Chronic kidney disease: the global challenge

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The worldwide rise in the number of patients with chronic kidney disease (CKD) and consequent end-stage renal failure necessitating renal replacement therapy is threatening to reach epidemic proportions over the next decade, and only a small number of countries have robust economies able to meet the challenges posed. A change in global approach to CKD from treatment of end-stage renal disease (ESRD) to much more aggressive primary and secondary prevention is therefore imperative. In this Seminar, we examine the epidemiology of CKD worldwide, with emphasis on early detection and prevention, and the feasibility of methods for detection and primary prevention of CKD. We also review the risk factors and markers of progressive CKD. We explore current understanding of the mechanisms underlying renal scarring leading to ESRD to inform on current and future interventions as well as evidence relating to interventions to slow the progression of CKD. Finally, we make strategic recommendations based on future research to stem the worldwide growth of CKD. Consideration is given to health economics. A global and concerted approach to CKD must be adopted in both more and less developed countries to avoid a major catastrophe.

Worldwide, increasing numbers of patients are affected by chronic kidney disease (CKD).[1,2] The progressive nature of chronic kidney failure and the ensuing end-stage renal disease (ESRD) is putting a substantial burden on global health-care resources. A better understanding of the nature of CKD, leading to early detection and prevention and effective therapy might alleviate the global burden.

Epidemiology

The worldwide rise in the number of patients with CKD is reflected in the increasing number of people with ESRD treated by renal replacement therapy—dialysis or transplantation.[2] In the UK, the annual incidence of ESRD has doubled over the past decade to reach about 100 new patients per million of population,[3] well below the European average (about 135 per million) and rates in the USA[4] (table 1). The UK trend, like trends in other more developed countries, is expected to continue to rise at an annual rate of around 5–8%.[2] Two factors are important. The first is the ageing of the population; the incidence of ESRD is higher in elderly people than in the general population (the annual incidence in people older than 65 years in the USA is more than 1200 per million[4]). The second factor is the global epidemic of type 2 diabetes mellitus; the number of people with diabetes worldwide (currently about 154 million) is predicted to double within the next 20 years.[5] This increase will be most notable in less developed countries, where the number of diabetic patients could rise from 99 million to 286 million by 2025,[5] with an expected parallel epidemic of diabetic nephropathy.

About 90% of treated ESRD patients come from more developed countries that can still afford the cost of renal replacement therapy.[6] In the USA, the annual expenditure on ESRD is estimated to increase to more than US$28 billion by 2010.[4] In Europe, dialysis alone takes up about 2% of health-care budgets with only a small proportion (<0·1%) of the population needing treatment. There is a clear and direct relation between the gross national product and the availability of renal replacement therapy, with less developed countries unable to meet the increasing demand.[6] The huge disparity in the prevalence of ESRD between the more and less developed countries probably stems from the inadequacy of health-care resource allocation to programmes of renal replacement therapy. However, disparities in the incidence of ESRD within and between more developed countries are likely to reflect the racial and ethnic mix. For example, in the USA and Australia the annual incidence of ESRD is substantially lower in white than in African-American or aboriginal people (table 1).[4,7]

The number of patients with ESRD probably underestimates the entire burden of CKD because the numbers with earlier stages of disease (stages 1 to 4, panel 1) are likely to exceed by as much as 50 times those reaching ESRD (stage 5).[8] For instance in the USA, data derived from the third National Health and Nutrition Examination Survey have implied that up to 11% of the general adult population (19 million) could have some degree of CKD, including more than 8 million individuals with glomerular filtration rates of less than 60 mL per min.[8] This analysis also estimated that 5·9 million people could have stage 1 CKD with normal renal function.[8] However, these observations have substantial limitations, including the basing of prevalence estimation on single serum creatinine measurements, which are subject to variations owing to

Search strategy and selection criteria

This review was built on a broad and intensive search of published papers, including some related clinical practice guidelines, clinical trials, and meta-analyses. This search was supplemented with a systematic MEDLINE search for publications on the subject with the key words: "chronic kidney disease"; "CKD", "chronic kidney failure"; "CKF", "end-stage renal disease"; "ESRD", "early detection", "prevention", "management", "risk factors", "pathophysiology", up to September, 2004. Only papers published in English were retrieved.

	Incidence of ESRD (per million per year)	Prevalence of ESRF (per million)
Europe		
UK	101	626
European average	135	700
Russia	15	79
Australia		
White people	94	658
Aboriginal people	420	1895
USA		
Overall	336	1403
White people	256	1004
African-American people	982	4432
Less developed countries		
India	34–240	Unknown
Nigeria	Unknown	2·5

Most data are for the period 2000–2003.

Table 1: **Incidence and prevalence of ESRD in various parts of the world**

differences in calibration systems between laboratories.[9] Subsequently, the estimates based on serum creatinine were converted into estimates based on glomerular filtration rate by use of the formula of the Modification of Diet in Renal Diseases study,[10] which has not been fully validated in different populations and at different stages of CKD.[11] In addition, age-related decline in glomerular filtration rate, affecting up to 40% of people aged over 65 years,[1] could have led to overestimation of the actual burden of CKD because many of these people have impaired but stable kidney function. Finally, the study based on the third National Health and Nutrition Examination Survey used the classification of CKD by the US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative. This classification is subject to debate:[12] some have argued that stages 1 and 2 would be better defined by the associated abnormalities (eg, microalbuminuria, haematuria; panel 1) rather being classed as CKD.[12] More advanced stages (3 and 4) should be characterised by the associated renal insufficiency.

Other screening surveys of representative samples of the whole population undertaken in Australia,[13] Japan,[14] and Europe[15] also identified between 6% and 11% as having some degree of CKD. The prevalence of CKD increases to 50–60% when at-risk individuals are screened.[16] Clearly, the early identification of such individuals and the prevention of progressive CKD are likely to be key factors in alleviating the future burden of end-stage renal failure (ESRF) and the associated mortality.

Panel 1: **Stages of CKD according to the US National Kidney Foundation and the Kidney Disease Outcomes Quality Initiative**

Stage 1
Kidney damage (pathological abnormalities or markers of damage including abnormalities in blood or urine tests or in imaging studies) with normal or raised glomerular filtration rate (⩾90 mL per min per 1·73 m^2)

Stage 2
Glomerular filtration rate 60–89 mL per min per 1·73 m^2 with evidence of kidney damage

Stage 3
Glomerular filtration rate 30–59 mL per min per 1·73 m^2

Stage 4
Glomerular filtration rate 15–29 mL per min per 1·73 m^2

Stage 5
End-stage renal failure; glomerular filtration rate <15 mL per min per 1·73 m^2

Risk factors and CKD

Much epidemiological and clinical evidence has shown a link between several factors and the initiation and the progression of CKD. These can be classified into two distinct categories: those proven to be causal (risk factors) and those that are associated with CKD in the absence of established causal relations (risk markers).

Susceptibility factors

CKD commonly clusters within families, which implies genetic or familial predisposition.[17] Genetic studies have suggested links between CKD and various alterations or polymorphisms of candidate genes encoding putative mediators, including the renin-angiotensin system. Racial factors also have a role in the susceptibility to CKD as shown by the high prevalence of CKD related to hypertension, diabetes, or both among African and Native Americans in the USA,[4] as well as Afro-Caribbean and Asian individuals in the UK.[18] Low birthweight and infant malnutrition in some ethnic minorities might be associated with a reduction in the number of nephrons, predisposing to hypertension and renal disease in later life.[19] Male and elderly people might also be more susceptible to CKD, which would explain the high proportions of these population groups in renal-replacement-therapy programmes.[3,4]

Initiation factors

Many cohort studies in the USA[20–22] and Japan[14] have identified hypertension, diabetes, hyperlipidaemia, obesity, and smoking as risk factors or markers in the general population for the development of CKD. Common risk factors and markers seem to be linked to both renal and cardiovascular diseases in more developed countries. Also, albuminuria itself is a predictor not only of CKD but also of cardiovascular morbidity and mortality.[23] Impaired kidney function is also a major risk factor for patients with cardiovascular disease.[24,25] Consequently, early detection and prevention could influence both renal and cardiovascular morbidity and mortality.

The risk factors listed above, in particular diabetes and hypertension, are also likely to affect individuals in less developed countries, where "western" lifestyle is adopted. Diabetic nephropathy is now one of the leading causes of ESRD (exceeding 30–40%) in countries such as Malaysia, Turkey, Korea, Qatar, and the Philippines.[4] Evidence is lacking on the aetiology of ESRD in many less developed countries owing to poor data collection and the absence of renal registries. In addition, these countries continue to suffer from the burden of infectious diseases with infection-related glomerulonephritis and consequent renal insufficiency. The infections include HIV (40 million infected worldwide), hepatitis C virus (170 million), malaria (300 million cases per year), schistosomiasis (200 million), and tuberculosis (200 million).[26] The growth in the number of cases of CKD attributable to these infections is likely to parallel the rising number of infected individuals.

Progression factors

The progression of established CKD is variable and depends on several risk factors or markers. Non-modifiable factors include genetics, race, age, and sex. For instance, there is much evidence that the rate of progression of CKD is faster among patients who are elderly,[27] male,[28] or African-American.[29]

Most notable among the modifiable progression factors is systemic hypertension.[30,31] Proteinuria is a reliable marker of the severity of CKD and a powerful and independent predictor of its progression.[32,33] Controversy prevails as to whether proteinuria is a risk factor for the progression of clinical nephropathies. Patients with persistently high rates of urinary protein excretion (>3–5 g in 24 h) in general have a much faster rate of progression than those with mild or moderate proteinuria (<1–3 g in 24 h).[33]

Metabolic factors have been implicated in the progression of CKD. The Diabetes Control and Complications Trial[34] and the UK Prospective Diabetes Study[35] established that poor diabetes control accelerates the progression of diabetic nephropathy in both type 1 and type 2 diabetes. Experimental evidence has also shown a link between hyperlipidaemia and the progression of diabetic and non-diabetic nephropathies.[36] A link between hyperuricaemia and the development of systemic hypertension, cardiovascular disease, and renal disease has been postulated.[37]

The worldwide pandemic of obesity could also affect the progression of CKD. According to the WHO, an estimated 1 billion individuals are now classified as overweight or obese.[38] In the USA, 35% of the adult population are thought to be overweight and another 26% are classed as obese.[38] Obesity has been associated with the initiation and progression of glomerulonephritides;[39,40] the incidence of focal and segmental glomerulosclerosis is higher in obese than in lean individuals,[41] and the progression of IgA nephropathy is thought to be faster in overweight patients.[42] Whether these links are causal or simply associated with CKD remains unclear; obesity is associated with hypertension, albuminuria, and dyslipidaemia, all of which are potential modifiers of the progression of CKD.

Cigarette smoking has been implicated in the initiation and progression of CKD. A graded increased risk of ESRD was noted in non-diabetic nephropathies with increasing cigarette smoking; the incidence of ESRD was increased by 5·9 times among heavy smokers (>15 pack-years).[43] In another study, heavy smokers (>20 pack-years) had a risk of developing albuminuria three times that of non-smokers.[44]

Preliminary experimental data in obese rats suggest a link between caffeine consumption and albuminuria.[45] This finding was associated in that study with worsening of tubulointerstitial renal lesions. Links between caffeine consumption and raised blood pressure have been postulated.[46] Regular and heavy (more than two drinks daily) consumption of alcohol might also increase the risk of ESRD according to a survey undertaken in the USA.[47] That study, like many linking alcohol with hypertension, showed a J-shaped risk curve; drinking one or two drinks per day could be protective whereas heavier drinking is detrimental. In the USA, one study suggested that individuals who use opioid drugs recreationally have a risk of developing ESRD of up to 19 times that in non-users.[48]

Some studies have linked the consumption of analgesics, especially paracetamol and non-steroidal anti-inflammatory agents with a higher risk of developing CKD.[49–51] One of the largest case-control studies (716 patients with ESRD) showed an odds ratio of 2·4 for patients with lifetime cumulative consumption of 5000 or more paracetamol tablets compared with individuals taking 1000 or fewer.[50] In the same study, consumption of non-steroidal anti-inflammatory agents was associated with an odds ratio of 8·8, whereas use of aspirin did not seem to be associated with increased risk of ESRD.[50] Many such studies have been criticised for major flaws, including confounding by indication and time-order considerations.

Mechanisms of kidney scarring

Glomerulosclerosis

Progressive glomerulosclerosis has many similarities to atherosclerosis.[52] They share risk factors, notably hypertension, dyslipidaemia, and smoking. They are both characterised by endothelial damage and dysfunction, proliferation of smooth-muscle or mesangial cells, and injury to the pericyte or podocyte (figure 1). As with atherosclerosis, hypertension-induced shear stress leads to injury, activation, and dysfunction of the glomerular endothelium, which in turn initiates glomerular microinflammation leading to interactions between inflammatory cells (macrophages/foam cells) and mesangial cells with the activation, proliferation, and

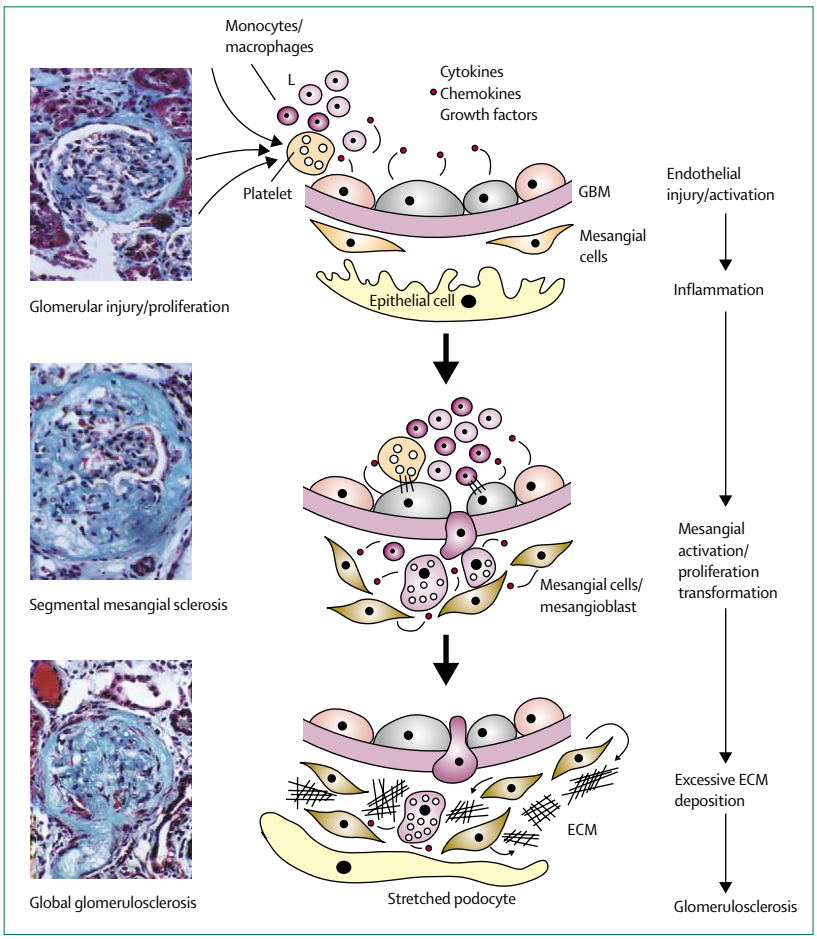

Figure 1: **Diagrammatic representation of the stages of glomerulosclerosis**
GBM=glomerular basement membrane; ECM=extracellular matrix.

dysfunction of the latter. Communication between cells depends on the release of a wide range of cytokines and growth factors.[53] Under the influence of growth factors, especially transforming growth factor β1 (TGF β1), mesangial cells regress to an embryonic mesenchymal phenotype (mesangioblasts) capable of excessive production of extracellular matrix (ECM) leading to mesangial expansion, an early sign of glomerulosclerosis.[54] Also, damage to the podocyte is now recognised as an important factor in the pathogenesis of glomerulosclerosis. Stretching of these cells leaves areas of denuded glomerular basement membrane and favours the formation of adhesion to the Bowman's capsule.[55]

The outcome of glomerular remodelling depends on the balance between healing and scarring influences. Resolution of microinflammation, return of glomerular cells to a mature phenotype, halting of excessive ECM synthesis, and the breakdown of the deposited ECM favour healing. By contrast, persistent and continuing activation damage of the glomerular endothelial-mesangial-epithelial axis will lead to cell death through apoptosis as well as their replacement by ECM. Irreversible scarring and glomerulosclerosis will ensue.

Tubulointerstitial fibrosis

Tubulointerstitial scarring and fibrosis are closely associated with the impairment of renal function. As with glomerulosclerosis, tubulointerstitial fibrosis involves inflammation, proliferation, apoptosis, and fibrosis (figure 2).[54,56]

Experimental evidence suggests that proteinuria has an important role in the initiation of tubulointerstitial inflammation.[57] Excessive reabsorption of albumin by proximal-tubule cells in vitro stimulates the release of various proinflammatory mediators including chemokines. These agents in turn could attract inflammatory cells to the renal interstitium and initiate interactions with interstitial fibroblasts. Activation and proliferation of fibroblasts and myofibroblasts and the associated excessive synthesis of ECM could culminate in interstitial fibrosis.[56,58]

Injured tubules undergo programmed cell death (apoptosis) leading to tubular atrophy and the formation of atubular glomeruli. Under the influence of TGF β1, some tubular cells become transformed into an embryonic phenotype, thus acquiring mesenchymal properties similar to those of fibroblasts and myofibroblasts.[54,58,59] Tubular cells could therefore contribute to the pool of cells directly involved in renal fibrogenesis.

The outcome of tubulointerstitial injury depends on the capacity of inflammation to regress, tubules to regenerate, fibroblasts to die, and ECM to be broken down. Continuing injury, inflammation, and fibroblast activation and proliferation will lead to irreversible fibrosis.

Role of stem cells in renal remodelling

Renal remodelling (repair/healing or scarring) might depend on influx into the injured kidneys of haemopoietic stem cells with the potential for repair or scarring. The detection of cells showing embryonic mesenchymal characteristics in glomeruli has led to the hypothesis that haemopoietic stem cells are involved in normal turnover of glomerular cells as well as in the response of glomeruli to injury. Experiments based on bone-marrow transplantation have shown that bone-marrow-derived cells are involved in the normal turnover of the mesangium[60] and in glomerular repair and repopulation after experimentally induced mesangial injury.[61]

The glomerulus seems to have a limited repertoire of options after injury: to enter a phase in which its cellular constituents dedifferentiate into their mesenchymal embryonic precursors (reverse embryogenesis); or to attract haemopoietic embryonic stem cells to re-enact embryogenesis (recapitulated embryogenesis).[54] The outcome of remodelling depends on the glomerular

environment the cells are in, with either recapitulated embryogenesis and maturation leading to healing or misdirected progression towards apoptosis and scarring.

Transplantation of bone marrow from glomerulosclerosis-prone mice to a previously resistant strain led to glomerulosclerosis, which suggests that this disorder also depends on the migration into the glomeruli of bone-marrow-derived mesangial progenitors with sclerosing phenotype.[62] Conversely, the phenotype of progenitor mesangial cells might be advantageous when these cells replace phenotypically abnormal cells, as in the case of experimental mesangial IgA nephropathy.[63] In the future, bone-marrow or stem-cell transplantation might be applied to manipulate the glomerular and mesangial phenotype. Therapeutic glomerular remodelling based on stem-cell transplantation might not be too far off.

A role has also been postulated for haemopoietic stem cells in the regeneration of injured tubules as well as in the pathogenesis of interstitial fibrosis. In preliminary experiments haemopoietic stem cells were able to acquire fibroblast characteristics, thus contributing to interstitial renal fibrosis.[54]

Renal remodelling and scarring depend on the interplay of resident and infiltrating cells, including those with potential for further damage and those with repair capacity. The balance between these various cells and actions will direct renal injury to either healing or scarring.

Mediators of renal scarring

Interactions between cells during renal remodelling rely on the release of chemokines, cytokines, and growth factors.[58] Autacoids such as angiotensin II and endothelin have also been implicated in renal scarring. Among growth factors, TGF β1 is thought to be the most fibrogenic, directly or indirectly through the action of connective-tissue growth factor.[64] By contrast, hepatocyte growth factor, vascular endothelial growth factor, and osteogenic protein 1 seem to have beneficial or protective influences.

Autacoids and growth factors activate intracellular signal transduction pathways shown to mediate the response to injury of renal cells. Mitogen-activated protein kinases, Rho-associated coiled-coil kinase (Rho-ROCK), and Jun N-terminal kinase/stress-activated protein kinase have all been implicated in renal cellular responses to vasoconstrictors as well as growth factors.[53] TGF β1 activates a family of intracellular signal transducers called the Smads. Smad3 is thought to be the most fibrogenic and Smad7 might be protective.[65] The nuclear translocation of some of these kinases and Smads and their interaction with DNA-binding sites, including activating protein 1, leads to regulation of DNA synthesis, cellular proliferation, and fibrogenesis. Also, the activation of the nuclear transcription factor κB (NFκB) appears to be a key step in the synthesis by kidney cells of chemokines and cytokines.[66] Peroxisome proliferator-activated receptors are involved in the regulation of cell cycling and ECM processing in response to injury of renal cells.[67] The turnover of renal cells in vivo appears to be regulated by a complex interplay of cyclin-dependent kinases and their inhibitors.[68] Interactions between intracellular and intranuclear signalling pathways could determine the fate of renal cells and kidney response to injury.

Prevention and management of CKD

Primary prevention: lifestyle modification

Primary prevention will rely on controlling the global epidemic of obesity and associated type 2 diabetes as well as hypertension. Lifestyle modifications, such as weight reduction, exercise, and dietary manipulations can be effective, as shown in clinical trials in which the incidence of type 2 diabetes in overweight individuals with impaired glucose tolerance was substantially lowered by these means.[69,70] Approaches to control

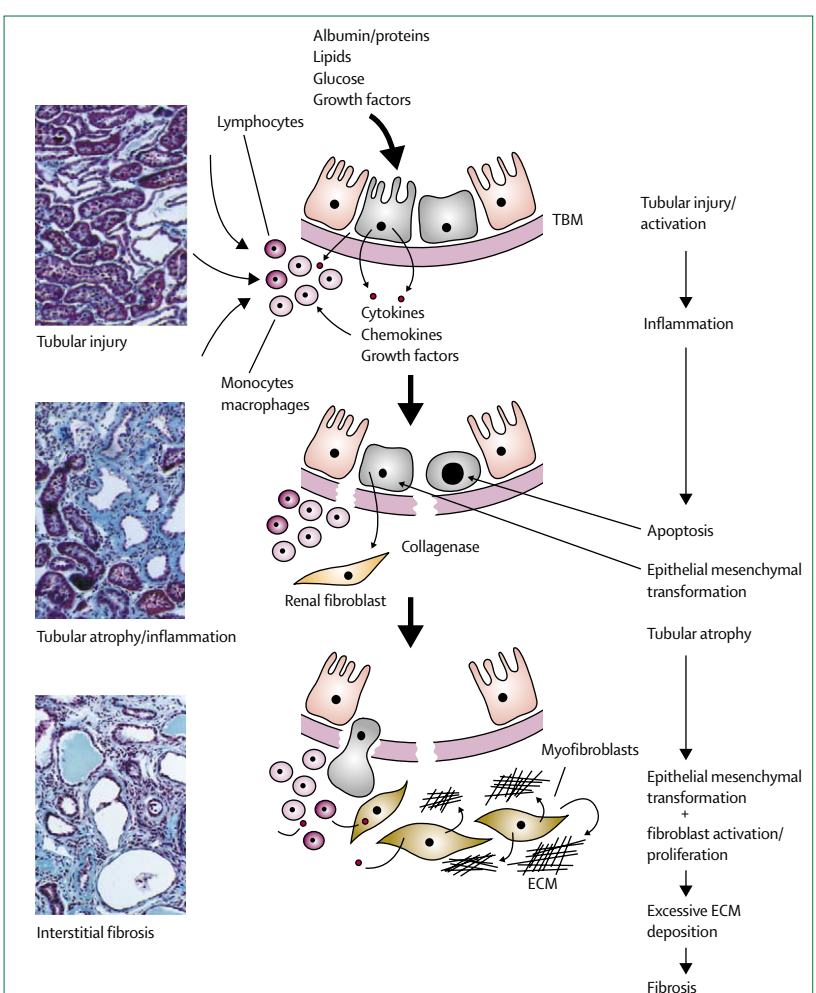

Figure 2: **Diagrammatic representation of the stages of tubulointerstitial fibrosis**
TBM=tubular basement membrane; ECM=extracellular matrix.

Panel 2: Interventions and objectives to slow the progression of CKD

Diet
Moderate protein restriction: 0·60–0·75 g/kg daily
Low salt: 60–80 mmol/day (4–6 g sodium chloride) to optimise blood-pressure control

Blood-pressure control
For blood pressure <130–135/80–85 mm Hg (mean arterial pressure 92 mm Hg), if proteinuria <1 g in 24 h
For blood pressure <125/75 mm Hg (mean arterial pressure 90 mm Hg), if proteinuria >1 g in 24 h
Initially with an ACE inhibitor
- Add salt restriction/diuretic to maximise the effect of the ACE inhibitor
- Add: angiotensin-2-receptor blocker; or non-dihydropyridine calcium-channel blocker, because they are more effective in reducing proteinuria than dihydropyridine calcium-channel blockers; or β or α blocker

Proteinuria
<1 g in 24 h—use an ACE inhibitor or angiotensin-2-receptor blocker alone or in combination; titrate to control proteinuria even if blood-pressure target is achieved

Blood-glucose control in diabetes mellitus
Haemoglobin A_{1c} 7–8%

Dyslipidaemia
Total cholesterol <5·17 mmol/L,
LDL cholesterol <3·10 mmol/L: use a statin

Smoking
No cigarette smoking

hypertension by means of dietary salt restrictions and diets rich in fruit and vegetables and low in saturated fat have been recommended.[71] The design of these trials is robust, and they have formed the basis of various national and international guidelines and recommendations, including the recently released Joint National Committee Guidelines on management of hypertension.[72] Improved public-health education with reduction of excessive bodyweight, regular exercise, and dietary approaches should lead in the long term to a reduction in the growing numbers of people with diabetes and hypertension who constitute the major future pool of CKD cases. Whether such lifestyle-based approaches are sustainable in the long term remains to be resolved. The success of lifestyle modifications for the prevention of obesity, diabetes, and hypertension will depend to a large extent on the commitment of policy-makers and governments to their implementation. Also, non-governmental organisations have an important role through lobbying of government agencies to take up and support such programmes. The WHO integrated non-communicable-disease prevention programme is targeting common risk factors for chronic diseases and is increasingly aware of the links between hypertension, diabetes, and cardiovascular disease and CKD.

Secondary prevention of progression: pharmacological approaches

In patients with established CKD, there is a wide range of interventions that offer the possibility of slowing progression. Control of hypertension is the single most effective intervention[31] (panels 2 and 3). In patients with CKD, target blood pressure should be less than 130/80 mm Hg in the absence of diabetes or substantial proteinuria (<1 g in 24 h) and less than 125/75 mm Hg in diabetic patients and those with protein excretion in excess of 1 g in 24 h.[73] These recommendations and guidelines are based on observations made in several clinical studies of diabetic and non-diabetic nephropathies (table 2).[74–77] A pooled analysis of many of these studies suggested that the lower the mean arterial pressure, the slower the progression of CKD.[78]

Control of proteinuria and the inhibition of the renin-angiotensin system are important factors in slowing the progression of diabetic and non-diabetic CKD.[57,79] Antihypertensive approaches with inhibitors of angiotensin-converting enzyme (ACE) or angiotensin-2-

Panel 3: Interventions and objectives to limit complications of CKD

Cardiovascular
Keep left-ventricular hypertrophy to a minimum and avoid congestive heart failure
Control hypertension
Control dyslipidaemia
Control anaemia
Control hyperparathyroidism
Cessation of smoking

Anaemia
Maintain haemoglobin above 110 g/L; avoid fall below 100 g/L
Correct haematinic deficiencies
Supplement with parental iron in CKD 4–5
Treat with erythropoietin in CKD 4–5

Renal osteodystrophy/hyperparathyroidism
Maintain serum calcium >2·2 mmol/L, serum phosphorus <1·8 mmol/L, parathyroid hormone between normal and twice normal
Reduce phosphate intake to about 800 mg/day
Calcium and vitamin D supplementation

Malnutrition
Adequate protein/calories supplementation
Correct metabolic acidosis
Timely initiation of renal replacement therapy (glomerular filtration rate 10 mL/min)

receptor blockers have been widely advocated.[79,80] The effect of inhibition of the renin-angiotensin system on the progression of CKD appears to be proportional to the antihypertensive and antiproteinuric effect. The efficacy of ACE inhibitors in African-Americans is similar to that in white patients according to the recent observations of the African-American Study of Kidney Disease and Hypertension.[81] However, dissociation of the protective effect of ACE inhibition from its potent antihypertensive effects has been difficult,[82] and many investigators have managed to achieve effective renoprotection, particularly in diabetic nephropathy, by merely lowering blood pressure whatever agent is used.[76,77,83]

Tight diabetes control slows progressive diabetic nephropathy.[76,83] Target concentrations of glycated haemoglobin of around 7% have been recommended on the basis of data derived from studies such as the Diabetes Control and Complications Trial[34] as well as the UK Prospective Diabetes Study.[35] Lowering of lipid concentrations with inhibitors of hydroxymethylglutaryl coenzyme A reductase (statins) is protective in experimental models of CKD. These drugs could have actions synergistic to the renoprotection afforded by ACE inhibitors and angiotensin-2-receptor blockers.[84] A systematic review showed that lipid lowering in patients with CKD might be protective.[85] However, that analysis was limited by the heterogeneous nature of the studies analysed, most of which included fewer than 25 patients. Statins are well known to lower cardiovascular morbidity and mortality beyond reductions in serum cholesterol concentrations, thus justifying their use in CKD patients who have a high risk of cardiovascular disease.

The concept of multidrug therapy was put forward after a meta-analysis of more than 750 trials involving around 400 000 participants suggested that up to 80% reduction in cardiovascular-disease events could be obtained by a combination treatment with ACE inhibitors, statins, and other cardioprotective agents such as aspirin and antioxidants.[86] Whether a similar therapeutic approach, based on a combination of generic drugs, would be appropriate in the future for some patients with progressive CKD remains to be determined. It could be a pragmatic and cost-effective approach to reduce the global burden of renal and cardiovascular diseases.

Trial	Sample size	Target blood pressure in active-treatment group	p
Modification of Diet in Renal Disease Study[74]	840	Proteinuria <1 g in 24 h: 125/75 mm Hg Proteinuria >1 g in 24 h: 130/80 mm Hg	0·001
Hypertension Optimal Treatment Study[75]	18 790	<139/86 mm Hg	0·001
UK Prospective Diabetes Study[76]	1148	<150/85 mm Hg	0·0046
Appropriate Blood Pressure Control in Diabetes Study[77]	950	Diastolic <75 mm Hg	0·001

Table 2: **Clinical trials of blood-pressure control**

Future therapies

Current management options for CKD are based on the control of known risk factors such as hypertension, proteinuria, hyperlipidaemia, and smoking. Future therapies could be based on the manipulation of putative mediators of renal scarring.

In animals with experimentally induced CKD, a range of novel interventions suggests potential benefits. Inhibition of fibrogenic growth factors such as TGF β1 by neutralising antibodies, specific antagonists, or antisense oligonucleotides has reduced renal fibrosis.[64,87] The administration of antifibrogenic growth factors such as hepatocyte growth factor and osteogenic protein 1 is also protective.[87] Other experimental approaches relied on administration of angiogenic factors such as vascular endothelial growth factor,[88] because a decrease in concentrations of this growth factor has been associated with the loss of glomerular and peritubular capillaries after renal injury. Administration of antifibrogenic hormones or autacoids such as relaxin also preserves renal function and attenuates interstitial fibrosis. Agents as diverse as aminoguanidine (an advanced glycation end-products inhibitor), heparinoids or glycosaminoglycans, and miscellaneous antifibrotic agents such as pirfenidone have all shown promise.

Attention has recently shifted from inhibition of a given mediator to inhibition of intracellular signalling pathways common to several putative mediators. Inhibition of tyrosine kinase activation mediated by platelet-derived growth factor has proven effective.[89] Administration of Y-27632, an inhibitor of the Rho-ROCK signalling pathway, has therapeutic potential in preventing renal fibrosis.[90] Inhibition of Smad3 with the small molecule halofuginone or overexpression of Smad7 protein greatly attenuates experimentally induced renal fibrosis.[65] Inhibition of NFκB was effective in reducing inflammation and fibrosis in an experimental model of glomerulonephritis.[66] Manipulations of the peroxisome proliferator-activated receptor system with thiazolidinediones were effective in reducing proteinuria in experimental models of diabetic and non-diabetic nephropathies.[67]

The translation of these approaches to patients with CKD will depend on the limitation of the efficacy of current interventions and the feasibility of such manipulations in human beings. Furthermore, such interventions could become widespread in clinical institutions in more developed countries while remaining inaccessible to low-resourced countries. For the latter, strategies of early detection and prevention of CKD could remain the most cost-effective approach. Alternatively, the pharmaceutical industry will have to take a progressive approach to provision of care in less developed countries by making new developments accessible to their patients.[91]

Recommendations and strategies

Detection and prevention research programmes are essential. Early detection of CKD and subsequent management has met many, but not all, the criteria of an ideal screening programme.[92,93] The stages of CKD are reasonably well defined (panel 1), but the natural history of the early phases is variable and unpredictable. Screening tests for the measurement of serum creatinine, urinary albumin, and urinary protein are subject to sex-related and racial variability[94] but are generally sensitive when calibration is standardised and the threshold well defined.[95] Interventions are available that slow the progression of established CKD, and cost-effectiveness analyses suggest benefit.[96,97] Another analysis suggested that screening for proteinuria in the general population (<60 years) was not cost-effective.[98]

Several cost-effectiveness analyses based on computer simulation models have suggested that screening for microalbuminuria in type 2 diabetes mellitus is cost-effective.[96] In one such analysis, the treatment of all patients with newly diagnosed type 2 diabetes mellitus by ACE inhibition was more cost-effective (marginal cost-effectiveness ratio US$7500 per quality-adjusted life-year) than screening for microalbuminuria.[96] A hypothetical model of non-diabetic kidney disease suggested that screening of individuals aged 50 years or older, by a single dipstick urine test, would prevent 205 ESRD cases.[97] These analyses are limited by assumptions about the natural history of early CKD, the reliability of screening methods, and the efficacy of early treatment. They also fail to take account of the effect of screening on cardiovascular disease.

Doubt remains as to whether population or targeted screening is justifiable and cost-effective. In cardiovascular disease, population screening is likely to be more effective than targeted approaches because most cases are not derived from the high-risk "tail".[99] Whether at-risk individuals requiring renal replacement therapy constitute a large enough subgroup of patients with ESRD will depend on the country and society in which the analyses take place. Recommendations will therefore vary accordingly. In the USA, the Kidney Disease Outcome Quality Initiative appears to favour a targeted screening approach of at-risk individuals, relying on initial urine testing followed by renal functional confirmation of the detected abnormalities.[100]

After identification of individuals at risk of developing CKD and those with the earliest signs of kidney involvement, primary preventive interventions might be justified. Carefully conducted and well-designed research will be needed to find out the true incidence and prevalence of all stages of CKD in different populations, the sensitivity of screening methods in early stages of CKD, the natural history of CKD stages 1 and 2, and the cost-effectiveness of primary and early secondary interventions. The Chronic Renal Insufficiency Cohort Study in the US, aiming to recruit 3000 patients and follow them up for 5 years, has been launched to address such issues, including risks associated with the development of CKD and cardiovascular disease.[101] Such a comprehensive analysis should inform decision-making and future strategies for the prevention and management of CKD.

Treatment of people with established CKD and renal insufficiency by a multifactorial pharmacological approach aimed at controlling all the risk factors associated with progression is likely to slow progression in most and even halt it in some.[102] In those whose CKD is progressive despite these interventions, prevention and management of the complications of advanced CKD are imperative.[103,104] Such an approach, including treatment of hypertension, anaemia, and dyslipidaemia as well as cessation of smoking (panels 2 and 3) might also have the advantage of limiting the cardiovascular complications of CKD. In patients who reach ESRF, timely initiation of renal replacement therapy is indicated (glomerular filtration rate 10 mL/min) to limit the comorbidity associated with advanced renal insufficiency.[1,104]

In patients with established and progressive CKD, predictions made through mathematical modelling have suggested that deceleration of the decline in GFR after 1999 by 10%, 20%, or 30% would lead to cumulative health-care savings in the USA by 2010 of about US$18 billion, $39 billion, and $60 billion, respectively,[105] undoubtedly a cost saving justifying substantial effort and commitment by the medical profession with the support of governments, non-governmental and charitable organisations, and the pharmaceutical industry. We hope that at long last these agencies will take seriously the global challenge of CKD and put forward serious resources to meet it successfully.

Conflict of interest statement

We declare that we have no conflict of interest.

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