Chronic kidney disease

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The definition and classification of chronic kidney disease (CKD) have evolved over time, but current international guidelines define this condition as decreased kidney function shown by glomerular filtration rate (GFR) of less than 60 mL/min per 1·73 m², or markers of kidney damage, or both, of at least 3 months duration, regardless of the underlying cause. Diabetes and hypertension are the main causes of CKD in all high-income and middle-income countries, and also in many low-income countries. Incidence, prevalence, and progression of CKD also vary within countries by ethnicity and social determinants of health, possibly through epigenetic influence. Many people are asymptomatic or have non-specific symptoms such as lethargy, itch, or loss of appetite. Diagnosis is commonly made after chance findings from screening tests (urinary dipstick or blood tests), or when symptoms become severe. The best available indicator of overall kidney function is GFR, which is measured either via exogenous markers (eg, DTPA, iohexol), or estimated using equations. Presence of proteinuria is associated with increased risk of progression of CKD and death. Kidney biopsy samples can show definitive evidence of CKD, through common changes such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis. Complications include anaemia due to reduced production of erythropoietin by the kidney; reduced red blood cell survival and iron deficiency; and mineral bone disease caused by disturbed vitamin D, calcium, and phosphate metabolism. People with CKD are five to ten times more likely to die prematurely than they are to progress to end stage kidney disease. This increased risk of death rises exponentially as kidney function worsens and is largely attributable to death from cardiovascular disease, although cancer incidence and mortality are also increased. Health-related quality of life is substantially lower for people with CKD than for the general population, and falls as GFR declines. Interventions targeting specific symptoms, or aimed at supporting educational or lifestyle considerations, make a positive difference to people living with CKD. Inequity in access to services for this disease disproportionally affects disadvantaged populations, and health service provision to incentivise early intervention over provision of care only for advanced CKD is still evolving in many countries.

Introduction

Chronic kidney disease (CKD) arises from many heterogeneous disease pathways that alter the function and structure of the kidney irreversibly, over months or years. The diagnosis of CKD rests on establishing a chronic reduction in kidney function and structural kidney damage. The best available indicator of overall kidney function is glomerular filtration rate (GFR), which equals the total amount of fluid filtered through all of the functioning nephrons per unit of time.[1,2] The definition and classification of CKD have evolved over time, but current international guidelines define CKD as decreased kidney function shown by GFR of less than 60 mL/min per 1·73 m², or markers of kidney damage, or both, of at least 3 months duration, regardless of

Search strategy and selection criteria

We searched MEDLINE via OvidSP and the Cochrane Library during October–December, 2015. We combined the following search terms used by Cochrane kidney and transplant to identify publications related to pre-dialysis CKD (with or without uraemia): "renal insufficiency", "exp renal insufficiency, chronic/", "kidney diseases/", "(chronic kidney or chronic renal).tw.", "(ckf or ckd or crf or crd).tw.", "(pre-dialy$ or predialy$).tw.", "exp uremia/", "uremi.tw.", and "or/1-8". We then combined the results with methodological filters to find studies best suited to answer our seminar topics. The filters limited results to, in turn, systematic reviews and meta-analyses, (all questions), randomised trials (questions of intervention), cohort and cross sectional studies (for prevalence, incidence, cause, diagnosis, and prognosis questions). Full strategies are available from the authors.

For evidence of cost-effectiveness we searched MEDLINE using the terms above, combined with a methodological filter for "cost-effectiveness" or "QALY". We also searched the NHS Economic Evaluation Database and the Tufts Cost Effectiveness Analysis registry databases using the search terms "kidney" or "renal".

We focused largely on work published in the past 5 years, but did not exclude highly cited older publications. We also used text books and searched the reference lists of articles identified by this search strategy and selected those we judged relevant.

Key messages

- Chronic kidney disease (CKD) is defined as glomerular filtration rate (GFR) <60 mL/min per 1·73 m² or markers of kidney damage, or both, of at least 3 months duration (panel)
- In high-income and middle-income countries about one in ten people have CKD, principally caused by diabetes, hypertension, or glomerulonephritis
- Prevalence varies by ethnicity and socioeconomic indices, with disadvantaged groups disproportionately affected
- Symptoms are often non-specific until CKD is advanced
- Diagnosis is made on the basis of estimates of GFR, and pathophysiology such as glomerular sclerosis, tubular atrophy, and interstitial fibrosis found on kidney biopsy
- Complications of CKD include anaemia, bone disease, and increased risk of cardiovascular disease and cancer
- Premature death is up to ten times more likely than requiring dialysis
- People with CKD have diminished quality of life, and poorer socioeconomic circumstances as CKD progresses
- Health services for CKD are changing to focus on rewarding earlier achievement of better patient outcomes in preference to provision of services for advanced CKD

Panel: **Criteria of CKD, according to international guidelines**

Either one, or both, of the following two criteria for at least 3 months:

1 GFR <60 mL/min per 1·73m² (categories G3a–5, see table 1)
2 Markers of kidney damage (1 or more)
- Albuminuria (albumin : creatinine ratio [ACR] ≥30mg/g)
- Urinary sediment abnormality
- Electrolyte or other abnormality due to tubular disorder
- Abnormalities on histology
- Structural abnormalities detected by imaging
- History of a kidney transplantation

	GFR descriptors and range	Range (mL/min/1·73m²)	Persistent albuminuria categories, descriptors and ACR range		
			Normal to mildly increased (<30mg/g)	Moderately increased (30–300mg/g)	Severely increased (>300 mg/g)
G1	Normal or high	≥90	1 if CKD	1	2*
G2	Mildly decreased	60–89	1 if CKD	1	2*
G3a	Mildly to moderately decreased	45–59	1	2	3†
G3b	Moderately to severely decreased	30–44	2	3	3†
G4	Severely decreased	15–29	3*	3*	≥4†
G5	Kidney failure	<15	≥4†	≥4†	≥4†

CKD=chronic kidney disease. GFR=glomerular filtration rate; ACR=albumin creatinine ratio. Higher frequency monitoring is recommended for those categories at most risk of progression of CKD. Small fluctuations in GFR are common. Progression is considered to be a decline in GFR of ≥25% from baseline. Factors associated with progression include cause of CKD, level of GFR, concentration of albuminuria, acute kidney injury, age, sex, race or ethnicity, raised blood pressure, hyperglycaemia, dyslipidaemia, smoking, obesity, history of cardiovascular disease, and ongoing exposure to nephrotoxic agents. *Clinical practice guidelines suggest that clinicians discuss these patients with their local specialist nephrology service. †Clinical practice guidelines suggest that people in these categories are referred for specialist nephrology opinion. Data from the KDIGO CKD Work Group clinical practice guidelines.[102]

Table 1: **Classification of CKD, according to international guidelines**

underlying cause (panel and table 1).[1] When GFR is less than 15 mL/min per 1·73m² (category G5, table 1), a person has reached end stage kidney disease (ESKD), at which point kidney function is no longer able to sustain life over the long term. Options for patients with ESKD are kidney replacement therapy (in the form of dialysis or kidney transplantation), or conservative care (also called palliation or non-dialytic care). The focus of this seminar is on CKD, and not on kidney replacement therapies.

The burden of CKD is substantial. According to WHO global health estimates, 864 226 deaths (or 1·5% of deaths worldwide) were attributable to this condition in 2012. Ranked fourteenth in the list of leading causes of death, CKD accounted for 12·2 deaths per 100 000 people. Since 1990, only deaths from complications of HIV infection have increased at a faster rate than deaths from CKD. Projections from the Global Health Observatory suggest that although the death rate from HIV will decrease in the next 15 years, the death rate from CKD will continue to increase to reach 14 per 100 000 people by 2030.[2] CKD is also associated with substantial morbidity. Worldwide, CKD accounted for 2 968 600 (1·1%) of disability-adjusted life-years and 2 546 700 (1·3%) of life-years lost in 2012 (figure 1).

Epidemiology of CKD

The incidence and prevalence of end-stage kidney disease vary globally. More than 80% of patients receiving treatment for ESKD reside in countries with a large elderly population with access to affordable health care. Worldwide variations in the incidence and prevalence of CKD are less clear because data are mainly from cohort studies, which screen heterogeneous populations, estimate GFR using varying formulas, and measure proteinuria using variable methods (figure 1 and appendix). Despite these limitations, the prevalence of CKD is consistently reported to be around 11% in high-income countries, including the USA and Australia. The incidence, prevalence, and progression of CKD also vary within countries by ethnicity and social class. People in the lowest socioeconomic quartile have a 60% higher risk of progressive CKD than do those in the highest quartile. Black and Asian people in the UK, Hispanics in the USA, and Indigenous people in Australia, New Zealand, and Canada are at higher risk of developing CKD and of disease progression.[3] Untangling socioeconomic effects from effects of ethnicity can be challenging in societies in which disadvantage associates with racial background. Although socioeconomic status plays a specific role in the incidence and prevalence of CKD, it does not fully explain the increased risk for racial or ethnic minorities.

The causes of CKD vary globally (appendix). Diabetes and hypertension are the main causes of CKD in all high-income and middle-income countries, and many low-income countries. Diabetes accounts for 30–50% of all CKD and affects 285 million (6·4%) adults worldwide, though this number is expected to increase by 69% in high-income countries and 20% in low-income and middle-income countries by 2030. More than a quarter of the adult population was estimated to have hypertension in 2000 although this proportion is projected to increase by approximately 60% by 2025.[101] Observational studies consistently report increasing risk of developing CKD and more rapidly progressive CKD with worsening blood pressure control. In Asia, India, and sub-Saharan Africa, CKD from glomerulonephritis and unknown causes are more common. Herbal medicines used by rural populations in Asia and Africa have also become increasingly available in high-income countries with nephrotoxic effects resulting from consumption of toxic dosages of herbs or interactions with conventional medicines. Environmental pollution of water by heavy metals and of soil by organic compounds (including pesticides) have also been implicated in geographically localised epidemics of CKD (appendix).

HIV infection is endemic in sub-Saharan Africa, with kidney involvement varying between 5–83%. HIV nephropathy varies by race, affecting African-American

See Online for appendix

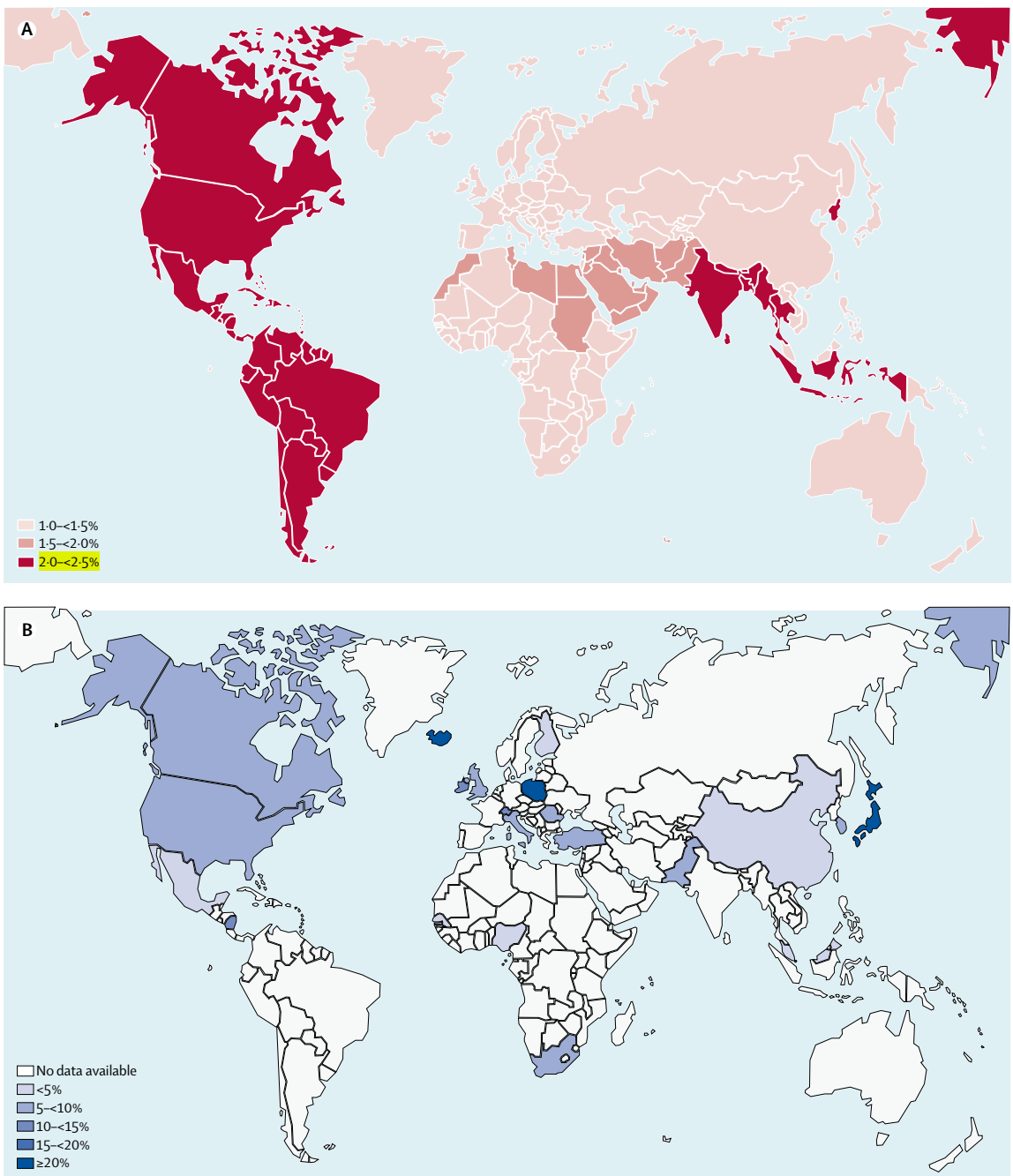

Figure 1: **Burden of kidney disease globally**
(A) Proportion of total mortality attributed to kidney disease. (B) Prevalence of chronic kidney disease. Chronic kidney disease was defined variably in different cohort studies; see appendix for specific details.

people more than white or Asian people. Antiretroviral therapies also have nephrotoxic effects including crystal deposition, tubular dysfunction, and interstitial nephritis. Hepatitis B and hepatitis C infections each affect 2–4% of the world's population and are both associated with severe kidney lesions and CKD.

Genetics and epigenetics

There are many single and polygenic causes of CKD. Some, such as the diseases that result in congenital abnormalities of the kidney and urinary tract, are evident from birth or early childhood, and others typically present later in life, such as autosomal dominant

polycystic kidney disease. Advances in genetic sequencing have permitted mapping of candidate genes for other hereditary CKD that have not yet been defined at the genetic level.[4]

People with genetic causes of CKD represent a few of the total number of patients with CKD. Other genetic factors contribute to inherited susceptibility to CKD and its progression, supported by familial clustering of kidney disease, differing prevalence of some causes of CKD across racial or ethnic groups, and variation in familial aggregation by race. This field is rapidly evolving, and genome wide association studies have identified several loci, genetic polymorphisms, and single nucleotide polymorphisms that might contribute to accelerated progression of CKD.[5]

There is also likely to be a strong environmental influence on susceptibility to CKD, separate from genetic risks. Epigenetic influence refers to changes in gene transcription and expression manifest in the phenotype that have not occurred through alteration in genotype, and which are heritable. Epigenetic mechanisms that mediate change include methylation of cytosine in DNA, chromatin remodelling (through histone modification), and presence of non-coding RNA. Epigenetics play a role in healthy physiological development as well as in disease, and might help explain susceptibility to obesity or type 2 diabetes—for example through so-called metabolic memory. There is mounting evidence that inflammation and oxidative stress, uraemia, and hyperhomocysteinaemia might induce changes in the epigenome that mediate fibrosis, and might be important in progression of CKD. Epigenetic influence is likely to be greater during development in utero and childhood than after CKD has developed (eg, via maternal drug use or diet in childhood), but might also mediate long-term changes in health and disease in response to environmental pressures at the population level (such as starvation and pollution). Exome capture and next generation sequencing techniques, together with advances in bioinformatics, have led to epigenome-wide association studies and the promise of more personalised medicine, in which treatments might be targeted to individuals with specific genetic and epigenetic profiles.[6,7]

Pathophysiology and risk factors for CKD

The final common pathological manifestation of many chronic kidney diseases is renal fibrosis. Renal fibrosis represents the unsuccessful wound-healing of kidney tissue after chronic, sustained injury, and is characterised by glomerulosclerosis, tubular atrophy, and interstitial fibrosis.

Glomerulosclerosis is prompted by endothelial damage and dysfunction, proliferation of smooth-muscle cells and mesangial cells, and destruction of podocytes that normally line the glomerular basement membrane. Risk factors for progressive glomerulosclerosis include hypertension, dyslipidaemia, and smoking. Glomerular microinflammation is initiated following activation of endothelial cells in response to hypertension, with inflammatory cells (including macrophages and foam cells) activating mesangial cells to proliferate. Transforming growth factor ß1 and other growth factors (including platelet-derived growth factor, fibroblast growth factor, tumour necrosis factor, and interferon gamma) stimulate mesangial cells to regress to mesangioblasts (immature mesangial cells). These mesangioblasts are capable of producing an excessive extracellular matrix, leading to mesangial expansion—an early sign of glomeruloscelrosis (appendix). Stretching of podocytes leaves areas of the glomerular basement membrane exposed to Bowman's capsule with which it forms adhesions, thus contributing to glomerulosclerosis.

Tubular atrophy, interstitial fibrosis, and scarring are closely associated with GFR and proteinuria. Tubular epithelial cells are stimulated to synthesise inflammatory products including reactive oxygen species and chemokines by various abnormally-filtered urinary proteins, including complement, cytokines, and albumin. These agents attract inflammatory cells into the renal interstitium and initiate interactions with interstitial myofibroblasts. As fibrosis evolves, injured tubular epithelia lose their regenerative capacity and undergo apoptosis leading to tubular atrophy and creating non-functional glomeruli. Histologically, measures of tubular cell area are closely associated with GFR.

Kidneys are metabolically highly active with a high oxygen requirement. Early in CKD injury, interstitial capillaries become increasingly permeable (the kidney capillary leak syndrome) meaning that many plasma proteins that normally never reach the renal interstitium are able to do so and trigger an inflammatory response. A progressive decline in the surface area of interstitial capillaries leads to hypoxia within the kidney and affects the function of cells usually involved in the degradation of collagen which is synthesised (and degraded by matrix metalloproteinases, serine proteases, the adamalysin [ADAMTS] family, and lysosomal enzymes) in healthy kidneys. Collagens (particularly fibrillar collagen I and II), basement membrane proteins, proteoglycans, and glycoproteins become deposited in the chronically-damaged kidney; the area of fibrotic interstitium affected is closely associated with both renal function and long-term renal prognosis.

Clinical presentation; signs and symptoms and uraemic toxins

Many people are asymptomatic of their CKD, and present after chance findings from screening tests—for example, through a routine medical examination or check-up—or not until they become unwell with advanced CKD. However, depending on the cause of CKD, some people have symptoms directly as a result of their impaired kidney function.

As CKD progresses, and kidney function becomes less effective, various substances known collectively as

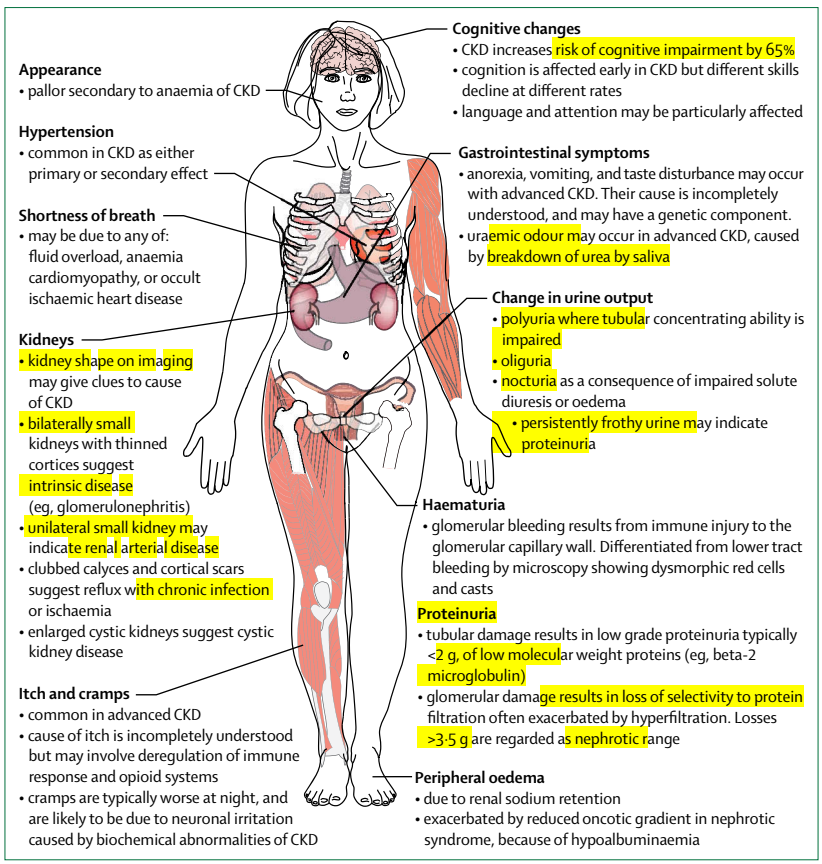

Figure 2: **Symptoms and signs of CKD**

uraemic retention solutes accumulate in the body, with those that exert adverse biological effects called uraemic toxins. Uraemic toxins have complex and incompletely understood biochemical and physiological effects, some mediated directly and some indirectly through interaction and alteration of the toxins themselves to form new compounds. They are thought to contribute to inflammation, immune dysfunction, vascular disease, platelet dysfunction and increased bleeding risk, dysbiosis in the gut including increased translocation of bacteria, altered drug metabolism, as well as CKD progression.[8,9] Retained solutes that accumulate can be broadly grouped into three, by their solubility, binding capacity and molecular size: small water soluble compounds such as urea, polyamines, guanidines, and oxalate; small lipid-soluble or protein-bound compounds such as homocysteine and indoles; and larger (over 500 Da) so-called middle-molecules which are poorly dialysed such as beta β2 microglobulin, parathyroid hormone, and advanced glycosylation end (AGE) products.[9,10]

Uraemic retention products affect nearly all body systems and organs, but do not always accumulate predictably, and their concentrations might not correlate with measures of kidney function.[10,11] Uraemic toxins are the focus of much research with the aim that their control or amelioration could mitigate the complications of CKD, or slow CKD progression, and reduce uraemic symptoms. Figure 2 illustrates possible signs and symptoms of CKD.

Differential diagnosis and diagnostic investigations

Glomerular filtration rate as a measure of kidney function

GFR can be measured indirectly as the renal clearance of exogenous filtration markers. The reference standard marker is inulin. Inulin is inert; does not bind to plasma protein; is freely filtered by the kidney; and does not undergo metabolism, tubular secretion, or reabsorption so is therefore rapidly excreted into the urine by glomerular filtration. Inulin is rarely used in practice because it is inconvenient and expensive, so other filtration markers are used, with choice mostly driven by local provision (appendix).[13,14] GFR is measured as the clearance of the exogenous marker after a single bolus injection of marker and can be based in plasma and urine concentration measurements (usually referred to as renal or urinary clearance), or in plasma concentration measurements alone (usually—somewhat misleadingly—referred to as plasma clearance).[14] Although plasma measurement obviates the need for timed urine collections and avoids the inconvenience and risks of indwelling bladder catheters, the trade-offs include increased bias and substantially reduced precision in clearance estimates.[15]

A simpler and cheaper method of monitoring change in kidney function is to use an endogenous filtration marker to estimate GFR through an algorithm, with results usually designated eGFR (appendix). The precision and accuracy of the eGFR cannot be any better than that of the marker selected. Common biomarkers used to estimate GFR are creatinine and cystatin C, and eGFR is routinely done by most pathology services. The prime limitation of use of biomarkers is that their measured concentrations vary for reasons other than differences in GFR.

Creatinine is a by-product of muscle metabolism, usually produced at a fairly constant rate and freely filtered by the glomerulus. Concentrations increase with decreasing GFR, but they are also increased by increased muscle mass. In an attempt to capture the variability in creatinine caused by muscle mass, eGFR estimating equations include variables such as age, sex, ethnicity, and body size as imperfect surrogate measures of muscle mass variation across populations. Additional factors influencing the creatinine concentration include meat intake or use of protein supplements, physical activity, tubular secretion, extra-renal excretion, and creatinine degradation, effects of which might change as GFR declines. These effects are often difficult to predict from easily obtained demographic or clinical variables and compromise accurate detection of true differences in GFR between people as well as changes within individuals over time. Several medications can

cause falsely raised creatinine concentrations because of drug-induced inhibition of tubular creatinine secretion (eg, trimethoprim, cimetidine, fenofibrate, or pyrimethamine); decreased breakdown by gut creatininase (eg, antibiotics); or interference with the assay technique (eg, cephalosporins, ascorbinic acid, methyldopa, levodopa, glucose, bilirubin, or flucytosine). Overall, performance of eGFR is generally poorer for populations outside of North America, Australia, and Europe, and accuracy decreases at the extremes in the distribution of age, body composition, and GFR.[16] Although most laboratories standardise assays to an international reference method (isotope-dilution mass spectrometry), variability exists between labs that use different assays and the results of GFR estimating equations depend on the assay used.[17]

Cystatin C is a low-molecular-weight protein produced in all nucleated cells which varies less by muscle mass and diet. However, cystatin concentrations are influenced by age and sex and appear to increase with corticosteroid use and inflammation, and also in smoking and hyperthyroidism.[12,14] Use of a combination of Cystatin C and creatinine for eGFR estimation might improve accuracy, especially for the lower ranges of GFR.

Notes on interpreting eGFR estimated with endogenous filtration markers

For estimating equations, the proportion of values of eGFR that lie within 30% of measured GFR reaches 75– 85% at best. Put differently, up to 25% of people will have estimates more than 30% above or below the measured GFR. For those with an eGFR of 10 mL/min per 1·73 m², up to a quarter will have a measured GFR less than 7 or more than 13 mL/min per 1·73 m². For those with an eGFR of 60 mL/min/1·73 m², up to a quarter will have a measured GFR less than 42 or more than 78 mL/min per 1·73 m² (figure 3). Some of the non-GFR determinants of creatinine can be taken into account by the clinician in interpretation of eGFR results (eg, for extremes in muscle mass the deviations can be guessed). However, other factors such as diet, and especially metabolism, cannot be estimated, causing unavoidable random variability and imprecision overall.

Renal creatinine clearance can also be measured on the basis of the concentration of creatinine measured in serum and in a timed (usually 24 h) urine collection. However, this is less practical, and there is convincing evidence that across the entire range of GFR and independent of patient characteristics, creatinine clearance overestimates GFR to a greater extent and is less precise than other methods for estimating GFR from the serum creatinine concentration alone.[15]

Proteinuria as measure of kidney damage

Healthy adults lose less than 150 mg of protein and less than 30 mg of albumin in urine every day. Persistent losses above these values could imply kidney damage

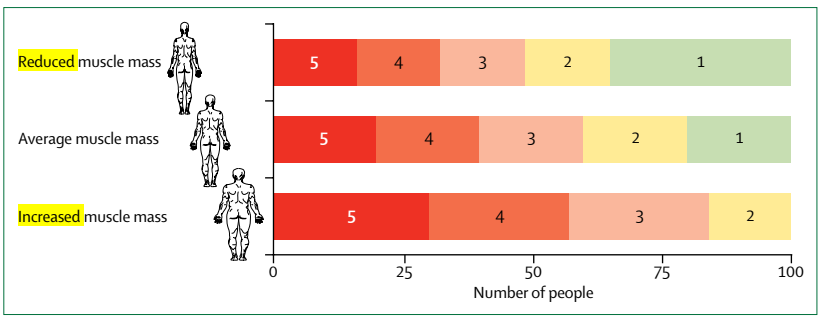

Figure 3: **Accuracy of estimating equations and implications for interpretation of eGFR in practice**
Influence of body composition and diet on GFR estimation and classification of CKD. All three bars contain 100 people with equal distribution of true GFR, categorised according to the KDIGO CKD classification in G5 to G1. The second bar represents the reference category with men and women of average muscle mass assuming estimated GFR equals true GFR. The first bar represents a group of people with a muscle disease, limb amputation, or general malnourishment. In this subgroup, creatinine generation can be low, causing systematic overestimation of the GFR regardless of the estimating equation used. The third category represents a group of bodybuilders and meat-eaters. In this group, serum creatinine generation can be high with systematic underestimation of the true GFR.

	Proteinuria	Total albumin/ creatinine ratio	RBC	RBC casts	WBC	WBC casts
Diabetic kidney disease	+	≥30 mg/g	–	–	–	–
Hypertensive kidney disease	±	0–1000 mg/g	–	–	–	–
Myeloma	±	..	–	–	–	–
Cystic kidney disease	-	..	±	–	–	–
Tubulointerstitial/obstructive kidney disease	±	≤1000 mg/g	–	–	+	+
Pyelonephritis	±	≥30 mg/g	–	–	+	–
Vasculitis	±	≥30 mg/g	+	+	–	–
Glomerulonephritis	+	>1000 mg/g	+	+	±	±

+present, –not present, ±might or might not be present. RBC=red blood cell. WBC=white blood cell.

Table 2: **Typical findings of proteinuria and urine sediment abnormalities in differential diagnosis of common causes of CKD**

with increased glomerular permeability allowing the filtration of macromolecules that should remain within the circulation (table 2). Transient elevations of albuminuria can occur with menstrual blood contamination, urinary tract infection, strenuous exercise, upright posture (orthostatic proteinuria), or other conditions that increase vascular permeability such as sepsis. Proteinuria is associated with an increased risk of ESKD and early death, and greater early reductions in proteinuria are associated with slower progression of kidney disease.[18] Either total urine protein or just the albumin part can be measured for calculation of total albumin loss or total protein loss, using various different methods.

The reference standard for measuring urinary protein loss is a timed 24 h urine collection of albumin.[19] More convenient methods used in routine practice involve urinary dipsticks or measurement of the albumin or total protein concentration in a spot urine sample. At the point of care, dipsticks have been used for more than 50 years to measure renal protein loss. These reagent

strip devices primarily detect albumin by a colorimetric reaction with the dipstick-impregnated reagent based on the albumin concentration within the sample. Some of these reagent strip devices simultaneously measure the creatinine concentration and come with automated devices capable of reading the colour changes of reagent strips. Using dipsticks for detecting glomerular albuminuria has two main limitations. First, most reagent strips are poor at detecting low grade but clinically relevant urinary albumin loss of 30–300 mg per day.[20] Second, tests are often falsely positive in situations of concentrated or highly alkaline urine, after use of iodinated contrast agents, or in case of gross haematuria.[21]

When using spot urine tests, albumin concentration is normalised for the urinary creatinine concentration to approximate 24 h albumin or protein loss, to account for hydration status and urinary concentration. People with body surface areas of 1·73 m² and healthy kidney function filter approximately 1 g of creatinine every 24 h, so a protein-to-creatinine ratio of 1 g protein per 1 g creatinine in an average-sized person approximates 1 g of proteinuria in 24 h. Similar to the limitations of measuring creatinine in serum, it is important to realise that creatinine excretion is dependent on both kidney function and muscle mass. A ratio of 2 g protein per 1 g creatinine in a muscular person who excretes 2 g creatinine in 24 h could in fact represent nephrotic-range proteinuria of 4 g per day. Similarly, that same ratio in a frail older woman with kidney disease who excretes 0·5 g of creatinine daily might represent 1 g of protein per day, and in this setting the spot ratio would overestimate her true proteinuria. Another important limitation is that urinary protein loss can vary substantially with the time of day, so morning samples are preferable.

Urine sediment; haematuria and pyuria

In addition to assessing GFR and proteinuria to identify the extent of chronic kidney damage, automated or manual microscopic examination of the urine sediment plays a central role in identifying underlying causes. Normal urine has up to four red blood cells and up to five white blood cells per high power field on microscopy. The presence of cells, casts, and crystals in the urinary sediment might give clues to the causes of underlying kidney disease. Glomerular disease can result in urinary red blood cells, whether visible or invisible to the naked eye, whereas white blood cells might be seen in tubulointerstitial nephritis or, along with haematuria, in various forms of glomerulonephritis.[22] Table 2 shows typical urinary sediment and proteinuria findings for some common causes of CKD.

Imaging studies

Renal ultrasound is generally considered the preferred first-line imaging technique for the assessment of people with previously undiagnosed kidney dysfunction. Long-standing kidney disease often results in small kidneys with increased echogenicity, which can help differentiate those with acute kidney injury. Ultrasound also differentiates between intrinsic causes of kidney disease and obstructive disease causing hydronephrosis. This technique can also identify congenital or hereditary kidney disease such as cystic kidney disease. Additionally, duplex can be useful to assess blood flow and renal artery stenosis. Other imaging techniques, such as isotope scans, CT, and MRI, can be informative in specific situations, but are not routinely used in diagnosing CKD.[23]

Percutaneous ultrasound guided kidney biopsy and pathology

In someone presenting with suspected CKD, percutaneous kidney biopsy might be required to establish a diagnosis, help guide therapy, and identify the degree of active and chronic changes. As with any invasive procedure, kidney biopsy has risks, including severe bleeding (occurrence around 1 in 1000 patients), requiring angiographic intervention (1 in 2000 patients), unilateral nephrectomy (1 in 10 000 patients) or even death (1 in 5000 patients) in a few patients, and benefits should be weighed against harms.[24] Transjugular or laparoscopic approaches for kidney biopsy are potential alternatives in patients at high risk of bleeding.

The kidney biopsy procedure uses a 14–18 gauge needle to take samples from the lower pole of the left kidney under direct visualisation, typically with ultrasound. The procedure uses local anaesthesia with disposable, automatic, spring–loaded devices, to obtain two cores of tissue, which are placed into medium for transport to the laboratory for examination. Biopsy specimens are processed and examined using light microscopy, immunofluorescence or immunohistochemistry, and electron microscopy. The light microscopy specimen is embedded in paraffin, cut in 2–3 μm thin slices and stained using several routine stains providing complementary information about the condition of the glomeruli and interstitium. A second specimen is either frozen and sectioned for immunofluorescence or embedded in paraffin and cut for immunohistochemistry. The slices are then incubated with monoclonal antibodies against immunoglobulins (IgA, IgG and IgM) and components of the classic or alternative complement pathway (C1q, C3c and C4) and κ-light chain and λ-light chain to visualise both location and pattern of deposition. Finally, a specimen can be kept for possible electron microscopy, which might be required for the definite diagnosis of a few underlying diseases such as Alport's disease, dense deposit disease, or minimal change nephropathy (appendix).[25]

Progression, complications, management and prognosis of CKD

Monitoring people with CKD could help to identify those patients whose CKD will progress and who might require kidney replacement therapy in the future. An

internationally validated risk prediction model based on age, sex, eGFR, and proteinuria might help to distinguish those at high versus low risk.[26] Over any five-year period, fewer than 2% of people with CKD progress to requiring treatment for ESKD, with 1·1% of people with CKD stage 2, 1·3% of people with CKD stage 3, and 19·9% of people with CKD stage 4 needing to start dialysis or have a kidney transplant.[27] However, there is increasing recognition that CKD is an important risk factor for other morbidity and for all-cause and cardiovascular mortality. The interaction of CKD with other chronic diseases and with mortality is entwined with the complications of CKD. People with CKD are five to ten times more likely to die than they are to progress to ESKD.[28] This increased risk of death rises exponentially with progressively worsening kidney function and is largely attributable to death from cardiovascular disease.[29,30]

Anaemia

Anaemia—typically normocytic, normochromic and hypoproliferative—is a common feature of CKD and prevalence increases as GFR declines. The kidney is the main source of erythropoietin (EPO), a glycoprotein hormone with a molecular weight of 34 kDa produced by interstitial fibroblasts around peritubular capillaries and proximal convoluted tubules. EPO stimulates red blood cell production in the bone marrow and drives haemoglobin homoeostasis. Although erythropoietin concentrations can be normal or slightly increased in people with anaemia of CKD, they are usually considered inappropriately low, with similarly anaemic patients without CKD having EPO concentrations 10–100 times higher. Uraemia-induced inhibitors of erythropoiesis, shortened red blood cell survival, and iron deficiency (from excess hepcidin impairing dietary absorption or functional iron deficiency from reticulendothelial cell iron blockade) can also contribute to the anaemia of CKD. Anaemia in CKD is associated with poor outcomes including reduced quality of life, increased incidence of cardiovascular disease, higher rates of hospital admission, cognitive impairment, and mortality.[31,32] Iron and recombinant erythropoietin and its synthetic derivatives (epoetin alfa, epoetin beta, darbepoetin alfa, methoxy polyethylene glycolepoetin beta; collectively known as erythropoiesis-stimulating agents [ESAs]) are widely used to treat anaemia and have been shown to reduce the need for blood transfusion in people with CKD, particularly when used in combination. However, correction of CKD-related anaemia to population levels is not beneficial. A systematic review[33] of 27 trials (10 452 participants) indicated that use of ESAs to target a higher haemoglobin (typically 120–150 g/L) was associated with increased risks for stroke, hypertension, and vascular access thrombosis compared with a lower haemoglobin target (95–115 g/L). No difference in the risks for mortality, serious cardiovascular events, or progression to ESKD were shown.[33] Treatment response with ESAs is often limited by iron deficiency, which is common in patients with CKD.[34] Oral iron is less expensive and more commonly used in early stages of CKD, though a systematic review of six trials[35] found that treatment with intravenous iron conferred a greater increase in haemoglobin, reduced ESA dosage requirement, and was not associated with any increased risks for all-cause death.

CKD mineral bone disease

The healthy kidney tightly regulates serum calcium and phosphate concentrations by regulating intestinal absorption (by converting Vitamin D to calcitriol) and renal tubular excretion (under the negative feedback control of parathyroid hormone). Mineral bone disease is a common complication of CKD and can show as any combination of: abnormalities of calcium, phosphate, parathyroid hormone (PTH), or vitamin D metabolism, which are usually recognised on abnormal biochemistry tests such as increased serum phosphate and PTH concentrations, while amounts of serum calcium might be low, normal, or increased; abnormalities in bone turnover, mineralisation, growth, or strength, which can manifest as bone pain or increased bone fragility; or extra-skeletal calcification (including blood vessels and skin) (figure 4). As CKD progresses, active vitamin D deficiency increases and results in hypocalcaemia and secondary (and eventually tertiary) hyperparathyroidism leading to stimulation of bone osteoclast activity. Resulting bone abnormalities are typically classified in terms of turnover, mineralisation, and volume, and typically manifest in ESKD after some years of dialysis treatment. However, subclinical changes in bone metabolism occur from much earlier stages of CKD, and some people have severe derangement at earlier stages of CKD.[36–38] Data from a study in 2013[39] indicate that bone-derived hormone fibroblast growth factor 23 and cofactor klotho might also be involved in bone abnormalities in CKD patients — particularly in the early stages of CKD, when adynamic bone disease (characterised by low bone turnover) appears to predominate.

Treatment guidelines recommend dietary restriction of phosphate and the use of either calcium or non-calcium-based phosphate binders to obtain serum phosphate concentrations of between 0·87 mmol/L and 1·49 mmol/L.[40] A systematic review[41] of 60 trials found that although sevelamer hydrochloride reduced serum phosphate and PTH significantly more than calcium-based agents, use of sevalamer was associated with a higher risk of gastrointestinal side-effects but lower risk of hypercalcaemia. There was no significant reduction in all-cause mortality with sevelamer hydrochloride compared with calcium-based phosphate binders.[41] The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guideline recommends that oral activated vitamin D treatments are given to people with CKD stage 3 and 4 when serum calcitriol concentrations are replete (>30 ng/mL) and serum PTH amounts are above normal ranges. Although

treatment with active vitamin D might be associated with increased serum phosphate and calcium concentrations, a meta-analysis of 16 studies[42] found that vitamin D compounds significantly reduced serum PTH (mean difference –22·3 pmol/L; 95% CI –34·0 to –10·7) with no effect on the risk of progression to ESKD (risk ratio 1·34; 95% CI 0·34–5·24).

Metabolic acidosis is another commonly encountered feature of CKD because of the reduced capacity of the damaged kidney to synthesise ammonia and excrete hydrogen ions. Bone disease, skeletal muscle wasting, and progressive GFR loss are thought to be consequences of chronic metabolic acidosis; guidelines recommend serum bicarbonate be maintained at a concentration of 22mEq/L to lessen these complications.[40] To date, there is no randomised trial evidence that alkali therapy improves bone density in patients with non-dialysis-dependent CKD. However, in people with ESKD on haemodialysis, oral sodium bicarbonate supplementation decreases the progression of secondary hyperparathyroidism in patients with high bone turnover, and reduces stimulated bone turnover in patients with low bone formation.

Cardiovascular disease

Cardiovascular mortality is estimated to be 57% higher in people with a GFR less than 60 mL/min per 1·73 m² and 63% higher in people with micro-albuminuria compared with people without CKD.[43, 44] The risk of having a non-fatal myocardial infarction is increased by 33% when GFR is less than 60 mL/min per 1·73 m² and by 48% with micro-albuminuria, with risk of both myocardial infarction and cardiovascular death increasing as GFR declines and quantity of albuminuria increases.[45,46] Similarly for cerebrovascular disease, a large systematic review and meta-analysis of 83 studies[47] including data for 30 392 strokes among 168 516 participants found that there was an inverse linear association between GFR and risk of stroke and a dose-response association between albuminuria and stroke risk. Stroke risk increased by 7% for every 10 mL/min per 1·73 m² decrease in GFR and by 10% for every 25 mg/mmol increase in albumin: creatinine ratio. Although there have been several attempts at developing risk prediction models for estimating an individual's future risk of these outcomes, none has yet been sufficiently validated in external cohorts or across different ethnicities to allow acceptable confidence in its ability to provide accurate predictions to improve clinical decision making and patient outcomes.[26]

Clinical practice guidelines recommend antiplatelet treatment approaches similar to that of the general population in individuals with CKD and acute coronary syndromes and CKD.[48] However, a systematic review of 50 studies[49] with 27 139 participants with CKD found that although antiplatelet agents were effective at reducing the risk of further myocardial infarction by 13%, they had uncertain effects on cardiovascular and all-cause death and the risk of stroke. Treatment with antiplatelet agents was also associated with a 33% increased risk of major bleeding and a 49% risk of minor bleeding events, meaning that among people with lower risk of vascular events (CKD stages 1 and 2) the harms of antiplatelet treatment might exceed the benefits. For hyperlipidaemia, variations between international guidelines reflect uncertainties in the effectiveness of statins among people with CKD.[50] In a systematic review of 80 trials[51] including 51 099 participants, statins were shown to reduce all-cause mortality by 19%, cardiovascular mortality by 22%, and cardiovascular events by 24% in people with CKD not receiving dialysis. Statins effectively reduced total and low-density cholesterol concentrations and proteinuria but had no effect on slowing progression of CKD. For blood pressure, current guidelines recommend a target of less than 130/80 mm Hg for patients with CKD.[52,53,40] A meta-analysis of 11 trials[54] providing data on 9287 patients with CKD found that intensive blood pressure lowering in people with CKD reduced the risk of progression to ESKD by 21% but only among people with proteinuria. Intensive blood pressure control had no effect on cardiovascular outcomes or death. Angiotensin converting enzyme inhibitors (ACE inhibitors) reduce vascular events in the general population when used in secondary prevention regimens.[55] Although ACE inhibitors were found to reduce all-cause mortality in people with diabetic nephropathy in one systematic review[57] of 43 trials of 3331 people with CKD, for people with CKD stages 1–3 without diabetes another systematic review[56] of four trials of 2177 people found no benefit from ACE inhibitors on all-cause mortality. Neither review found any reduction in the risk of cardiovascular events or risk of progression to ESKD with ACE inhibitors.[56, 57]

Cancer

Population based cohort studies have indicated that people with ESKD on dialysis have an excess cancer risk of 10–80%, whereas kidney transplant recipients have between a 1·9–9·9 times increased risk of cancer compared with the general population.[58] Cancer risk differs by cancer site, with cancers of the renal tract and thyroid particularly increased. After transplantation, rates of cancers associated with immune deficiency and with virus infection, including genitourinary sites, Kaposi sarcoma, lymphoma, melanoma, and cancers of the head and neck, increase substantially.[59] There is no evidence of increased risk of breast or prostate cancer for people with ESKD, regardless of their renal replacement therapy. The cause of the risk increases is likely to be multifactorial and the relative contribution of each factor might affect cancer sites differently. Potential factors include the cause of CKD, exposure to immunosuppressive agents, acquired renal cystic disease, and immune dysregulation caused by chronic uraemia. For people with less advanced CKD, sex differences in cancer risk might exist; men (but not women) have a 17% increased risk of

cancer with every 10 mL/min per 1·73 m² decline in GFR. Men with moderate CKD (GFR<55 mL/min per 1·73 m², estimated to affect approximately one third of the male population) have a 39% increased risk of cancer compared with healthy men.[60] Presence of proteinuria might also increase cancer risk; those with an albuminto creatinine ratio (ACR) of more than 1·11 mg/mmol had a 57% higher risk of developing cancer than people with an ACR less than 0·34 mg/mmol.[61] Considering cancer mortality, data from two cohort studies suggest a graded association between severity of CKD and cancer mortality. An Australian study[62] found that for every 10 mL/min per 1·73 m² reduction in GFR there was an 18% increase in cancer-specific mortality, whereas a Taiwanese study[63] of 123717 adults showed a significant increase in cancer mortality with a decreasing GFR in progressive stages of CKD (p=0·004), particularly for liver and urological cancers (p<0.001).[62,63]

Despite the increased cancer risk among people with CKD, enhanced cancer screening beyond that offered to the general population is not currently recommended. This is because cancer screening implies that the benefits of early detection and access to treatment will improve survival, whereas in CKD populations there is considerably increased mortality from other causes, and higher risks of adverse events and toxicity from treatments. There is also suggestion that cancer screening tests perform differently in people with CKD, and so test outcome might not be generalisable. There are similar concerns about diagnostic imaging and monitoring in people with CKD.[64]

Renal replacement therapy and kidney transplantation

Most people reaching ESKD are treated with either haemodialysis or peritoneal dialysis, with a global prevalence of 280 per million people, compared with 65 per million people who have a functioning kidney transplant. Five-year survival of people with ESKD on dialysis is between 13% and 60% lower than people in the general population of similar ages.[65] Approximately 56% of people with ESKD on dialysis are actively waiting for a kidney transplant, but demand outstrips availability, so only 25% receive a kidney whereas 6% die while waiting for a transplant each year.[66,67] Comparing outcomes in people treated with dialysis to kidney transplant recipients, a systematic review of 110 cohort studies[68] found reduced mortality, cardiovascular events, and better reported quality of life among kidney recipients.

Quality of life in CKD

Health-related quality of life refers to patient-reported outcome measures of how disease and treatment affect a patient's sense of subjective wellbeing. A patient's health-related quality of life is influenced by their lived experience of illness across a broad range of dimensions. These dimensions, often called domains, might include: symptoms of CKD and other comorbid conditions; side-effects from medicines or medical treatment; physical functioning; role functioning; psychological, social, sexual, and cognitive functioning; satisfaction with care; financial status; and spiritual wellbeing. Understanding health-related quality of life outcomes is especially important in CKD as this measure can be an independent predictor of disease progression as well as cardiovascular and all-cause mortality.[69] CKD patients have much lower health-related quality of life than those in the general community, yet quality of life is so important to them that some patients might decline new treatments if they are perceived to reduce quality of life, even when a survival benefit is present.[70]

Most health-related quality of life data have been obtained among patients with ESKD, receiving either dialysis or kidney transplantation. Fewer studies have been done in less advanced CKD stages, although a consistent reduction in quality of life has been shown as GFR decreases.[71–74] One large cross-sectional population-based study[75] of Korean community dwellers with CKD reported a 2% reduction in health-related quality of life for stage 2 and stage 3a CKD, a 5% reduction for stage 3b, and a 7% reduction for stage 4 or 5, compared with stage 1. A meta-analysis[71] reported a quality of life weight of 0·79 (95% CI 0·70–0·89) for pre-dialysis CKD patients on a zero to one (death to full health) scale.

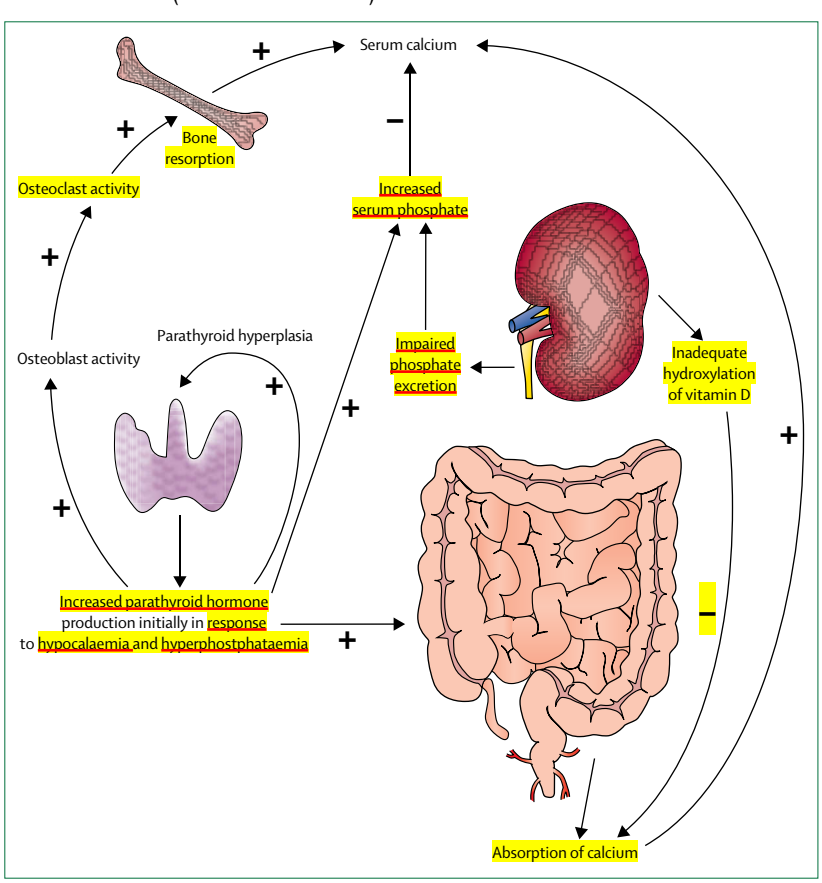

Figure 4: Pathophysiology of CKD mineral bone disease

CKD can affect a patient's health-related quality of life in many ways. The diagnosis alone might cause fear or anxiety. Symptoms of CKD such as hypertension, fluid retention, bone pain, peripheral neuropathy, itch, or sleep disturbance, and side-effects from medicines, can all negatively affect wellbeing and everyday roles and activities (figure 4). Anaemia, frailty, coexisting comorbidities, and depression are also major contributory factors to quality of life in CKD. Some patients with advanced CKD report a health-related quality of life equivalent to those with a terminal malignancy.[72]

Health-related quality of life is best measured using a validated instrument, commonly a questionnaire. Generic instruments enable comparison with the general population and other groups but can be insensitive to the effect of disease-specific symptoms. Common generic tools are The Medical Outcomes Study Short Form 36 (SF-36) or the EuroQol 5 instrument (EQ-5D). Disease-specific instruments are more sensitive to relevant symptoms but cannot be used for comparison with other populations. Common disease-specific instruments include Kidney Disease Quality Of Life—short form (KDQOL-SF). Health-related quality of life data can be obtained for use in research, such as in clinical trials of intervention efficacy, or used in clinical practice to highlight relevant symptoms and changes in symptoms, promote patient engagement in treatment, and improve patient outcomes.[76] These data have been used as an indicator of the quality of dialysis provision, and more recently have been routinely collected within renal registries.[76]

Modest improvements in health-related quality of life can be achieved when the underlying cause can be addressed. There is some evidence that interventions targeting specific symptoms, or aimed at supporting educational or lifestyle considerations, do make a positive difference to people living with CKD (appendix).

Cognitive effects of CKD and health literacy

Cognitive impairment is the deterioration in cognitive function beyond that which might be expected from normal ageing and is usually chronic and progressive. People with CKD have an increased risk of cognitive impairment compared with people without CKD.[77] The pattern of cognitive impairment appears to be different from normal ageing, with some evidence that orientation and attention and executive function are more affected.[78] Cognitive skills are needed to access health services; process, understand, and recall written and spoken information; and assimilate and express decisions about health care. Impaired cognition has been linked to reduced health literacy, decreased medication adherence, impaired physical and mental health, and a greater risk of death. Low health literacy is common in CKD, and affects people's capacity to navigate the health-care system.[79] People with reduced health literacy have limited ability to self-manage their care, participate in shared decision making, adhere to treatment and medication plans, and monitor lifestyle factors such as diet and exercise. There is evidence that clinician–patient communication fails to accommodate these aspects of CKD.[80] Decreased health literacy and cognitive impairment are associated with reduced quality of life.

Health service implications of CKD

Equity of access to specialist care and medicines

Recent studies have[81–85] found differences in access to specialist CKD services (eg, to nephrologists or tertiary renal units) on the basis of differences in individual patient characteristics. A Canadian study[81] reported Aboriginal people with severe chronic kidney disease (ie, eGFR<30 mL/min/1·73 m²) were 43% less likely than non-Aboriginal people with severe chronic kidney disease to visit a nephrologist (hazard ratio [HR] 0·57, 95% CI 0·39–0·83). Similarly, an Australian study[82] reported reduced access to kidney transplantation and reduced access to palliative care services for Indigenous compared with non-Indigenous patients. A US Department of Defense study[83] examining the quality of CKD care for stage 3 and 4 patients found monitoring of low density lipoprotein cholesterol was significantly less common among black people versus white; and patients categorised as other races were less likely to achieve targets for monitoring of phosphorous, haemoglobin, and vitamin D. However in this study, black people were more likely than white people to have their hypertension treated with ACE inhibitors or angiotensin II receptor blockers, and there was no significant difference in the prescription of statins for those with known hypercholesterolemia. Other US studies[84,85] have examined the effect of health insurance status on the prescription of antihypertensives for people with CKD. These studies reported that uninsured people were less likely to be treated for their hypertension (OR, 0·59; 95% CI, 0·40–0·85) and less likely to receive recommended therapy with angiotensin inhibitors (OR, 0·45; 95% CI, 0·26–0·77) compared with those with insurance coverage.

Differences in how and when services are accessed also affects patient outcomes. A Cochrane review[86] of the effect of early referral to a nephrologist versus late referral reported significantly reduced mortality and admission to hospital and better dialysis preparation with early referral. However, both nephrologists and non-nephrology physicians managed blood pressure, lipid profile, and early complications of CKD equally well. Data from 2012[84] indicate that socially disadvantaged adults with CKD are more likely to use acute care services (ie, emergency department visits) for CKD treatment (p<0·001) than housed counterparts.

Cost-effective interventions in CKD

Evidence of economic benefit is frequently required in decision making about whether a new treatment or

programme should be adopted and reimbursed. Cost-effectiveness analysis, which refers to a formal and systematic assessment of resource use (costs) and effectiveness (health benefits such as quality adjusted survival), can provide such evidence. Several economic evaluations have been undertaken in CKD for preventive, diagnostic, and treatment interventions. The results from full economic evaluations that reported an aggregated outcome in the form of an incremental cost effectiveness ratio (or incremental net benefit) for survival or quality adjusted survival (QALY) are shown in the appendix. An intervention was deemed to be cost -effective at a willingness to pay of US$50 000 per quality-adjusted life-year gained.

Funding and reimbursement issues—financing care for CKD

Although it is not possible to provide a global overview of the private and government funding arrangements for CKD in this paper, as health systems in every country, state, and province differ markedly, it is worth noting a few important points. First, many services for ESKD (such as the US Medicare ESRD Act), do not provide coverage to people who are non-dialysis dependent (ie, pre-ESKD). This lack in provision has implications for the funding and reimbursement of treatment programmes and medicines (such as anti-hypertensives) designed to prevent or slow progression of CKD. Patients often need to take out private health insurance for CKD care, or pay out-of-pocket for these treatments. Second, there has been change in the past decade in many countries to incentivise performance, rather than pay CKD service providers a fee for service.[87] This incentivising means setting a rate of reimbursement to individual primary care doctors, specialist clinicians, or health districts for achievement of particular CKD quality targets, and delivering care according to clinical practice guidelines. This realignment of payment aims to reward improved patient outcomes—for example, prescribing recommended anti-hypertensive medicines and achieving good blood pressure control in CKD patients. An evaluation of this funding model in the UK reported a significant reduction in hypertension among CKD patients (from 146/79 mm Hg to 140/76; p<0·01) in the first 2 years after implementation of the pay-for-performance scheme.[88] In the US in 2010, Medicare introduced reimbursement for up to six one-hour kidney disease education sessions for patients with stage 4 CKD. The aims of the education were to inform patients about management of comorbidities, prevention of uraemic complications, and provide information about ESKD treatment options to promote informed decision making. An assessment[89] after 1 year found 60% of US renal centres (predominantly large rather than small or mid-size) adopted the programme for all patients regardless of insurance status. Assessment of the effect on patient outcomes is ongoing.

Controversies and uncertainties in CKD

Although the CKD diagnostic framework encompassing a chronic change in GFR and evidence of renal structural damage was aimed at identifying people who would go on to have poor outcomes through unrecognised or late presentation for advanced kidney disease, not all people who meet the CKD criteria have these outcomes.[90] Although the relative risk of death and progression to ESKD on average increases with decreasing eGFR and increasing proteinuria, people within the same CKD classification can have very different absolute risks and there is substantial overlap between the categories.[91, 92] Applying the modern CKD classification at the population level found as many as one in six adults categorised as having CKD.[93] There is justifiable debate about the effect of labelling otherwise well people without modifiable risk factors with a diagnosis of CKD in terms of psychological effects and costs to health services.[94] Deciding who should be monitored, and how often, is a common dilemma for clinicians. A recent well-validated risk prediction model accessible online that uses four variables (age, sex, eGFR, and proteinuria) might help distinguish those at high from those at low risk of progression to CKD.[95]

Although over-diagnosis of healthy people as having CKD is one problem, there is growing awareness that diagnostic tests for other diseases common in CKD might be less reliable when used in people with CKD, such as tests that rely on intact functioning of the immune system—eg, the tuberculin skin test loses sensitivity to detect latent tuberculosis in people treated with dialysis.[96] In diagnosis of cardiac ischaemia, using general population normative distributions for troponin when interpreting tests for people with CKD might also be unreliable. In CKD, troponin concentrations can be persistently and variably increased for reasons other than acute ischaemia, such as cardiac injury due to chronic structural heart disease, or reduced clearance.[97] Cardiac imaging tests can also lose both sensitivity and specificity because of an attenuated response to diagnostic vasodilators or reduced coronary flow reserve in people with CKD.[98]

Despite potentially having most to gain, people with CKD are among the least likely to be included in trials of interventions to prevent and treat diabetes, cardiovascular disease, and cancer, with up to 75% of trials excluding people with CKD.[99] As a result of their exclusion in clinical trials, interventions are relatively untested in people with CKD, and extrapolating benefits from the general population to the CKD population can be problematic.[100] Altered drug absorption, metabolism and excretion, potential for increased toxicities, and interactions with medications prescribed for multiple other conditions means that the balance of benefits and harms of treatments might be different in people with CKD than among the general population.

Contributors
All authors did the literature search and were involved in the compiling of tables and figures; ACW structured the seminar and interpreted data from the literature. ACW wrote the first draft. EVN, RLM, and PM edited the first draft. All authors were involved in editing further drafts of the manuscript. ACW finalised the manuscript.

Declaration of interests
ACW is an editor for Cochrane kidney and transplant (unpaid role), and is Funding Arbiter for Cochrane (unpaid role). Several Cochrane reviews have been referenced in this submitted work. EVN, RLM, and PM have nothing to disclose.

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