# Evolving importance of kidney disease: from subspecialty to global health burden

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# Evolving importance of kidney disease: from subspecialty to global health burden

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**In the past decade, kidney disease diagnosed with objective measures of kidney damage and function has been recognised as a major public health burden. The population prevalence of chronic kidney disease exceeds 10%, and is more than 50% in high-risk subpopulations. Independent of age, sex, ethnic group, and comorbidity, strong, graded, and consistent associations exist between clinical prognosis and two hallmarks of chronic kidney disease: reduced glomerular filtration rate and increased urinary albumin excretion. Furthermore, an acute reduction in glomerular filtration rate is a risk factor for adverse clinical outcomes and the development and progression of chronic kidney disease. An increasing amount of evidence suggests that the kidneys are not only target organs of many diseases but also can strikingly aggravate or start systemic pathophysiological processes through their complex functions and effects on body homoeostasis. Risk of kidney disease has a notable genetic component, and identified genes have provided new insights into relevant abnormalities in renal structure and function and essential homoeostatic processes. Collaboration across general and specialised health-care professionals is needed to fully address the challenge of prevention of acute and chronic kidney disease and improve outcomes.**

## Introduction

More than 50 years ago, nephrology emerged as a medical subspecialty dealing with the effects of severely impaired kidney function on body homoeostasis. At that time, the understanding of renal physiology and the complex and diverse involvement of kidney function on various body functions was ahead of its clinical application. Few options to treat renal disorders of mineral and electrolyte handling existed, hormonal deficiencies resulting from kidney disease could not be corrected, and almost no techniques were available to prolong the life of individuals with kidney failure.

Nephrology progressed gradually with the establishment of renal pathology and a better understanding of disease entities, but the first major change occurred when dialysis and transplantation became widely available in the 1960s. The ability to provide life-sustaining renal replacement therapy was an outstanding achievement in medicine. Unsurprisingly, nephrologists have since strived to optimise renal replacement therapy and the prevention and treatment of comorbidities in patients with renal failure. However, the costs associated with these achievements are high. In countries that can afford to offer renal replacement therapy to all patients with renal failure, the proportion of health-care expenditure for this group of patients is far out of proportion to its size.[1,2] In most countries, economic constrains allow only restricted access to this expensive chronic treatment, which creates striking social inequalities and pressure on constrained health-care resources.[3]

By contrast with the importance and obvious relevance of chronic kidney failure requiring replacement therapy, the effect of less severe chronic kidney disease, which affects far more patients, had for a long time been largely ignored by the medical community, policy makers, and the public. Reduced kidney function was thought to be of little importance until the glomerular filtration rate reached less than 15%. This viewpoint resulted in two sets of terms to distinguish between patients with so-called end-stage renal disease and others with a lesser degree of renal impairment, who were often collectively summarised as pre-end-stage renal disease or pre-dialysis patients. Moreover, numerous vague and poorly defined terms were commonly used (eg, renal insufficiency or pre-uraemia) in parallel to nomenclature

describing the cause of kidney disease (eg, glomerulonephritis, polycystic kidney disease, or diabetic nephropathy). However a uniform and unequivocal definition of chronic kidney disease was unavailable.

Only in 2002 did the medical community first agree on a uniform definition and staging system for chronic kidney disease, based on measures of kidney function and independent of the cause of impaired kidney function.[4,5] Application of this uniform concept to large databases showed that chronic kidney disease is far more frequent than was appreciated previously.[6] More than 10% of people have chronic kidney disease and the overall prevalence at least equals that of diabetes.[7] As with many other chronic diseases, the prevalence of chronic kidney disease increases with age, exceeding 20% in individuals older than 60 years and 35% in those older than 70 years.[8] The importance of chronic kidney disease became apparent when large analyses showed that even early-stage disease is associated with increased prevalence and severity of numerous disorders and adverse outcomes. In particular, chronic kidney disease is now recognised as a very relevant and independent cardiovascular risk factor (see paper 5 in this Series).[9,10]

Similar considerations hold true for acute changes in kidney function. Acute renal failure was well known to be associated with poor prognosis, but was regarded as harmless and reversible for a long time, provided patients survived the critical condition during which it occurred. However, even small, transient changes in serum creatinine (suggesting temporary decreases in glomerular filtration rate) have been associated with significantly worsened prognosis, including a strikingly increased risk of mortality and development and progression of chronic kidney disease.[11,12] After several initiatives were undertaken, a uniform definition and staging of what is now known as acute kidney injury was developed, which could potentially further advance the specialty.[13]

These developments, which were not based on technical, surgical, or immunological progress, but rather on a consensus for a uniform terminology and its application with rigorous epidemiological methods, has greatly expanded the focus on kidney disease beyond nephrology. Standardised terminology has stimulated research, affected patient care, and influenced public policies. And, as for any major advancement, it has also raised new questions. The seemingly most straightforward, but most pressing, of these questions are why is kidney disease so frequent and why is it associated with such a poor prognosis? To answer these two questions, researchers might need to return to the physiology of the organ to better understand why the kidney is a frequent target of many chronic disturbances and why, conversely, disorders of kidney function affect extrarenal tissues so strikingly, in particular the cardiovascular system. Aspects of renal function generally accepted to be understood need to be revisited. Additionally, linkage of the new definitions and staging of acute and chronic kidney disease with genomic, proteomic, and metabolomic information offers new opportunities to understand underlying mechanisms of disease.

Here, we aim to review the central role of the kidney for body homoeostasis and its fate as a target organ of disease. We will also describe the current definitions and staging systems for chronic kidney disease and acute kidney injury, and advances in understanding of the genetic predisposition to kidney disease. Subsequent articles in this series will focus on the global effects, clinical consequences, and management of chronic kidney disease[14] and acute kidney injury;[15] the link between kidney disease and cardiovascular disease;[16] the effects of maternal, neonatal, and child health on kidney health;[17] and future perspectives of the specialty.[18]

## The kidney and body function

Each kidney contains about 1 million functional units, nephrons, consisting of numerous specialised cell types originating from distinct embryological lineages (figure 1). Each nephron contains a filtrating body, the glomerulus, and a long tubule made of a dozen differentiated segments. The final parts of these tubules are interconnected to form the collecting ducts, which open into the renal pelvis.

The basic principles of kidney physiology dictate the central role played by this organ in excretory, metabolic, and endocrine functions. Although the kidneys excrete only about 1·5 L of urine daily, they are perfused with 20% of the cardiac output and form about 180 L of ultrafiltrate every day, which is profoundly modified during tubular passage. This function exposes the kidney to the interior milieu unlike any other organ and at the same time makes the body composition very sensitive to changes in kidney function.

The glomerular filtration barrier consists of the fenestrated endothelial cells, an elaborate basement membrane, and an intricate layer formed by the foot processes of highly differentiated epithelial cells called podocytes.[19] The filtration barrier is permeable to water, small solutes, and low-molecular-weight proteins up to the mass of albumin, but largely precludes the filtration of plasma proteins with a mass of more than 60–70 kDa, especially if they are negatively charged. Thus the glomerular filtration rate, the product of the filtration area, the hydraulic permeability, and the net ultrafiltration pressure, yields a large ultrafiltrate containing plasma solutes and several grams of low-molecular-weight proteins. Any disturbance in glomerular haemodynamics or structure can result in reduced glomerular filtration rate or increased leakage of proteins into the urine—two classic signs of renal disease.

Along the tubular segments of the nephron, the ultrafiltrate undergoes a series of modifications with massive reabsorption of low-molecular-weight proteins, solutes, and water, secretion of a gel-like protein called uromodulin (Tamm-Horsfall protein) and elimination of excess potassium, acids, and bases (figure 1).[20]

The processes affecting urine composition are mediated by polarised transport systems operating in the epithelial cells lining the tubules. The proximal tubule reabsorbs the bulk (about two-thirds) of filtered solutes and water. In addition the cells lining these tubules possess multiligand receptors involved in the endocytic uptake of filtered proteins that include hormones, carrier proteins (eg, for vitamins), and enzymes. Once reabsorbed, these proteins are metabolised by proximal tubular cells, as the human urine is virtually devoid of plasma proteins under physiological conditions. This massive uptake of proteins plays an important role in metabolic clearance, hormone homoeostasis, and conservation of essential vitamins (vitamin D, vitamin A, and vitamin B12), and provides a protein-free milieu for the cells lining distal nephron segments.[21] Organic molecules and drug metabolites are secreted into the urine via specific transporters located in the last part of the proximal tubule.

The tubule segments forming the loop of Henle generate the hypertonic environment in the medulla, necessary for concentrating the urine, and mediate the paracellular reabsorption of $Ca^{2+}$ and $Mg^{2+}$ under the control of the $Ca^{2+}/Mg^{2+}$-sensing receptor.[22] Specialised epithelial cells, located at the junction between the thick ascending limb of the loop of Henle and the distal nephron (macula densa) sense the tubular NaCl concentration and interact with renin-containing granular cells in the afferent arterioles to regulate the glomerular blood flow through a mechanism called tubuloglomerular feedback.[23] The distal nephron, which includes the distal convoluted tubule, the connecting tubule, and the collecting ducts, is responsive to aldosterone and vasopressin and regulates the final urine composition and concentration.[24] Several tubular transport processes can be targeted by specific drugs, including diuretics, aquaretics, calcimimetics, and the more recently developed inhibitors of glucose reabsorption.[25]

Excretory, metabolic, and endocrine functions of the kidney mediate essential interactions with several organs, sustaining an array of vital functions (figure 2), including regulation of body water and thirst, blood pressure, ventilation, drug metabolisation, potassium balance, erythropoiesis, calcium and phosphate metabolism, and acid-base homoeostasis.

The regulation of NaCl excretion, which is crucial for extracellular fluid volume and blood pressure control, is influenced by the renin-angiotensin-aldosterone system, the atrial natriuretic peptide, the sympathetic nervous system and, to a lesser extent, the antidiuretic hormone arginine vasopressin.[26] Renal excretion of potassium is mainly dependent on the distal tubular flow rate and the release of aldosterone and its action on the principal cells of the distal nephron. The regulation of body water content (osmoregulation) involves the action of vasopressin on aquaporin-mediated transport of water.[27,28] The regulation of the phosphorus and calcium balance reflects complex interactions between bone, parathyroid glands, intestine, and tubular segments, involving fibroblast growth factor (FGF) 23, klotho, parathyroid hormone, and vitamin D.[29,30] The kidney is also a main site of systemic oxygen sensing, regulating the oxygen supply to red blood cells and hence tissue oxygen supply by hypoxia-inducible erythropoietin production in peritubular fibroblasts of the renal cortex.[31]

Apart from control of body homoeostasis, the kidney is also involved in immune function. Dendritic cells and macrophages, which form a network in the renal interstitium, contribute to innate and adaptive immunity and are increasingly recognised for their sentinel role against kidney injury and infection and their potential contribution to progression of kidney disease.[32] The renal tubule epithelial cells also express Toll-like receptors (TLRs), including TLR4, of the innate immune system and could be involved in triggering an innate immune response to bacterial and viral infections or ischaemic stress.[33]

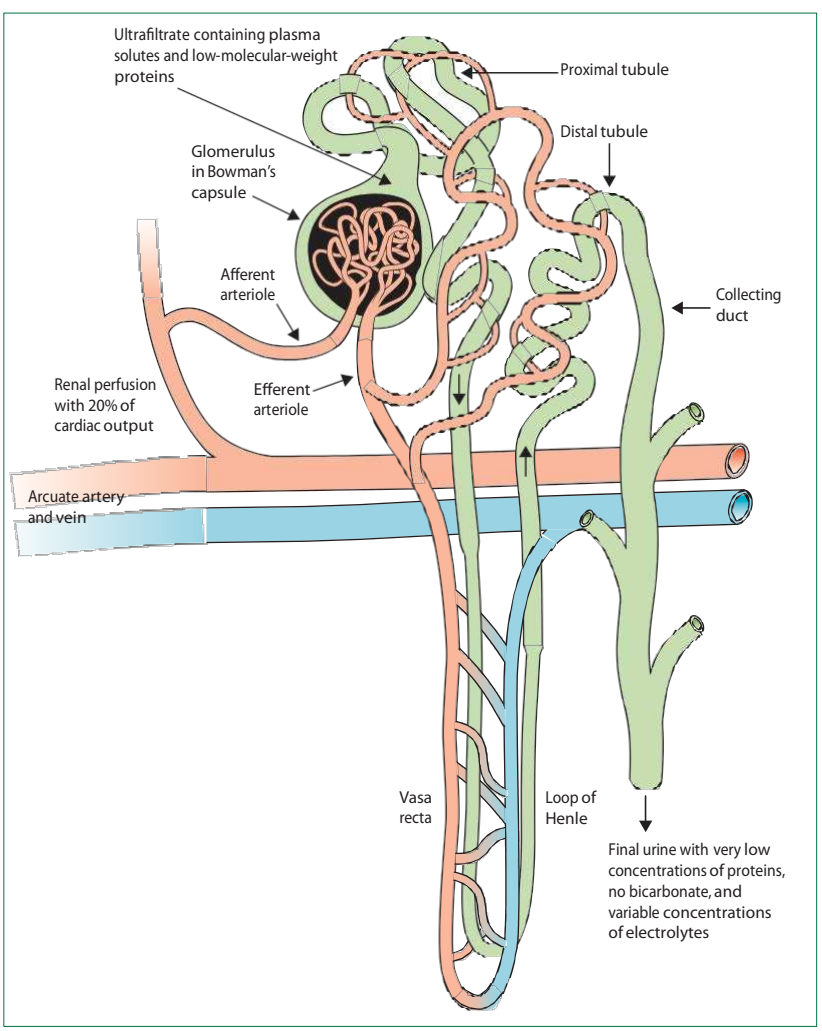


*Figure 1:* Structure of the nephron

## Kidney disease

The present definition and staging of chronic kidney disease and acute kidney injury were proposed by independent guideline development workgroups.[13,34] The criteria were based on, or were partly validated by, major research efforts that have revolutionised the understanding of outcomes of kidney disease. The foundation for the definition and staging systems is the strong, graded, and consistent association of measures of abnormalities in kidney structure and function with clinical prognosis, independent of age, sex, ethnic group, location, and comorbid conditions.[35] The rationale for development of definitions and staging systems based on these measures is the belief that uniform terminology and explicit and objective criteria for assessment enable early identification of kidney disease, recognition of its health effects, including regional and ethnic differences and—most importantly—the development of tailored interventions to improve outcomes.

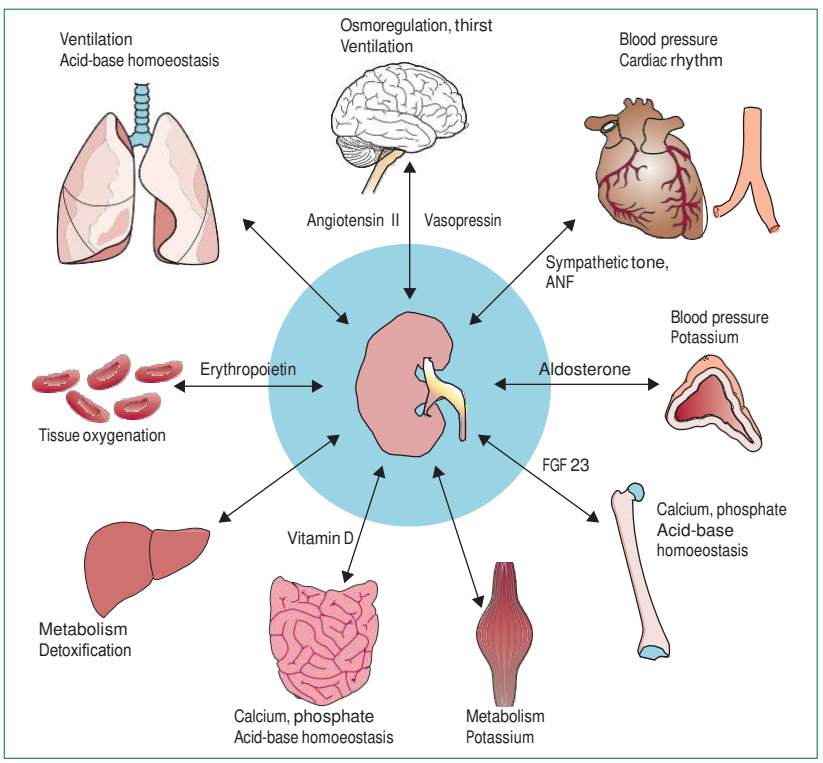


*Figure 2:* **Effect of kidney function on essential homoeostatic processes**
FGF=fibroblast growth factor. ANF=atrial natriuretic factor.

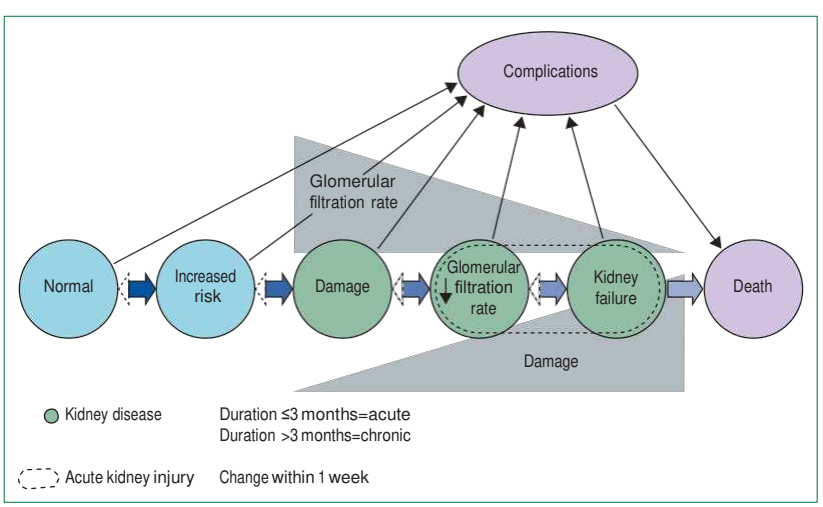


*Figure 3:* **Factors associated with increased risk of kidney disease (blue), stages of disease (green), and complications (including death; purple)**
Horizontal arrows show transitions between stages (kidney outcomes). Solid arrows pointing from left to right show progression of kidney disease. Dashed arrowheads pointing from right to left show remission. Grey triangles show continuous nature of changes in glomerular filtration rate and kidney damage.

Chronic kidney disease and acute kidney injury can be detected straightforwardly by the non-nephrologist in clinical practice, and their prevalence and prognosis have been rigorously studied as they relate to public health. However, measurements for assessment of kidney function and structure continue to evolve, the definitions of chronic kidney disease and acute kidney injury are not yet fully harmonised with each other, and evidence for improved outcomes because of the introduction of these definitions is not strong.

Figure 3 shows a conceptual model of the association of kidney disease, irrespective of duration, with adverse outcomes. Kidney disease is defined as a heterogeneous group of disorders affecting kidney structure and function. Even mild abnormalities in measures of structure and function are associated with increased risk of kidney failure or development of complications in other organ systems, especially cardiovascular disease. The clinical presentation and course of the disease are variable. Kidney disease can be defined as acute or chronic, dependent on duration (≤3 months vs >3 months). Acute kidney injury is defined as a subgroup of acute kidney disease in which changes in kidney function occur within 1 week. The association between acute kidney injury and chronic kidney disease is complex: acute kidney injury can lead to chronic kidney disease, and chronic kidney disease increases the risk of acute kidney injury.[36]

Table 1 summarises the definitions, stages, and burden of chronic kidney disease and acute kidney injury. Both disorders are defined by objective measures of kidney damage (albuminuria, abnormalities in the urine sediment, imaging, or biopsy) and function (decreased glomerular filtration rate, increasing serum creatinine concentrations, or decreased urine output), without reference to the cause of kidney disease. This feature is of particular importance because inclusion of the cause of kidney disease would have precluded the application of the definition in epidemiological studies and in many clinical scenarios in which the cause was unknown or undocumented. Chronic kidney disease and acute kidney injury are categorised into stages on the basis of the severity in abnormalities in these measures. Clinical practice guidelines for both disorders emphasise a stage-based approach to evaluation and management, complementing the traditional approaches emphasising

| | Chronic kidney disease | Acute kidney injury |
|---|---|---|
| Definition | | |
| Functional criteria | GFR <60 mL/min per 1·73 $m^2$ for >3 months | Increase in serum creatinine by 50% within 7 days; increase in serum creatinine by 26·5 µmol/L (0·3 mg/dL) within 2 days; or oliguria |
| Structural criteria | Kidney damage for >3 months (albuminuria is the most common marker of kidney damage and is also associated with rapid progression) | None |
| Staging | GFR categories (mL/min per 1·73 $m^2$) and related terms†: G1 ≥90 (normal or high); G2 60–89 (mildly decreased‡); G3a 45–59 (mildly to moderately decreased); G3b 30–44 (moderately to severely decreased); G4 15–29 (severely decreased); G5 <15 (kidney failure)<br>Albuminuria categories, approximate equivalent for AER (mg per day) and ACR (mg/g) and related terms: A1 <30 (normal to mildly increased); A2 30–300 (moderately increased‡); A3 >300 (severely increased‡) | Stages based on serum creatinine or urine output; stage 1: serum creatinine ≥1·5–1·9 times baseline, ≥26·5 µmol/L increase, or urine output <0·5 mL/kg per h for 6–12 h; stage 2: serum creatinine ≥2·0–2·9 times baseline or urine output <0·5 mL/kg per h for ≥12 h; stage 3: serum creatinine ≥3·0 times baseline, ≥353·6 µmol/L (≥4 mg/dL), renal replacement therapy, or (in patients <18 years) a decrease in estimated GFR to <35 mL/min per 1·73 $m^2$, urine output <0·3 mL/kg per h for ≥24 h, or anuria for ≥12 h |
| Burden* | | |
| Prevalence | ~10% of adults (from 4% at 20–39 years to 47% at ≥70 years in the USA)[6,8,37,38] | Not applicable for a short-term illness (history of acute kidney injury of any severity present in 45% at chronic kidney disease stage ≥4)[39] |
| Annual incidence | ~1% in middle age; twice as frequent in black compared with white populations[40–42] | Acute kidney injury requiring hospital admission in Alberta, Canada for patients without chronic kidney disease 0·1% (0·01% requiring dialysis); for patients with stage 3 disease 0·5–7·1% (0·03–0·17%); for patients with stage 4 disease 7·0–11·7% (0·5–2·5%); and 34·8% for acute kidney injury of any severity in chronic kidney disease stage ≥4[39,43]<br>For patients already admitted to hospital, rates are ~10–20% for any acute kidney injury with 0·3% requiring dialysis (highest with sepsis, cancer and surgery) |
| Lifetime cumulative incidence | ~50% for chronic kidney disease[44] and ~2% in white and ~7% in black populations for end-stage renal disease[45,46] | .. |

GFR=glomerular filtration rate. AER=albumin excretion rate. ACR=albumin-to-creatinine ratio. *Varies by age and risk factor distribution. †In the absence of evidence of kidney damage, GFR category G1 or G2 do not fulfil the criteria for chronic kidney disease. ‡Terms for categories G2 and A2 are relative to young adult levels; category A3 includes nephrotic syndrome (albumin excretion usually >2200 mg/day [ACR >2220 mg/g]).

*Table 1:* Definitions, stages, and burden of chronic kidney disease and acute kidney injury

cause of disease.[4,13,34] The estimates of burden of disease are an approximation made on the basis of a synthesis of available data; substantial variation is noted dependent on the number of risk factors assessed and availability of data in different countries and regions.

The juxtaposition of new definitions and staging systems (based mainly on laboratory measures) and traditional notions (based primarily on causes of disease) has created substantial controversy within the specialty.[47] Such controversy has been inherently valuable in stimulating research, which has ultimately validated the new concepts and subsequently led to international collaborations and consensus.[48]

## Chronic kidney disease

The impetus for the first guidelines defining chronic kidney disease in 2002 stemmed from the rising incidence and prevalence of chronic kidney failure, with associated high cost and poor outcomes, and concerns about late referral to nephrologists.[4] The recommendations focused on estimation of glomerular filtration rate from serum creatinine and ascertainment of markers of kidney damage (primarily albuminuria). Methodological issues about which measurements to use were a key discussion point. Widespread variation in clinical laboratory procedures for assaying and reporting of serum creatinine concentration drove international initiatives to standardise assays and develop more accurate equations to estimate glomerular filtration rate.[49,50] Through integrated efforts of the clinical chemistry and nephrology communities, laboratories are now expected to use standardised methods for creatinine assays and report estimated glomerular filtration rate with validated estimating equations whenever possible.[51,52] Subsequently, cystatin C was added as a variable to estimate glomerular filtration rate and prognosis, leading to advances in detection and classification of chronic kidney disease.[53,54] Standardisation and international consensus about urine albumin measurements is an active area of work.[55] In 2013, the global organisation Kidney Disease: Improving Global Outcomes (KDIGO) published a chronic kidney disease guideline update[34] that adds cause of kidney disease and albuminuria stages to the staging system, thus acknowledging the prognostic importance of albuminuria concentrations.[16,35,48]

## Acute kidney injury

KDIGO also developed an acute kidney injury guideline,[13] recognising that the prognosis of acute kidney failure had not improved in decades, despite substantial improvements in intensive care and methods of dialysis, and that small declines in glomerular filtration rate, which are not severe enough to be classified as acute kidney failure, are associated with adverse outcomes. The acute kidney injury guideline is based on earlier efforts to define the disorder[56,57] and concentrates on changes in serum creatinine or reduction in urine output as manifestations of direct injury to the kidney and acute impairment of function. Unlike chronic kidney disease, markers of damage are not included in the definition of acute kidney

injury, but there is an intensive investigation of urinary biomarkers that precede the reduction in glomerular filtration rate (eg, kidney injury molecule 1, neutrophil gelatinase-associated lipocalin, and interleukin 18), and might allow early identification and treatment.[15,58]

## Kidney as a cause and target organ of disease

Diseases affecting the kidney are usually categorised into primary and secondary diseases (table 2). However, with increased understanding of the underlying causes of disease, this classification becomes indistinct, because most diseases that mainly manifest in the kidney are associated with extrarenal pathogenesis and systemic manifestations. In view of its notable role in the circulation, the kidney is frequently a target organ of systemic vascular, haemodynamic, metabolic, and inflammatory disorders. Involvement of the kidney in many pathogenic processes originating outside the kidney aggravates disease and impairs prognosis. Although many kidney diseases are rare (and are the centre of specialised nephrological care), increasing evidence suggests an important role of the kidney in highly prevalent, complex disorders, including obesity, diabetes, and hypertension.

## Obesity, metabolic syndrome, and diabetes

Prevalence of obesity has increased substantially in the past century. In the USA, obesity (body-mass index >30 kg/m$^2$) has increased in men aged 60 years from 3·4% in 1890 to more than 30% in 2000.[59] Obesity also presents a serious health threat in developing countries.[60] The increase in obesity has been accompanied by notable increases in hypertension, diabetes, cardiovascular disease, and chronic kidney disease.[8,61] The association of chronic kidney disease with an increased frequency of obesity is partly because hypertension and diabetes are known causes of kidney disease and failure. Notably, however, kidney disease begins very early in people who go on to become obese. Thus, in individuals with the metabolic syndrome (a fat storage disorder that affects up to 25% of high-income populations, and is characterised by truncal obesity in combination with any two of the following factors: increased triglyceride concentrations, low HDL cholesterol, increased blood pressure, increased fasting plasma glucose levels, or previously diagnosed type 2 diabetes), the prevalence of chronic kidney disease increases with the number of traits.[62] In turn, the presence of chronic kidney disease in patients with metabolic syndrome increases their risk of development of cardiovascular disease. Why individuals with metabolic syndrome develop albuminuria and decreases in glomerular filtration rate before the development of significant hypertension or diabetes is not known. One possibility is that underlying mechanisms might drive both kidney damage and metabolic syndrome, such as endothelial dysfunction and oxidative stress (which are common to both disorders). Diets high in added sugars might have a key role in development of metabolic syndrome and kidney disease, particularly from the ingestion of fructose (present in sucrose and high-fructose corn syrup) that can lead to generation of uric acid.[63] Mild kidney disease is induced in rats fed a high fructose diet.[64] Low-grade systemic inflammation, which is also present in these disorders, might also result in changes in adipokines and other substances that can affect glomerular capillary wall function.[65]

## Arterial hypertension

The pathogenesis of hypertension shows that the kidney can have an important role in health and disease even when renal function, defined by glomerular filtration rate, is normal. Primary hypertension, defined as a blood pressure of more than 140/90 mm Hg, was once present in only 5–10% of the adult population in the early 1900s, but has meanwhile increased to a prevalence of 20–40% in most developed countries, and has been projected to affect more than 1·5 billion people worldwide by 2025.[66] Most studies suggest that the underlying defect involved is a relative inability of the kidney to excrete salt, and this defect can be shown despite a normal or only slightly depressed glomerular filtration rate.[67,68] A characteristic haemodynamic finding in the kidney is renal

| | Examples of primary kidney diseases | Examples of systemic diseases affecting the kidney |
|---|---|---|
| Glomerular diseases | Diffuse, focal or crescentic proliferative glomerulonephritis; focal and segmental glomerulosclerosis, membranous nephropathy, and minimal change disease | Obesity, metabolic syndrome and diabetes, systemic autoimmune diseases, systemic infections, drugs, complement diseases, and neoplasias and haemopoietic diseases |
| Vascular diseases | ANCA-associated renal limited vasculitis, and fibromuscular dysplasia | Hypertension, atherosclerosis, ischaemia, cholesterol emboli, systemic vasculitis, thrombotic microangiopathy, and systemic sclerosis |
| Tubulointerstitial diseases | Urinary-tract infections, stones, and obstruction | Systemic infections, sarcoidosis, drugs, urate, environmental toxins (eg, lead, aristolochic acid), and neoplasia (myeloma) |
| Cystic and other congenital diseases | Renal dysplasia, medullary cystic disease, and podocytopathies | Autosomal-dominant polycystic kidney disease, Alport syndrome, and Fabry disease |

ANCA=antineutrophil cytoplasmic antibody.

*Table 2:* Classification of causes of chronic kidney disease based on presence or absence of systemic disease and location within the kidney of pathological-anatomical findings

| | Monogenic disease | Complex disease or trait |
|---|---|---|
| Inheritance pattern and genetic risk | Mendelian; mutations are necessary and often sufficient for disease manifestation, non-genetic risk factors have few associations | Complex; many genetic factors with weak to moderate effects (relative risk 1·05–1·5) combined with multiple non-genetic risk factors (relative risk 1·5–4·0) |
| Disease and genetic susceptibility prevalence | Most monogenic diseases are individually rare* (eg, <1 in 40 000 livebirths for recessive and <1 in 1000 for dominant diseases); ADPKD prevalence highest at ~1 per 1000 | High for CKD (prevalence ~100 per 1000 adults); common risk allele frequencies (10–50%); much lower for specific chronic kidney disease subtypes such as IgA nephropathy or idiopathic membranous nephropathy |
| Methods for discovery | Linkage analysis, positional cloning, homozygosity mapping, sequencing (candidate genes or regions, whole exome, or genome) | Association studies (candidate gene, genome-wide arrays) or sequencing, admixture mapping when a large genetic difference between populations is anticipated |
| Examples | ADPKD, Alport's disease, and UAKD | Population-based chronic kidney disease, estimated glomerular filtration rate, and albuminuria, IgA nephropathy, and idiopathic membranous nephropathy |
| Cause | ADPKD†: mutations in *PKD1* or *PKD2* (currently 929 germline mutations in *PKD1* and 167 in *PKD2* classified as likely or definitely pathogenic; Alport's disease: >500 pathogenic mutations in *COL4A3-COL4A6*; and UAKD: >50 pathogenic mutations in *UMOD* | Multifactorial; genetic risk variants for chronic kidney disease or end-stage renal disease: *APOL1*, *UMOD*, *PRKAG2*, *AFF3*, *RGMA/MCTP2*, and *WDR72*; for estimated glomerular filtration rate: *ANXA9/LASS2*, *GCKR*, *ALMS1/NAT8*, *TFDP2*, *SHROOM3*, *DAB2*, *SLC34A1*, *VEGFA*, *PRKAG2*, *PIP5K1B*, *ATXN2/SH2B3*, *DACH1*, *UBE2Q2*, *UMOD*, *SLC7A9*, *SLC47A1*, *CASP9*, *CDK12*, *INO80*, *DDX1*, *MPPED2*, *MHC* region, and *UNCX*; for albuminuria: *CUBN*; for IgA nephropathy: *HLA-DRB1/DQA1*, *PSMB8*, *HLA-DPA1/DPB2*, *CFHR3/R1*, *HORMAD2*, *TNFSF12/13*, *DEFA9P-10P*, *HLA-DQB1/A2*, *MTMR3*, *HCG9*, and *SOX15/MPDU1*; for idiopathic membranous nephropathy: *HLA-DQA1* and *PLA2R1* |

Genes shown are the gene closest to the SNP with the lowest p value in an associated region, unless functional evidence points towards another nearby gene in the region. Only genome-wide significant findings ($p<5\times10^{-8}$) are reported. CKD, estimated glomerular filtration rate, and albuminuria loci are reported for findings from population-based studies, end-stage-renal disease findings are reported from case-control studies. ADPKD=autosomal-dominant polycystic kidney disease. UAKD=uromodulin-associated kidney disorders. *Affecting fewer than five per 10 000 population. †For the *ADPKD* mutation database see http://pkdb.mayo.edu.

*Table 3:* Monogenic and complex kidney diseases

vasoconstriction, especially of the preglomerular arteriolar vasculature. Genetic factors affect the ability of the kidney to excrete salt[69] and determine the risk of development of primary hypertension[70] and hypertensive kidney disease.[69,70] Intrauterine factors, known as fetal programming, are also important. In particular, intrauterine malnutrition can be associated with impaired fetal development, resulting in infants with a low birthweight who have a reduced number of nephrons in their kidney and are predisposed to the development of hypertension.[71] Hypertension can also be caused by subtle acquired injury to the kidney, resulting in microvascular damage, peritubular capillary loss, and the infiltration of T cells and macrophages.[72] The inflammatory infiltrate enhances local oxidative stress and intrarenal angiotensin activity, amplifying the renal vasoconstriction and impairing the excretion of salt. T cells reacting to specific antigens in the kidney, possibly induced by local ischaemia, might contribute to the hypertensive response,[73] thus suggesting an autoimmune component of primary hypertension. These mechanisms might also explain how factors associated with the metabolic syndrome, such as endothelial dysfunction, sympathetic nervous overactivity, and hyperuricaemia can induce hypertension, thus providing an important link for the common coexistence of obesity and hypertension.

## Genetic predisposition to kidney disease

Clustering of kidney disease in families is well established, but underappreciated. From the 1980s, linkage analysis and subsequently positional cloning emerged as a technique that allowed for the detection of disease-causing mutations in one gene (termed monogenic or Mendelian diseases). In 2010, more than 110 genes underlying monogenic diseases with a renal phenotype had been described.[74] The most prominent example is autosomal-dominant polycystic kidney disease (table 3). Although this disease, which is the most frequent monogenic renal disorder usually manifests during adulthood, many other rare monogenic renal diseases have an early and severe onset. With the advent of whole-exome and whole-genome sequencing, the number of identified single-gene defects causing renal disease in affected families is expected to increase rapidly.[75,76] Such studies will also allow researchers to investigate the combined effect of rare mutations and common disease susceptibility variants, which might help explain some of the high phenotype heterogeneity reported for many monogenic kidney diseases. Overall monogenic diseases are the presumed cause of kidney failure in more than 10% of patients undergoing dialysis, with autosomal-dominant polycystic kidney disease accounting for about 7% of all failures.[77]

Susceptibility to complex multifactorial diseases such as chronic kidney disease is influenced by variation in many genes and non-genetic components. Since 2005, unbiased genome-wide mapping approaches such as admixture linkage disequilibrium and genome-wide association studies have emerged as methods to search for complex kidney disease susceptibility variants (table 3). These studies have identified genomic regions associated with intermediate traits such as estimated glomerular filtration rate,[78,79] albuminuria,[80] and chronic kidney disease when applying the aforementioned definition of chronic kidney disease in the general population.[79] Moreover, genomic regions have been identified that are associated with more specific disease entities such as non-diabetic end-stage renal disease, focal-segmental glomerulosclerosis,[81–83] immunoglobulin A nephropathy,[84] and idiopathic membranous nephropathy.[85]

As for other complex diseases, identified genetic risk variants usually only confer small increases in disease risk, with identification requiring large study populations. Common risk variants in the MYH9/APOL1 region that increase the risk of kidney disease in black populations are an impressive exception because the associated relative risks are very large (fivefold to 17-fold for focal-segmental glomerulosclerosis, threefold in case-control studies of non-diabetic end-stage renal disease, and 29-fold for HIV-associated nephropathy) and the population attributable risk amounts to 70%.[81,82,86] These risk alleles also contribute to the risk of diabetic kidney disease but the associated risk is smaller, suggesting that non-genetic factors have a larger role than do genetic ones.[87] The African American Study of Kidney Disease and Hypertension[88] provided convincing evidence that progressive kidney disease that was labelled hypertensive nephrosclerosis on clinical grounds could be attributed to risk variants in the APOL1 region, explaining why blood-pressure lowering often failed to halt disease progression in this population. The precise roles of MYH9/APOL1 in predisposition to kidney disease remain to be identified, but apolipoprotein L1 confers protection against trypanosomiasis, which might have provided a survival advantage in Africans and thereby explains why this group is particularly at risk of focal-segmental glomerulosclerosis and non-diabetic chronic kidney disease.[83]

The notion that a continuum of genetic risk variants from small to large effects results in different degrees of disease severity is compelling. Rare mutations in UMOD—which codes for uromodulin, a protein secreted in large amounts into the urine in the thick ascending limb of loop of Henle—cause monogenic kidney disease,[89] whereas common UMOD variants increase chronic kidney disease susceptibility in the general population.[90,91] Thus, disorders in uromodulin secretion are of widespread pathophysiological relevance. Other rare inherited diseases that have provided key insights into common disorders of kidney function include monogenic disorders affecting renal handling of NaCl, which improved our understanding of blood pressure regulation and mechanisms of action of diuretics;[92,93] inherited disorders involving the proximal tubule such as renal Fanconi syndrome, which evidenced the role of receptor-mediated endocytosis in acquired proximal tubule dysfunction and renal disease progression;[94] and the discovery that several genes causing cystic kidney diseases code for proteins that are located in the primary cilium, which enlarged the scope of these disorders and provided essential information about their multisystemic nature.[95]

Improved understanding of genetic causes of kidney disease has already started to inform treatment decisions. Identification of a genetic cause affecting the glomerular filtration barrier can help avoid ineffective exposure to steroid treatment in children with nephrotic syndrome.[96] Genotyping for atypical haemolytic uraemic syndrome can enable prediction of the risk for relapse after renal transplantation.[97] The clinical relevance of genotyping in patients with kidney disease will probably increase rapidly in the near future. However, genetic insights into complex kidney diseases have not yet proved useful in terms of prediction of chronic kidney disease in the general population.[98]

## Complications of kidney disease

In general, all acute and chronic diseases have a worse prognosis in the presence of kidney disease. This association is of particular relevance for the various types of cardiovascular disease,[9] including acute myocardial infarction,[99] stroke,[100] and heart failure.[101] Chronic kidney disease also worsens the prognosis of patients with metabolic disease and diabetes, chronic pulmonary disease, pneumonia,[102,103] and other acute infections. An increased incidence of cancer in patients with chronic kidney disease has also been reported, but seems to be linked to increased prevalence of liver cancer and urological cancer in these patients[104] rather than a general increase in cancer risk.

Reasons for the consistent association of kidney disease with poor outcomes are only partly understood. For patients whose kidney disease is a result of systemic disease processes leading to target organ damage at different sites, the severity of kidney disease might show the severity of the systemic, damage-causing process. In addition, direct links exist between kidney function and the damage of extrarenal tissues. Acute kidney injury, for example, induces inflammation and aggravates the response to injury in the lung and other organs.[105,106] The term cardiorenal syndrome has been coined to describe the complex interaction between impaired cardiac function and kidney disease, to which not only impaired renal salt and water handling but also enhanced renal sympathetic activity contribute.[107] Mechanisms through which kidney disease accelerates atherosclerosis and enhances vascular calcifications also warrant attention, with impaired renal phosphate-handling presumably playing a dominant role.[108] Not only is vascular disease advanced in patients with chronic kidney disease, but several other characteristics of kidney disease might also be regarded as advanced ageing, possibly related to reduced renal expression of the anti-ageing proteohormone klotho.[29]

Presence of kidney disease also affects management strategies and is associated with a reduced implementation of best practice, presumably because of uncertainties about the risk-benefit balance of diagnostic procedures and therapeutic interventions. Thus, restrictions in the use of imaging procedures that require the application of radiocontrast agents or gadolinium can lead to underdiagnosis in patients with kidney disease. Another potential source of impaired prognosis is error or uncertainty in drug dosing, including drug toxicity

and underdosing. Therapeutic nihilism is especially obvious in the management of acute myocardial infarction in patients with chronic kidney disease, who receive fewer acute coronary interventions and reduced prescription of standard drugs, despite being at increased risk of adverse outcomes of myocardial ischaemia.[109,110]

## Implications for general practice

In view of the importance of kidney function on body homoeostasis and the high prevalence of kidney disease, its recognition is important to all providers of health care. Serum creatinine concentrations and urinary excretion of albumin related to creatinine in spot urine samples are straightforward and robust techniques to exclude or diagnose and stage chronic kidney disease.[4,34] Although the quantitative association between serum creatinine concentrations and glomerular filtration rate is confounded by muscle mass, different formulas have been developed to correct for this influence and to estimate glomerular filtration rate from one-off creatinine readings.[34] Use of these formulas in clinical chemistry laboratories allows automatic reporting of estimated glomerular filtration rate and thereby aids detection of kidney disease by the treating physician. Although screening for chronic kidney disease in the general population has not been shown to be cost-efficient, screening is recommended in high-risk groups, such as people with diabetes, hypertension, or a family burden of disease.[111]

Treatment strategies for chronic kidney disease are diverse and depend on the underlying disease and severity of impaired kidney function, complications, and comorbidities. However, blood-pressure control is a mainstay of secondary prevention for most patients. Inhibitors of the renin angiotensin system (angiotensin-converting-enzyme inhibitors or angiotensin receptor blockers) retard kidney disease progression beyond their blood-pressure-lowering effects, presumably because of their influence on glomerular haemodynamics with a reduction in filtration pressure.[112] Attempts to further reduce kidney disease progression and cardiovascular complications through dual blockade of the renin-angiotensin system, however, have failed.[113,114] Irrespective of specific interventions, the recognition of patients with chronic kidney disease and acute kidney injury as individuals with high risk in all health-care settings is of utmost importance.

## Future challenges

Despite the compelling evidence for strong associations of kidney disease with adverse outcomes and increasing insight into possible mechanisms, the ultimate proof for a causal association between impaired kidney function and poor health will rely on proof of benefit after improvements in kidney function. Unfortunately, therapeutic strategies that would enable such a hypothesis to be addressed, are very limited. The number of randomised clinical trials in nephrology continues to lag behind most other medical specialties.[115] In the context of clinical trials, kidney disease is usually an exclusion criterion and very rarely a therapeutic target.

Because of the diverse mechanisms that can affect kidney function and the heterogeneity of natural courses of the disease, therapeutic interventions will probably not be effective unless they are tailored to specific subgroups or stages of kidney disease. Thus, although a unifying perspective has proven crucial, the challenge of the future will be to subdivide the syndromes of chronic kidney disease and acute kidney injury into distinct entities defined by similar pathogenesis, disease states, and complications. New biomarkers will be needed that predict the risk of kidney disease in unaffected individuals and causes, pathomechanisms, and outcomes (renal and non-renal) in individuals with the disease. Integration of multilevel information, including genetics, pathological changes, biomarkers, clinical course, and drug response could eventually result in advanced versions of the present staging systems and form the basis for personalised therapies. The recent discovery of phospholipase A2 as the main glomerular antigen causing membranous nephropathy, the most frequent cause of the nephrotic syndrome in adults,[116] the recognition of a specific genetic predisposition for this disease,[85] the demonstration of increased antigen expression in glomeruli of affected individuals,[117] and the assessment of phospholipase A2 antibody titres as diagnostic techniques and indicators of disease activity provides an impressive example for such an integrative approach.[118] Apart from studies in single-disease entities, the establishment and prospective assessment of large cohorts of carefully characterised patients with chronic kidney disease will probably have an important role in unravelling distinct categories of kidney disease.[119,120] If such approaches continue to be successful, the next major breakthrough in renal medicine will hopefully lead to effective halting of kidney disease and its adverse outcomes through specific interventions, and ultimately regeneration of kidney function.[121]


### Contributors

All authors discussed the overall concept, contributed to specific sections, and reviewed and approved the final version. K-UE prepared the first outline and integrated and edited contributions from all coauthors.

### Conflicts of interest

We declare that we have no conflicts of interest.


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