiovascular disease, acute kidney injury (AKI) and increased hospital admissions are a more important consideration. A Global Burden of Disease study has identified CKD as the 10th leading cause of death in countries with a middle sociodemographic index.

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Moreover, the treatment of CKD represents a considerable economic burden. In 2009–2010, the cost of CKD to the NHS in England was estimated at £1.44–1.45 billion, which accounted for 1.3% of the total NHS budget.[1] In the USA, Medicare spending for patients with ESKD reached $35.4 billion in 2016, representing 7.2% of total Medicare spending; an additional $79 billion was spent on CKD.

To reduce the burden of ESKD for individuals and healthcare systems, and facilitate interventions to reduce risk, it is essential to understand the causes of CKD and its associated risk factors. This allows high-risk individuals to be identified for testing and monitoring. CKD can complicate the management of many other diseases because of interactions between different pathologies and the impact on drug dosing. Treatment aims to minimize the effect of associated risk factors on the rate of CKD progression and cardiovascular risk. All healthcare professionals should therefore have a basic understanding of CKD. This article discusses the definition and epidemiology of CKD and reviews risk factors for its development and progression.

Definition and staging of chronic kidney disease

The publication in 2012 of the Kidney Disease: Improving Global Outcomes (KDIGO) clinical practice guideline for evaluation and management of CKD modified the classification of CKD first proposed in 2002. Diagnosis still requires evidence of kidney damage that has been present for at least 3 months, but classification is then based on a combination of the glomerular filtration rate (GFR) and the urinary albumin:creatinine ratio (UACR) (see Table 1 in Management of chronic kidney disease,

pages 567–575 of this issue). This allows a person's risk of developing CKD-associated morbidity to be stratified into low, moderate and high. Treatment and frequency of follow-up can then be tailored according to risk category. The KDIGO classification has also been adopted by the National Institute for Health and Care Excellence.

GFR is estimated from a measurement of serum creatinine, using a mathematical formula that also includes age, sex and ethnicity. The formula now recommended is the CKD Epidemiology (CKD-EPI) equation as it has less bias, improved precision and greater accuracy compared with the previously used Modification of Diet in Renal Disease (MDRD) equation.

Epidemiology

CKD is a common condition and is present in all adult populations that have been studied. There appears to be some variation in prevalence in different populations (Table 1), but the average global prevalence has been reported to be 13.4% in adults.[2] A similar prevalence has been reported in the UK. These figures may represent an overestimate of the true prevalence because almost all studies have relied on a single estimated GFR value (and not two values at least 90 days apart, as required by the KDIGO definition). In 2010, the estimated number of persons with any stage of CKD worldwide was estimated to be 225.7 million men and 271.8 million women. The prevalence of CKD rises steeply with age, such that >23% of persons aged 70 years or above are affected.[3]

In 2014, data from 60 countries identified 2,217,350 individuals with ESKD globally. The prevalence of ESKD depends on the prevalence of CKD as well as the provision of RRT and survival rates on RRT, and therefore varies widely between countries. The highest prevalence of ESKD was reported in Taiwan, at 3219 per million population (pmp), and the lowest in Bangladesh at 113 pmp. In 2016 in the UK, the prevalence of ESKD was 962 pmp.

Risk factors

It is important to identify factors that are associated with an increased risk of developing CKD, so that screening programmes can be targeted at high-risk groups. Risk factors relating to CKD can be divided into two main groups: predisposing and initiating factors that increase the risk of developing CKD; and perpetuating factors that increase the risk of CKD progression to ESKD (Table 2).

Prevalence of CKD in a range of populations

Country	Study	Number of subjects	Age of subjects (years)	Definition of CKD	Prevalence of CKD (%)
Australia	AUSDIAB	11,247	≥25	CKD 1–5	16
DR of Congo	Sumaili et al.	503	≥20	CKD 1–5	12.4
Norway	HUNT 2	65,604	≥20	CKD 3–5	4.7
South China	Chen et al.	6311	>20	CKD 1–5	12.1
UK	HSE 2010	6000	≥16	CKD 1–5	13
USA	NHANES IV	13,233	≥20	CKD 1–4	13.1

Table 1

Risk factors for CKD

Predisposing and initiating factors	Perpetuating factors
Increasing age	African–American race
Gender	Proteinuria
Ethnicity	Hypertension
Family history of CKD	High dietary protein intake
Lower socioeconomic status	Obesity
Metabolic syndrome	Anaemia
	Dyslipidaemia
Nephrotoxins (NSAIDs, antibiotics, radiological contrast, light chains)	Nephrotoxins
Primary renal disease (glomerulonephritis)	
Urological disorders (obstruction, recurrent urinary infections)	
Cardiovascular disease	Cardiovascular disease
Diabetes mellitus	
AKI	AKI

AKI, acute kidney injury; NSAID, non-steroidal anti-inflammatory drug.

Table 2

Genetic factors

Hereditary renal diseases that result from single-gene defects make up only a small proportion of cases. More significant are genetic factors that increase the risk of developing multifactorial CKD in a person with a family history of CKD. For example, the risk of ESKD has been shown to increase 1.3 times (95% confidence interval (CI) 0.7–2.6) if one first-degree relative has ESKD, and 10.4 times (95% CI 2.7–40.2) if two are affected.

Ethnicity

Ethnicity is difficult to identify as a risk factor in isolation because of its association with a number of confounding factors related to socioeconomic status. However, in epidemiological studies, ethnicity remains a significant risk factor even after socioeconomic factors have been taken into account. The US Renal Data System reports that the annual incidence of ESKD in African-Americans and Native Americans is 3.4 and 1.6 times greater, respectively, than in white Americans.

In several ground-breaking studies, the high prevalence of ESKD among African-American individuals has been linked to specific risk alleles of the *APOL1* gene. Interestingly, these alleles also confer resistance to the tsetse fly-borne parasite *Trypanosoma brucei*, which causes 'sleeping sickness' in parts of Africa; they would therefore confer survival advantage in endemic areas, providing an explanation for the high prevalence of the risk alleles in the African-American population.[4]

Socioeconomic factors Socioeconomic factors affecting CKD incidence, prevalence and progression include income, education and environmental factors, which are all potentially modifiable. In the UK, there is an approximate 40% increase in CKD incidence in the highest quintile of social deprivation compared with

the lowest. Similarly in the USA, white Americans have an 86% increased odds of having CKD if they are in the lowest income quintile compared with the highest.

Age

The prevalence and incidence of CKD increases sharply with increasing age, implying that nephron loss could be a 'normal' part of ageing. One study has estimated that 6207 glomeruli are lost per year. In some studies, the rate of GFR decline is reported to be greater with increasing age but, paradoxically, the risk of progression to ESKD is decreased because of the competing risk of death. Thus, most elderly patients with CKD die from other causes before they progress to ESKD.

Sex

Although there is some variation between studies, the most consistent finding is that the incidence of CKD and ESKD is greater in men than women. This can in part be explained by the observation that men tend to have a higher prevalence of risk factors for CKD. Men also demonstrate greater progression rates for some types of kidney disease compared with women. Postmenopausal status may affect the risk in women, but this requires further investigation.

Hypertension

Hypertension is an almost universal consequence of CKD but also contributes to its progression. Population-based studies have identified hypertension as an independent risk factor for ESKD, but whether or not hypertension per se causes kidney disease remains controversial. All patients with newly diagnosed hypertension should be screened for CKD as a possible cause, and treatment of hypertension is essential for slowing the rate of CKD progression.

Causes of chronic kidney disease

The most consistent data regarding the relative prevalence of different causes of CKD are derived from incident RRT cases (i.e. persons starting RRT for the first time). As shown in Table 3, there is significant variation in different countries, but diabetes mellitus is the dominant cause in most. Despite advances in knowledge and diagnostic techniques, the proportion of patients with ESKD in whom the cause is unknown remains high in many countries.

Diabetes mellitus

Diabetes mellitus is the most common cause of CKD in most developed and developing countries. Approximately 40% of patients with diabetes develop CKD, so all patients with diabetes should have their GFR and UACR checked annually. Achieving good glycaemic control and early treatment of hypertension with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker are the most important interventions to slow the progression of CKD.

Glomerulonephritis

The term 'glomerulonephritis' refers to a wide range of primary and secondary conditions that cause inflammation in and damage to the glomerulus. The pathogenesis involves the immune system in most cases but understanding of the specific mechanisms remains incomplete. The hallmark of glomerulonephritis is haematuria with proteinuria. A urine dipstick test should be therefore performed on every patient presenting with CKD or AKI. Renal biopsy is usually required to make a specific diagnosis. The treatment depends on the specific diagnosis and cause, as do the progression rate and prognosis.

Genetic diseases

Adult polycystic kidney disease is the most common monogenic disorder causing CKD. It is inherited in an autosomal dominant fashion and typically presents in the third and fourth decades of life. It is frequently associated with extra-renal manifestations, including cysts involving other organs (liver, spleen), cerebral aneurysms and cardiac valvular abnormalities. Family members

Causes of kidney disease in incident RRT patients

Diagnosis	UK		Netherlands		Norway		USA		Australia
	%	pmp	%	pmp	%	pmp	%	pmp	%
Glomerulonephritis	12.8	13.7	7.9	9.5	15.9	16.3	6.3	23.2	19
Chronic pyelonephritis	6.1	6.5	3.6	4.3	3.5	3.6	n/a	n/a	n/a
Diabetes	23.7	25.3	16.3	19.6	16.5	16.9	43.9	159.2	36
Renovascular disease	4.1	4.4	12.3	14.7	1.0	1.0	n/a	n/a	n/a
Hypertension	6.9	7.3	12.0	14.4	28.1	28.9	27.8	102.2	12
Adult polycystic kidney disease	6	6.5	4.3	5.2	11.0	11.4	2.2	8	5
Urological	n/a	n/a	n/a	n/a	n/a	n/a	1.3	4.7	n/a
Other	18.1	19.3	19.4	23.3	21.3	21.9	12.9	47.5	17
Unknown	16.1	17.1	10.5	12.6	2.7	2.8	3.2	11.7	6
Missing data	6.2	6.6	13.7	16.4	0	0	2.3	5.6	0

All data from 2011/2012. %, percentage of incident RRT population.
n/a, not applicable.

Table 3

are screened using ultrasonography to identify renal cysts, but genetic testing is also now available to identify the specific mutation and screen family members.

Alport's syndrome is a condition associated with a progressive hereditary nephritis and sensorineural deafness. Inheritance is X-linked in 80% of cases, autosomal recessive in 15% and autosomal dominant in 5%. Many other rare genetic disorders can result in CKD, and a family history is therefore critical in evaluating a new patient. A recent study has reported a genetic cause encompassing 66 monogenic disorders in 9.2% of persons with CKD,[5] indicating that genetic testing is likely to play an increasingly important part in the investigation of CKD.

Cardiovascular diseases

Cardiovascular disease is frequently associated with CKD. Atherosclerosis can narrow the main renal arteries to cause renal artery stenosis, or affect the smaller intrarenal arteries and arterioles to cause ischaemic nephropathy. Cardiac failure results in reduced renal perfusion, and diuretics used to treat fluid retention further reduce GFR. The association between cardiac and renal failure is referred to as cardiorenal syndrome.

Multisystem diseases

Diseases that affect multiple organ systems can also cause kidney disease by a variety of different mechanisms. The multisystem disorders that most frequently cause CKD include systemic lupus erythematosus, sarcoidosis, amyloidosis and multiple myeloma.

Drugs

A number of drugs can cause AKI and CKD, usually by provoking interstitial nephritis. Drugs associated with acute interstitial nephritis include non-steroidal anti-inflammatory drugs, proton pump inhibitors, antiretrovirals, penicillins and diuretics. Overall, the incidence is low but, because of the large number of individuals given these drugs, cases are regularly seen. Chronic treatment with lithium can provoke an interstitial nephritis as well as nephrogenic diabetes insipidus, requiring a change to an alternative drug.

Urological conditions

Reflux nephropathy almost always develops in childhood and results from recurrent infections caused by vesico-ureteric reflux. Children presenting with recurrent urinary tract infections should be investigated for evidence of vesico-ureteric reflux. Urinary tract obstruction caused by prostatic hypertrophy, renal calculi or pelvic malignancies is an important potentially reversible cause of AKI/CKD. Patients with CKD (and AKI) should be asked about symptoms suggestive of urinary obstruction and investigated with abdominal ultrasonography.

Infections

Post-infectious glomerulonephritis is typically associated with streptococcal infection but can occur after any infection. It is uncommon as a cause of CKD in developed countries but is still a significant cause of CKD in the developing world. Other infections that can cause CKD include HIV, hepatitis B and C, tuberculosis and malaria. Pathogenesis and management differ for each infection.

Acute kidney injury

AKI is increasingly recognized as both an initiating and a perpetuating risk factor for CKD. Incomplete recovery from AKI results in residual damage and fibrosis that can progress over time. In observational studies, people who recover from AKI are at substantially increased risk of subsequently developing CKD (hazard ratio 8.8) and ESKD (hazard ratio 3.1). The risk of ESKD is further amplified in people who had CKD before developing AKI. Those who show incomplete recovery after AKI should therefore have regular monitoring of GFR and UACR as well as clinical follow-up. ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 72-year-man presented for review of his type 2 diabetes mellitus which has been present for 17 years. He also has hypertension.

On clinical examination, he looked well. His blood pressure was 154/96 mmHg.

Investigations

- Urea 6.5 mmol/litre (2.5–7.0)
- Creatinine 122 micromol/litre (60–110)
- HbA_{1c} 75 mmol/mol (20–42); 9.0% (4.0–6.0)
- Estimated glomerular filtration rate 52 ml/minute/1.73 m^2 (>60)
- Urine albumin:creatinine ratio 84 mg/mmol (<2.5)

What is the most likely cause of his chronic kidney disease?

A. Glomerulonephritis
B. Diabetic nephropathy
C. HIV/AIDS
D. Urinary obstruction
E. A genetic disorder

Question 2

A 43-year-old woman presented because her father, aged 76 years, had recently started dialysis for end-stage kidney disease (ESKD). She is well but wanted to know if she should be tested.

What is the most appropriate advice to give?

A. She should be tested for chronic kidney disease (CKD) only if her father is found to have ESKD caused by a genetic disorder.
B. She does not require testing for CKD because she is relatively young and unlikely to have developed CKD.
C. She should be tested for CKD regardless of any other factors.
D. She does not require testing for CKD because she is female and is therefore at lower risk than her father.
E. She should be tested for CKD only if other female members of her family have been found to have CKD.

Question 3

An 83-year-old woman has severe heart failure as a result of ischaemic cardiomyopathy. She is treated with bisoprolol 2.5 mg/day, enalapril 20 mg/day, furosemide 40 mg BD and spironolactone 25 mg/day. On routine testing she is found to have a reduced estimated glomerular filtration rate of 43 ml/minute/1.73 m^2. Urine dipstick testing reveals no abnormalities.

There is no family history of CKD. What is the most likely cause of her CKD?

A. Cardiorenal syndrome.
B. Glomerulonephritis.
C. Obstructive uropathy.
D. Adult polycystic kidney disease (APKD).
E. Myeloma.