Chronic kidney disease: Global dimension and perspectives

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Global Kidney Disease 3

Chronic kidney disease: global dimension and perspectives

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This is the third in a Series of six papers about global kidney disease

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Chronic kidney disease is defined as a reduced glomerular filtration rate, increased urinary albumin excretion, or both, and is an increasing public health issue. Prevalence is estimated to be 8–16% worldwide. Complications include increased all-cause and cardiovascular mortality, kidney-disease progression, acute kidney injury, cognitive decline, anaemia, mineral and bone disorders, and fractures. Worldwide, diabetes mellitus is the most common cause of chronic kidney disease, but in some regions other causes, such as herbal and environmental toxins, are more common. The poorest populations are at the highest risk. Screening and intervention can prevent chronic kidney disease, and where management strategies have been implemented the incidence of end-stage kidney disease has been reduced. Awareness of the disorder, however, remains low in many communities and among many physicians. Strategies to reduce burden and costs related to chronic kidney disease need to be included in national programmes for non-communicable diseases.

Introduction

In 2002, the US National Kidney Foundation Kidney Disease Outcomes Quality Initiative clinical practice guidelines defined chronic kidney disease as kidney damage or glomerular filtration rate lower than 60 mL/min per 1·73 m² for 3 months or longer, and proposed a classification scheme based on glomerular filtration rate.[1] Later analyses have shown that albuminuria also has an important effect on outcomes,[2] which prompted the Kidney Disease: Improving Global Outcomes (KDIGO) Work Group on Evaluation and Management of Chronic Kidney Disease to include albuminuria in the revised 2012 classification.[3] Causes of chronic kidney disease are also included in the new scheme because they can affect outcomes and the choice of treatments. Early identification of chronic kidney disease is needed to prevent disease progression and reduce the risk of cardiovascular morbidity and mortality. Public health approaches to enabling early identification are, therefore, receiving increasing attention.

As part of this Series on global kidney disease, we examine the worldwide differences in the burden, risk factors, and causes of chronic kidney disease in relation to levels of socioeconomic development and health-care systems. We also review the different types of chronic kidney disease encountered in various parts of the world, controversies in methods of screening, and the

Key messages

- Chronic kidney disease is an important cause of death and loss of disability-adjusted life-years worldwide, but awareness is low among patients and health-care providers
- The number of patients with chronic kidney disease is expected to grow at the fastest rate in the poorest parts of the world, but a strong association is seen between low levels of economic development and reduced availability of renal replacement therapy
- Variations in methods used to estimate concentrations of creatinine in serum and albuminuria affect estimation of the number of cases of early-stage chronic kidney disease
- Unique causes and risk factors for chronic kidney disease, such as exposure to herbal preparations and environmental factors, exist in some parts of the world
- Care for advanced chronic kidney disease is associated with catastrophic health expenditure in developing countries
- Early detection of chronic kidney disease requires development of cost-effective approaches relevant to the local level of economic development and resources
- Integration of screening and management strategies for chronic kidney disease into national programmes for non-communicable diseases can reduce the burden and cost of care of chronic kidney disease
- Because of a shortage of trained nephrologists, general practitioners must be involved in caring for patients with chronic kidney disease

Search strategy and selection criteria

We searched PubMed and Medline for articles published in English between July 6, 2012, and Dec 28, 2012, with the terms "chronic renal failure", "end stage renal failure", "chronic kidney disease", "epidemiology", "health-care costs", "kidney failure, chronic/economics", and "hemodialysis". The following terms were used to obtain geographically specific information: "developing countries OR Asia/epidemiology OR Latin America/epidemiology OR Africa south of the Sahara/epidemiology OR Tropical climate OR Tropical climate/adverse effects". Abstracts of all the publications were reviewed. We selected 749 potentially relevant articles for in-depth review of abstracts and, where relevant, of the full text. Additional references were selected from relevant articles, chapters of recent textbooks, and other web resources. Conference presentations and position papers were also reviewed.

cost-effectiveness, feasibility, and effects of screening and prevention programmes for chronic kidney disease in different countries.

Epidemiology of chronic kidney disease

Mortality

According to the 2010 Global Burden of Disease study[4] chronic kidney disease was ranked 27th in the list of causes of total number of global deaths in 1990 (age-standardised annual death rate of 15·7 per 100 000), but rose to 18th in 2010 (annual death rate 16·3 per 100 000).[4] This degree of movement up the list was second only to that for HIV and AIDS. The overall increase in years of life lost due to premature mortality (82%) was third largest, behind HIV and AIDS (396%) and diabetes mellitus (93%). An analysis of data on cause of death in the USA and Australia by Rao and colleagues[5] showed that a substantial proportion of individuals who had died from diabetes had renal failure, but the cause of death was coded as diabetes without complication. Reported mortality from diabetes-related renal disease was estimated to be four to nine times less than the actual rate.

Incidence and prevalence

The incidence and prevalence of end-stage kidney disease differ substantially across countries and regions (figure 1). More than 80% of all patients receiving treatment for end-stage kidney disease are estimated to be in affluent countries with large elderly populations and universal access to health care.[6] The lower figures reported from poor countries are largely due to patients not being accepted into renal replacement therapy (RRT) programmes, although where economies are growing, the numbers of patients being accepted for RRT are rising strikingly.[7] Projected worldwide population changes suggest that the potential number of cases of end-stage kidney disease will increase disproportionately in developing countries, such as China and India, where the numbers of elderly people are expanding. This effect will be enhanced further if the trends of increasing hypertension and diabetes prevalence persist, competing causes of death—such as stroke and cardiovascular diseases—are reduced, and access to treatment improves.

In contrast to clinically apparent advanced-stage chronic kidney disease, precise calculation of the burden of less symptomatic or asymptomatic early-stage chronic kidney disease, which accounts for 80–90% of all cases, is difficult.[3] Although data on early-stage chronic kidney disease from different parts of the world have been published (appendix), they are confounded by heterogeneity in the populations screened, methods used to determine glomerular filtration rate, and proteinuria assays. The estimates are usually based on a single-time measurement rather than on sustained demonstration of abnormality. Even within countries, subgroups are at increased risk of developing chronic kidney disease, disease progression, or both, including black and Asian people in the UK, black, Hispanic, and Native Americans in the USA, and Indigenous Australians, South American Aborigines, Maori, Pacific, and Torres Strait Islanders in New Zealand, and First Nation Canadians.[8–10]

Demographic characteristics

The demographics of people with chronic kidney disease vary widely worldwide. The mean age of 9614 patients presenting with stage 3 chronic kidney disease in India was 51·0 (SD 13·6) years,[11] whereas in 1185 patients in China it was 63·6 (14·7) years.[12] In India, patients with chronic kidney disease of unknown origin were younger, poorer, and more likely to present with advanced chronic kidney disease than were people with known causes.[11] Young adults aged 20–50 years in sub-Saharan Africa mainly develop chronic kidney disease owing to hypertension and glomerulonephritis.[13] In the USA, African American and Hispanic people reach end-stage kidney disease at younger ages than white people (mean age 57 and 58 years *vs* 63 years).[8]

Causes

Diabetes and hypertension are the leading causes of chronic kidney disease in all developed and many developing countries (figure 2), but glomerulonephritis and unknown causes are more common in countries of Asia and sub-Saharan Africa. These differences are related mainly to the burden of disease moving away from infections towards chronic lifestyle-related diseases, decreased birth rates, and increased life expectancy in developed countries.[14] By contrast, infectious diseases continue to be prevalent in low-income countries, secondary to poor sanitation, inadequate supply of safe water, and high concentrations of disease-transmitting vectors.[15] Environmental pollution, pesticides, analgesic abuse, herbal medications, and use of unregulated food additives also contribute to the burden of chronic kidney disease in developing countries.[16] Rapid urbanisation and globalisation have accelerated the transition in south Asian and Latin American countries, which has led to an overlap of disease burdens, with continued high prevalence of infectious diseases and an increasing prevalence and severity of lifestyle disorders, such as diabetes and hypertension.[17,18] Genetic factors also contribute. Variations in *MYH9* and *APOL1* are associated with non-diabetic chronic kidney disease in individuals of African origin.[19,20]

Identification of chronic kidney disease

See Online for appendix

Identification and staging of chronic kidney disease rely on measurement of glomerular filtration rate and albuminuria. Calculation of actual glomerular filtration rate by measurement of external filtration markers is cumbersome and impractical. Values are, therefore, estimated on the basis of creatinine concentrations in plasma. Creatinine concentrations in serum might also be affected by creatinine generation (dependent on

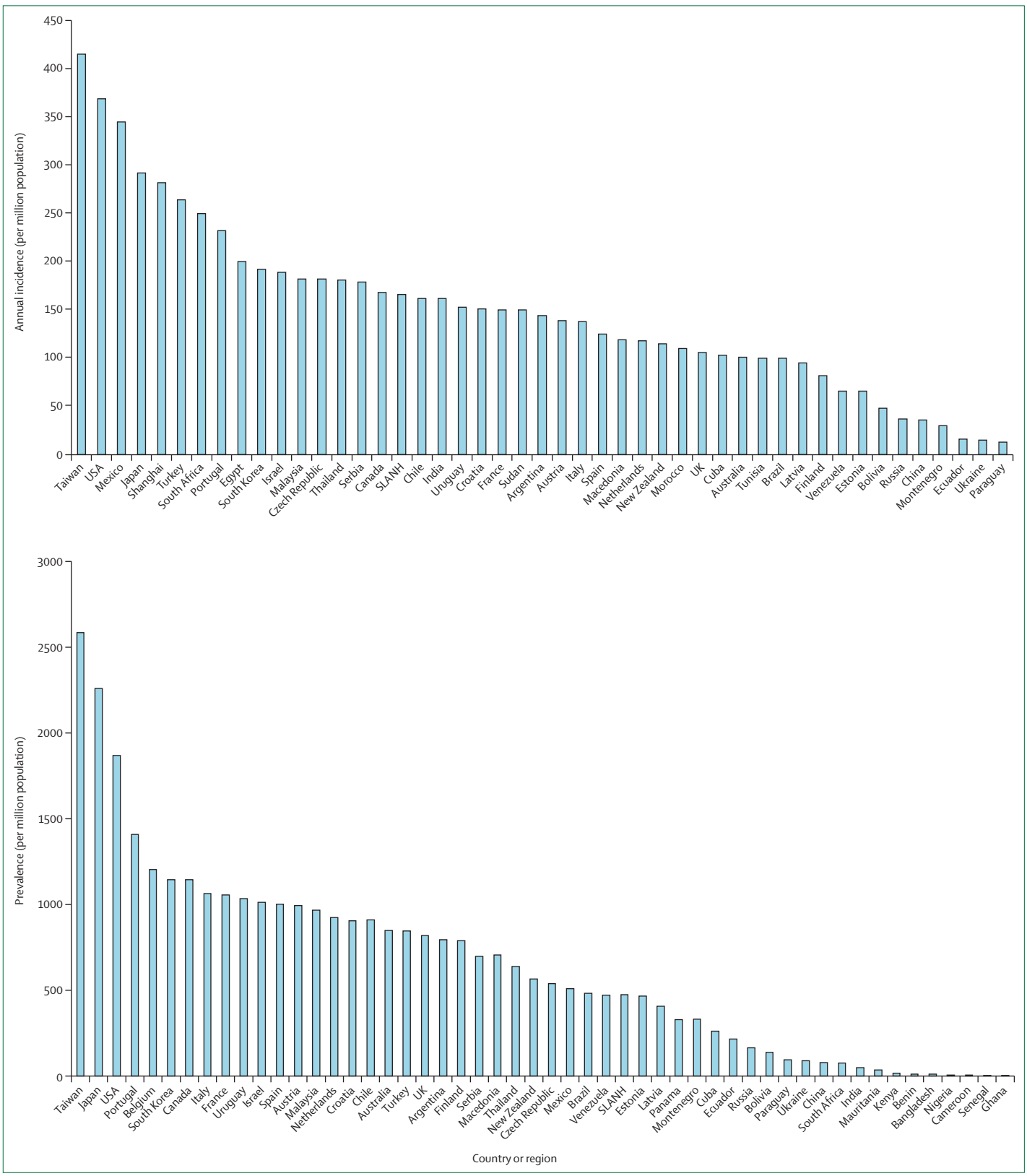

***Figure 1*: Annual incidence (A) and prevalence rates (B) of end-stage kidney disease in different countries**
SLANH=Sociedad Latinoamerica de Nefrología e Hipertensión.

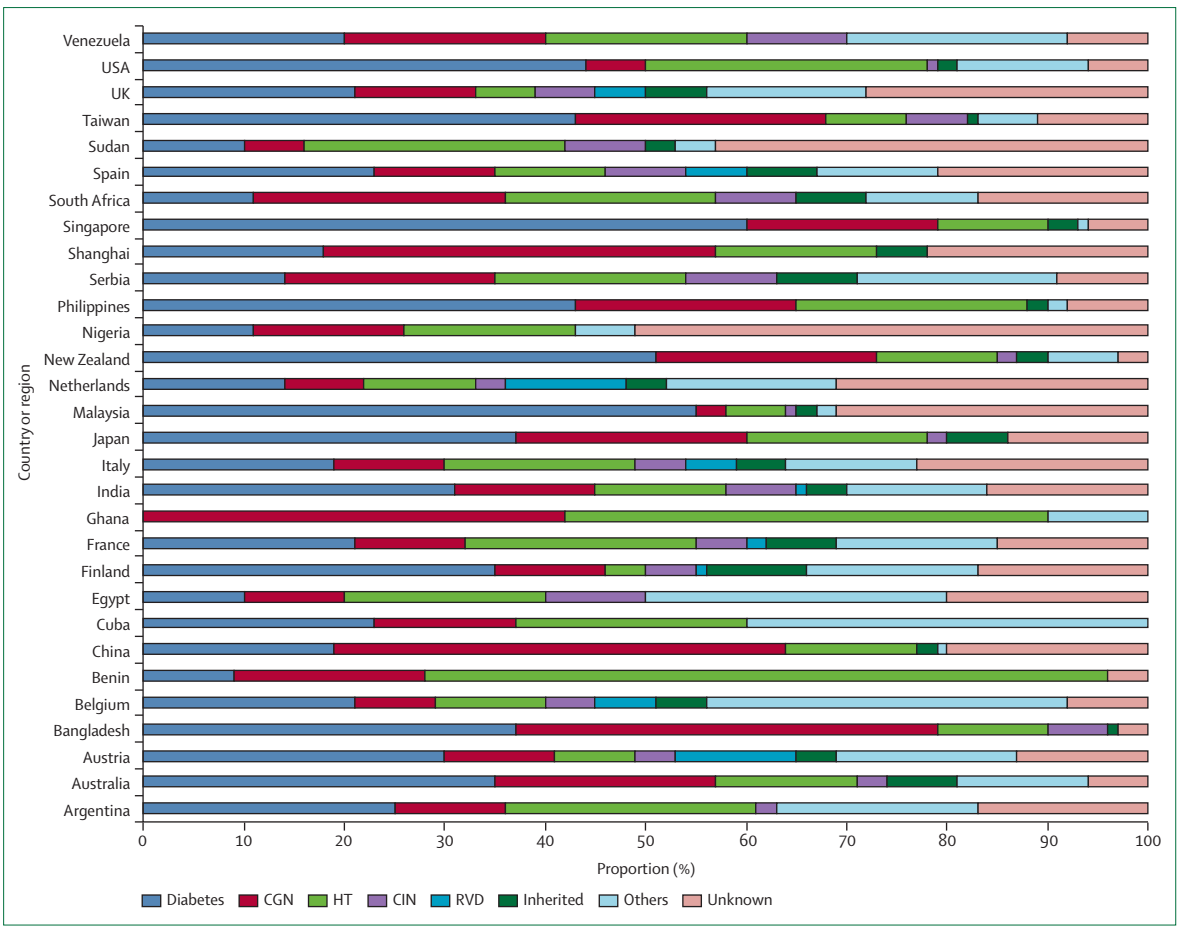

***Figure 2*: Distribution of causes of chronic kidney disease worldwide**
CGN=chronic glomerulonephritis. HT=hypertensive nephrosclerosis. CIN=chronic interstitial nephritis. RVD=renovascular disease.

muscle mass and dietary intake), tubular secretion, and extrarenal removal[3] and, therefore, variations between populations are expected. The Modification of Diet in Renal Disease study (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatine equations have correction factors for African Americans. Chinese, Japanese, and Thai investigators found that the MDRD equation underestimated the absolute glomerular filtration rates in populations from those countries and developed new equations or correction factors.[21–23] The applicability of these modified equations to similar populations, such as the South Asians and most indigenous races, has not been widely explored.

The accuracy of equations is affected by the reference method used to measure glomerular filtration rate. The MDRD and CKD-EPI equations were developed with ^{125}I-iothalamate clearance as the gold standard, the Chinese MDRD equation uses ^{99m}Tc-diethylene triamine penta-acetic acid (^{99m}Tc-DTPA) clearance, and the Japanese MDRD equation uses modified inulin clearance. In a head-to-head comparison study, ^{99m}Tc-DTPA clearance gave 10 mL/min per 1·73 m² higher values than did inulin clearance (figure 3).[24] These different approaches might substantially alter outcomes, as noted in the Japanese general population when two equations were used.[25]

The characteristics of the population assessed during equation development can also affect accuracy. If an equation is developed in patients with advanced chronic kidney disease, output values are generally low.[26] If the same equation were applied to the general population, an artificially high prevalence of low glomerular filtration rates would be seen. This feature led to the development of the CKD-EPI equation.[27] The average glomerular filtration rate reference values for the MDRD and CKD-EPI cohorts assessed for equation development were 39·8 and 68·0 mL/min per 1·73 m², respectively. The MDRD equation showed 7·8% prevalence of chronic kidney disease in the National Health and Nutrition Examination Survey population, but the CKD-EPI showed a 6·3% prevalence.[27] The 2012 KDIGO guideline suggests use of the CKD-EPI equation to calculate estimated glomerular filtration rates in adults.[3] Specific paediatric equations, which require knowledge of height, should be used to estimate

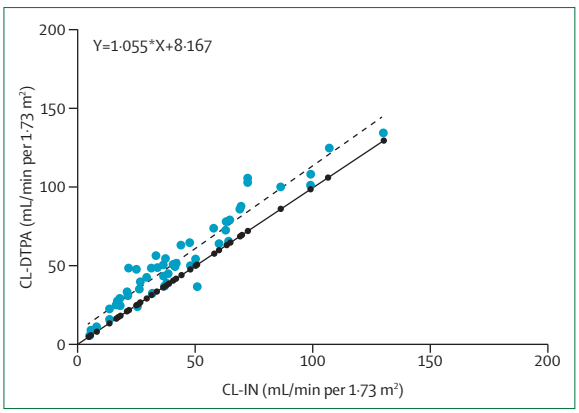

***Figure 3*: Relation between dual plasma sampling ^{99m}Tc-DTPA plasma clearance and modified renal inulin clearance**
Red dots indicate estimated glomerular filtration rate. DTPA=diethylene triamine penta-acaetic acid. CL-DTPA=plasma clearance of ^{99m}Tc-DTPA. CL-IN=renal inulin clearance. Regression line shows an intercept of 8·2 (95% CI 3·9–12·5) and slope of 1·055 (95% CI 0·969–1·141). Reproduced from reference 24 by permission of Elsevier.

glomerular filtration rates in children. Older equations, the most popular of which is the Cockroft-Gault formula, continue to be used in some areas.

The accuracy of estimated glomerular filtration rate and albuminuria assessments is affected by biases in creatinine and urine albumin assays. Assays should be calibrated against reference material traceable to isotope dilution mass spectrometry standard.[3] Several assays are used in laboratories around the world, but most do not meet these standards, which probably leads to inaccuracy, inconsistency, or both, in results. Laboratories in many developing countries do not report estimated glomerular filtration rate values.

Accurate assessment of differences by ethnic origin, region, or both, will require validation of existing equations for estimated glomerular filtration rate against the same glomerular filtration rate reference method and creatinine assay. In the meantime, the CKD-EPI equation is recommended to calculate estimated glomerular filtration rate, with recognition of the possibility of misclassification in some clinical settings and populations.

Risk factors

Hypertension, diabetes mellitus, and obesity

Chronic kidney disease is viewed as part of the rising worldwide non-communicable disease burden. Hypertension, diabetes mellitus, and obesity are among the growing non-communicable diseases and are important risk factors for chronic kidney disease. The global prevalence of hypertension in adults was estimated to be about 26% (972 million cases) in 2000,[28] with most cases (639 million [66%]) being in developing countries. Prevalence was 37%, 21%, and 20% in established market economies, India, and China respectively. In Latin America, 40·7% of men and 34·8% of women had hypertension, whereas in sub-Saharan Africa the values were 27·0% for men and 28·0% for women.[28] Prevalence is higher in urban populations than in rural populations in developing countries.[29] The worldwide hypertension prevalence, when age-specific and sex-specific adjustments are made to take into account changes in the world population, is projected to increase to 1·56 billion by 2025.[28] The actual number, however, might well exceed these projections, as suggested by a Canadian Hypertension Education Program Outcomes Research Taskforce study,[30] which projected increases in prevalence of 25·7% and 60·0% between 1995 and 2005, respectively, in Ontario, Canada, after adjustment for age and sex. Moreover, rates of hypertension control are dismal. Pereira and colleagues[31] showed that only 9·8% of men and 16·2% of women in developing, and 10·8% of men and 17·3% of women in developed countries had controlled hypertension.

Similar trends are apparent for diabetes. The worldwide prevalence of diabetes in adults is estimated to be 6·4%, affecting 285 million people, and is expected to rise to 7·7% by 2030 (439 million cases).[32] The largest increases in prevalence are expected in developing regions (the Middle East, 163%; sub-Saharan Africa, 161%; India, 151%; Latin America, 148%; and China, 104%).[33] Although diabetes is predicted to increase in all age strata, ageing populations and a shift towards urbanisation will contribute substantially. Similarly to hypertension, the projections are probably conservative, and could be exceeded by the actual growth.[34]

The prevalence of obesity worldwide is also increasing. 312 million adults worldwide were estimated to be obese at the beginning of the 21st century. Particularly alarming is the increase in the number of overweight and obese children. In China, the prevalence of people classified as overweight or obese increased by 49·3% from 1992 to 2002.[35] In contrast to the developed world, obesity in developing countries is rising in affluent and educated populations.[36]

Herbs

Herbal medicines are widely used by rural populations in Africa and Asia and have become popular in developed countries.[37] Nephrotoxic effects can result from consumption of potentially toxic herbs, incorrect substitution of harmless herbs with toxic herbs, contamination with toxic compounds, such as heavy metals, or interactions between herbs and conventional treatments.[38]

Herbs can cause acute kidney injury, tubular dysfunction, electrolyte disturbances, hypertension, renal papillary necrosis, urolithiasis, chronic kidney disease, and urothelial cancer.[37] Herbal causes should be considered in cases of unexplained kidney disease, especially in areas where consumption of herbal preparations is high.

Aristolochic-acid and Balkan endemic nephropathies

Aristolochic-acid nephropathy is a progressive interstitial nephritis that leads to end-stage kidney disease and urothelial malignant disease. It was first reported in 1993,

in young women who received a regimen containing a herb later identified as *Aristolochia fangchi* in Belgian slimming clinics.[39] Epidemiological data from Taiwan and China show an association between use of herbs containing aristolochic acid and chronic kidney disease.[40,41] Three clinical subtypes of aristolochic-acid nephropathy have been classified: chronic tubulointerstitial nephropathy (accounting for 93·3% of cases), acute kidney injury (4·3%), and tubular dysfunction with unchanged glomerular filtration rate (2·3%).[42] The worldwide incidence of aristolochic-acid nephropathy is probably higher than initially thought. In Asian countries, where traditional medicines are very popular and pharmaceutical medicines are frequently substituted or supplemented by botanical products that include herbs containing aristolochic acid.[43]

Balkan-endemic nephropathy affects people living along the tributaries of the Danube River, and is characterised by chronic interstitial fibrosis with slow progression to end-stage kidney disease and urothelial malignant disease. It arises from consumption of aristolochic acid in flour obtained from wheat grown in fields contaminated with *Aristolochia clematitis* and, therefore, is a deemed to be form of aristolochic-acid nephropathy.[42]

Infections

HIV infection is epidemic in sub-Saharan Africa. Population screening has shown kidney involvement in 5–83% of HIV-infected individuals in this region.[44,45] In the USA, HIV-associated nephropathy is seen in African Americans but not in white people. Despite a large HIV-infected population, HIV-associated nephropathy is rare in Asia.[46] The differences between regions could be explained by differential prevalence of high-risk alleles in *MYH9* and *APOL1*.[19,20] Early initiation of antiretroviral therapy reduces the burden of HIV-associated nephropathy but carries the risk of nephrotoxic effects, such as crystal-induced obstruction, tubular toxic effects, interstitial nephritis, lactic acidosis, and electrolyte disorders. Other specific infections that cause severe kidney lesions in populations worldwide include hepatitis B and C viruses.

Water

Various disorders directly or indirectly related to water can cause kidney disease. High temperatures frequently lead to water scarcity in tropical regions, which raises the risk of dehydration. Flowing water might be contaminated by heavy metals and organic compounds leached from soil, and grain in waterlogged fields can become contaminated with harmful substances.[47] Many waterborne diseases (eg, schistosomiasis, leptospirosis, scrub typhus, hantavirus, and malaria) affect the kidneys. Children are particularly vulnerable to acute kidney injury because of diarrhoeal diseases.[48] Enteric infections can cause haemolytic-uraemic syndrome, which eventually leads to the development of chronic kidney disease in a substantial proportion of affected individuals. In Germany an outbreak was triggered by Shigatoxin-producing *Escherichia coli*,[49] and in South Asia, haemolytic-uraemic syndrome is frequently seen after infection with *Shigella dysenteriae*.[50]

Chronic kidney disease of unknown origin

Clusters of cases of chronic kidney disease of unknown origin have been reported in some areas of Sri Lanka and India.[7] The affected individuals are mainly young male farmers. Clinical presentation resembles that of interstitial nephritis. Histology shows interstitial fibrosis, tubular atrophy, and interstitial mononuclear-cell infiltration.[51] Contamination of water, food, or both, by heavy metals, industrial chemicals, fertilisers, and pesticides has been suspected.[51] Nevertheless, in a study funded by the Research and Prevention Committee of the International Society of Nephrology, no excess of heavy metals was found in the water in the Srikakulam district of India (Ravishankar MS, Sevenhills Hospital, Mumbai, India, personal communication).

Awareness of chronic kidney disease

Despite its recognition as an important public health issue, awareness of chronic kidney disease remains low.[52,53] In a nationwide health screening programme in the USA that involved around 90 000 adults at high risk of chronic kidney disease, the prevalence and awareness rates were, respectively, 29·7% and 8·6% for white respondents, 22·8% and 6·3% for African Americans, 29·2% and 6·8% for Native Americans, 20·3% and 11·1% for Hispanics, and 23·4% and 11·9% for Asians and Pacific Islanders.[54] Awareness was higher among people with advanced chronic kidney disease (overall 7·8% for stage 3 and 41·0% for stage 4) and those with diabetes, hypertension, and proteinuria.[55] Furthermore, use of nephrology care was low, with less than 6% of participants with stage 3 disease and less than 30% of those with stage 4–5 disease ever having seen a nephrologist. Studies from Taiwan reported that the overall awareness rate for chronic kidney disease was 3·5–9·7%, and was lowest among people with low socioeconomic and educational statuses.[56] In a study of 2576 Uighur adults from Urumqi, China, the prevalence and awareness of chronic kidney disease were, respectively, 5·7% and 1·0%.[57] In another study, only 8% of the rural Chinese population with chronic kidney disease were aware of having the disorder.[58]

Low awareness has also been noted among health-care providers. In a nationwide audit of 451 548 adults followed up by general practitioners in Italy,[53] only 17% had undergone serum creatinine testing, of whom 16% had glomerular filtration rates lower than 60 mL/min per 1·73 m². Among these adults, chronic kidney disease had been correctly diagnosed in only 15%. In another study of 39 525 hypertensive patients, 23% had chronic kidney disease, but general practitioners diagnosed it

correctly in only 3·9%.[59] Incorrect diagnosis results in delayed referrals to nephrologists, which leads to missed opportunities to implement strategies for slowing disease progression, cardiovascular protection, and preparation for RRT.[60]

Data suggest that increased awareness does not necessarily translate to improved outcomes. The risk of progression to end-stage kidney disease and death was higher among people aware of their chronic kidney disease status at entry into the US Kidney Early Evaluation programme. Adjustment for socioeconomic and clinical variables and presence of cardiovascular disease and cancer reduced the difference, but it remained significant.[61] These data, however, might have been confounded by selection bias.

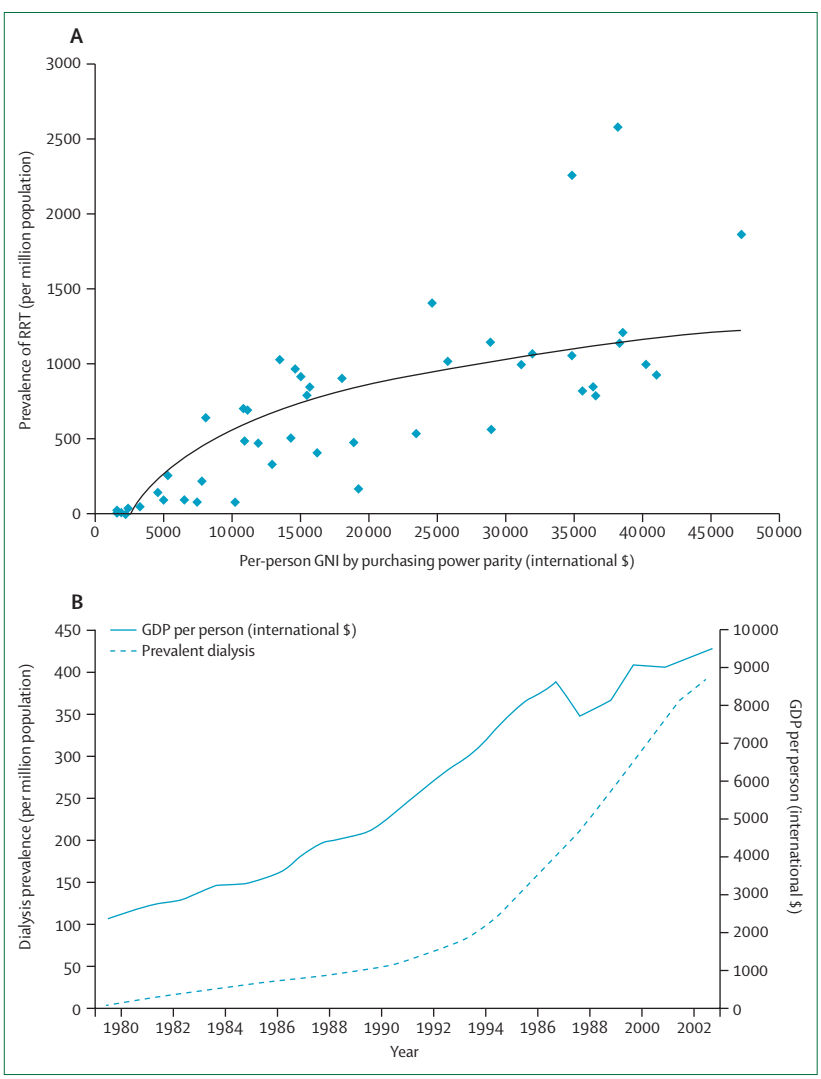

***Figure 4*: Relation between prosperity and access to RRT and dialysis**
(A) Patients receiving RRT worldwide in relation to GNI, based on purchasing power parity (converted to constant 2005 international $). (B) Patients receiving dialysis in relation to GDP in Malaysia from 1980 to 2003. Use of dialysis increased with increasing GDP. RRT=renal replacement therapy. GNI=gross national income. GDP=gross domestic product.

Interactions with other disorders

Cardiovascular disease

Cardiovascular mortality is ten to 30 times higher in individuals with end-stage kidney disease than in the general population when matched for age, ethnic origin, and sex. The association between chronic kidney disease and increased risk of cardiovascular disease is observed in high-risk groups and in people in the general population with low glomerular filtration rates and albuminuria.[2,62,63] The increased risks associated with low estimated glomerular filtration rates and albuminuria seem to be independent of each other. Furthermore, death seems to be a far more likely outcome than progression to end-stage kidney disease in all stages of chronic kidney disease, and the high death rates might reflect accelerated rates of atherosclerosis and heart failure.[64] Thus, individuals with chronic kidney disease should be viewed as being in the highest risk group for cardiovascular disease. Even among dialysis patients, decline in residual kidney function is associated with an increased risk of cardiovascular-related mortality and adverse outcomes.[65] Additionally, cardiovascular disease itself is a well recognised risk factor for chronic kidney disease and predicts progression to end-stage kidney disease.[2]

Acute kidney injury

Patients with chronic kidney disease are at an increased risk of acute kidney injury.[66] A transient increase in serum creatinine of as little as 27 μmol/L increases the risk of death.[67] Acute kidney injury might occur with the use of several medications, such as non-steroidal anti-inflammatory drugs, several antibiotics, and angiotensin-converting-enzyme inhibitors, and, therefore, chronic kidney disease must be taken into account when drugs are being prescribed to enable adjustment or complete avoidance of specific drugs.

A meta-analysis of 13 cohort studies confirmed that acute kidney injury is an important risk factor for chronic and end-stage kidney disease.[68] Severe, long, and repeated episodes of acute kidney injury increase the risk of progression of chronic kidney disease,[69–71] which suggests a bi-directional risk relation. Despite different initial presentations and expression over time, chronic kidney disease and acute kidney injury should be viewed as parts of the same clinical syndrome related to reduced glomerular filtration rates.

Socioeconomic effects and economic implications

The risk of chronic kidney disease is bi-directionally affected by level of economic development. Poverty increases the risk of disorders that predispose chronic kidney disease to develop or progress, and worsens outcomes in those who already have chronic kidney disease. Prosperity increases access to RRT (figure 4). In eastern European countries, the number of centres providing dialysis and transplantation has risen rapidly,

as has the number of patients accepted for RRT in countries or regions that have undergone political and economic liberalisation.[72] These effects might be reversed in times of conflict.[73]

An analysis of National Health and Nutrition Examination Survey data showed that poverty is associated with an increased risk of proteinuria even after correction for age, sex, ethnic origin, education, obesity, hypertension, diabetes, decreased glomerular filtration rate, and medication use.[74] People in the lowest socioeconomic quartile are at a 60% greater risk of progressive chronic kidney disease than are those who are in the highest quartile.[75] An interaction between ethnic origin and poverty has also been shown in minority and indigenous groups in many developed countries.[8]

Chronic kidney disease imposes substantial economic burden on affected individuals, especially in developing countries. Their families experience direct loss of income and changes in consumption patterns because of the spending of household finances on care and welfare costs. About 2–3% of the health-care expenditure in developed nations is used to provide treatment for patients with end-stage kidney disease even though they account for only 0·1–0·2% of the total population; in 2010 treatment costs accounted for 6·3% of the Medicare budget in the USA,[76] 4·1% of the total health-care budget in Japan in 1996, and 3·24% of national health expenditure in South Korea in 2004.[77] The economic costs associated with milder forms of chronic kidney disease are even higher. USA Medicare expenditures on chronic kidney disease patients in 2007 exceeded US$60 billion, which was 27% of the total Medicare budget. Acute kidney injury costs a further $10 billion per year.[78] The Australian Institute of Health and Welfare estimated that the total health expenditure on chronic kidney disease in 2000–01 was AUS$647 million. The estimated cost of chronic kidney disease to the UK National Health Service in 2009–10 was £1·44–1·45 billion, which is about 1·3% of all health spending; more than half this sum was spent on RRT, which was provided to only 2% of the population with chronic kidney disease.[79]

Most people in developing countries have no access to health insurance, which makes care for end-stage kidney disease unaffordable.[80] A session of haemodialysis costs US$100 in Nigeria.[15] This amount is twice the minimum monthly wage paid to federal government workers. The annual cost of dialysis treatment in China is around US$14 300 per patient. Although the Chinese Government plans to institute insurance schemes, patients in rural areas would still have to pay 35–45% of the cost, which will be prohibitive for most people.[81] In India, the cost of a dialysis session varies from US$20 to $60, dependent on the type of facility.[80] Some Indian states have started schemes to provide free RRT to the poor, but coverage is limited.[7]

Care of people with chronic kidney disease, particularly those who present for the first time with advanced disease, leads to catastrophic personal health expenditure in countries where treatment requires out-of-pocket spending. Patients frequently have to travel long distances, often with families, to receive specialised care.[80] Most patients with end-stage kidney disease have complications at presentation and need emergency admission to hospital and dialysis.[60] An analysis of the costs of treatment for 50 consecutive patients with end-stage kidney disease who underwent highly subsidised kidney transplantations in a public-sector hospital in India showed that 82% experienced financial crisis during treatment and more than half (56%) of patients lost their jobs (unpublished).

Prevention and screening

Prevention

Effective strategies can slow progression of chronic kidney disease and reduce the risk of cardiovascular mortality. Foremost are control of blood pressure, preferably with agents that block the renin–angiotensin pathway, and good glycaemic control.[3] Lipid-lowering therapy, irrespective of the starting cholesterol concentration, lowers the incidence of major atherosclerotic events in patients with chronic kidney disease,[82] although no evidence supports the use of statins to slow loss of renal function. Correction of acidosis is thought to slow decline in glomerular filtration rate,[83] but requires confirmation. A cheap and easily applicable approach is to achieve optimum intake of salt and protein.[3] Finally, self-management and support groups can improve lifestyle and dietary habits, knowledge of the disease, and adherence to treatment, and might improve anthropometric indices and glycaemic and blood-pressure control.[84] The cost-effectiveness of a self-management intervention for people with stage 3 chronic kidney disease is currently being investigated in a randomised clinical trial.[85] A multidisciplinary approach is needed to implement treatment strategies.[3]

Screening

Cost-effectiveness

The best way to screen people to identify who will benefit most from preventive measures is disputed. Current recommendations suggest screening individuals with diabetes, hypertension, cardiovascular disease, structural diseases of the renal tract, autoimmune diseases with potential for kidney involvement, and family history of kidney disease, during routine primary health encounters.[1]

Screening for chronic kidney disease is cost effective in people with diabetes. Models have shown that addition of screening for proteinuria followed by use of angiotensin-converting-enzyme inhibitors in people with abnormal proteinuria values reduced costs and the cumulative incidence of end-stage kidney disease, and improved life expectancy.[86] Similar findings were seen in an economic assessment of the Reduction in Endpoints with the Angiotensin Antagonist Losartan study.[87] Cost effectiveness of screening for chronic kidney disease in the general population, however, is unclear. Two studies done in the

USA[88,89] showed that targeted annual microalbuminuria screening, relative to no screening, was cost effective only in people older than 50 years and with diabetes, hypertension, or both: cost-effectiveness ratios per quality-adjusted life-year were US$21000 for those with diabetes, $55000 for those hypertension, and $155000 for those with neither diabetes nor hypertension.[89]

Treatment with fosinopril in people with urinary albumin excretion rates of 15–300 mg per day and blood pressure lower than 160/100 mm Hg in the Prevention of Renal and Vascular Endstage Disease intervention trial,[90] done in the Netherlands, cost €16700 per life-year gained, with a 56% probability of being under the Netherlands cost-effectiveness threshold of €20000.The proportion would increase to 91% if only people with urinary albumin excretion higher than 50 mg per day were treated. Limiting of screening to individuals older than 50 years or 60 years also improved cost-effectiveness.

Analyses of the cost-effectiveness of using estimated glomerular filtration rate to identify patients who will benefit most from treatment are scarce. Simulation modelling data from Canada showed that compared with no screening, population-based screening by estimated glomerular filtration rate in the general population cost CAN$22600 for people with diabetes and $572000 for those without diabetes per quality-adjusted life-year gained.[91] Thus, only screening in people with diabetes by this method seemed cost effective. Data are insufficient, however, to make generalisations.

Worldwide application

Most population-based screening approaches have been undertaken in developed nations. The applicability of these strategies to populations around the world is unclear. Because risk factors are not the same worldwide, the targeting of populations only on the basis of previously described risk factors in all regions might miss groups at risk of chronic kidney disease where these features are not the most common causes. The Asian Forum of Chronic Kidney Disease Initiative has suggested the addition of region-specific high-risk groups for screening, such as people exposed to harmful herbal preparations or environmental factors.[92] Haematuria raises the risk of developing advanced chronic kidney disease, including end-stage kidney disease, in some parts of the world.[93,94] Substantial proportions of individuals in developing countries have undiagnosed hypertension and diabetes and could be overlooked by a risk-factor strategy. Population-based approaches that integrate screening for chronic kidney disease with cardiovascular health programmes have the advantage of increasing health awareness in countries without advanced health systems.

The other issue is the definition of cost-effectiveness. According to the WHO Commission on Macroeconomics and Health, the cost-effectiveness of an intervention depends upon the local gross domestic product. Interventions are classified as highly cost effective (the cost of the intervention per disease-adjusted life-year saved is less than the gross domestic product per person), cost-effective (one to three times the gross domestic product per person), or not cost effective (more than three times the gross domestic product per person).[95] The 2010 per-person gross domestic product and cost-effectiveness thresholds for different regions of the world are shown in the table. Estimates are confounded by the variation in costs of tests, interventions, or both, across countries. Therefore, an intervention that is cost-effective in one region might not be somewhere else. Cost-effectiveness studies should, therefore, be done in all regions. Interventions targeted towards unique risk factors, such as use of herbs, or environment or lifestyle factors, might be more cost effective than screening for proteinuria or estimated glomerular filtration rate in affected areas.

	Per-person GDP*	Cost-effectiveness threshold
North America	41399	124196
High-income countries	33185	99555
European Union	27696	83089
East Asia and Pacific (all income levels)	8724	26171
Latin America and Caribbean	10180	30540
Middle East and north Africa	9491	28473
Upper-middle-income countries	8724	26171
Europe and Central Asia (developing only)	10645	31935
East Asia and Pacific (excluding Japan, South Korea, and Singapore)	6006	18017
Lower-middle-income countries	3169	9508
South Asia	2771	8314
Sub-Saharan Africa	2037	6112
Low-income countries	1141	3422

Values are given as constant 2005 international $. GDP=gross domestic product. *Annual GDP per person, based on purchasing power parity.

Table: **Thresholds for cost-effectiveness of interventions worldwide in 2010, by income group or region**

Integration into national programmes

Notwithstanding the controversies, screening and management programmes for chronic kidney disease, diabetes, hypertension, and cardiovascular disease must be implemented, particularly in developing countries. The training of local experts, implementation of management plans, and the establishing of partnerships between the local community, caregivers, governments, non-governmental organisations, and the pharmaceutical industry will all be required.[96] Methods should suit local needs, and factors such as health awareness and availability of human and material resources should be taken into account.

Benefits from prevention strategies have already been seen in several countries. A kidney health promotion project was started in Taiwan in 2003, with a budget of US$15·0 million per year. The components included a

ban on herbs containing aristolochic acid, public-awareness campaigns and education of patients, funding for research into chronic kidney disease, and the setting up of teams to provide integrated care. In 2007, a programme of integrated care for patients before they developed end-stage kidney disease was also introduced in Taiwan, with an annual budget of US$1·5 million per year.[56] The Cuban Ministry of Public Health has implemented a national programme that supports epidemiological research, continuing education for nephrologists, family doctors, and other health professionals, and reorientation of primary health care towards increased nephrology services, surveillance, and intervention.[97] Similar programmes have been established in Uruguay[98] and Chile.[99] In Mexico, the Ministry of Health has set up a network of health services against chronic renal disease.[100] The cost of implementing this network is estimated to have been $US50 million. The goal is to have reduced the number of patients with end-stage kidney disease by 50% by 2025. According to official reports, the annual incidence of end-stage kidney disease in Taiwan declined from a peak of 432 per million of the population in 2005, to a 361 per million of the population in 2010.[76] The programme has resulted in savings of US$36 million per year, owing to reduced dialysis costs and improved quality of life.[101] In Uruguay, the average annual growth in the incidence and prevalence of end-stage kidney disease declined from 1·6% and 5·4%, respectively, in 1994–2003, to 0·13% and 1·6% in the following decade.[76,102] In Chile, the annual incidence and prevalence of end-stage kidney disease were lowered after the introduction of a prevention programme, from 13·3% and 14·5%, respectively, in 2005–08 to 1·9% and 4·6% in 2009–10.[76] This outcome is notably better than the 10% incidence drop intended by the Chilean health authorities for 2020. Nevertheless, these official country statistics remain to be independently validated, and what the overall effects of these programmes will be is difficult to judge.

Nephrology resources

The resources for nephrology care remain critically low in many parts of the world. Even in developed countries, nephrologists are frequently in short supply. In Latin America the number of nephrologists varies from 1·7 per million of the population in Honduras to 53·9 per million of the population in Uruguay.[103] In Asia, the range is from 0·2 per million of the population in Burma and Indonesia to 5·0 per million of the population in Thailand.[7] With the exception of Nigeria, Sudan, Kenya, and South Africa, most countries in sub-Saharan Africa have fewer than ten nephrologists.[104] The shortage of nephrologists has multiple causes. In developed countries, physicians are reluctant to pursue a career in nephrology because the field is scientifically and clinically demanding and the remuneration is frequently less than that for other specialties.[105] By contrast, in developing countries with poorly developed health-care systems, limited capacity to provide expensive treatments, such as dialysis and transplantation, and few or non-existent nephrology training programmes have led to shortages in care.[105] Globalisation has increased migration of health-care professionals, including nephrologists, from developing to developed countries. The numbers of nephrology nurses and dialysis technicians are also insufficient worldwide.

Detection and prevention programmes for chronic kidney disease also require substantial manpower resources. Although leadership must be provided by nephrologists, most cases of non-progressive chronic kidney disease could be managed by general practitioners. Nephrology referral can be reserved for patients with advanced-stage chronic kidney disease, rapidly declining kidney function, persistent proteinuria, uncontrolled hypertension, or diabetes. Educational interventions in low-income countries increase the clinical competence of general practitioners.[106] After an educational intervention, family doctors used more angiotensin antagonists and statins.[106] In Chile, consistent improvement in outcomes was noted in patients treated by a general practitioner, with kidney function being stabilised in 56%.[99]

Conclusions

Chronic kidney disease is a global public health issue with different features to take into account in different parts of the world. The burden of chronic kidney disease is rising worldwide, as shown by increases in attributable deaths and incidence and prevalence of end-stage kidney disease. Chronic kidney disease and its complications, which involve most organ systems, can be prevented, but awareness and use of accurate methods are needed to enable timely diagnosis. Cost-effectiveness of preventive approaches must be assessed in relation to the local levels of economic development and resources. Prevention programmes will function best as part of national non-communicable disease strategies, with the involvement of general practitioners.

Contributors

All authors contributed equally to the content of the paper, the researching of data, and the writing of the paper. VJ reviewed and edited the paper before submission and all authors approved the final version.

Conflicts of interest

AY-M has received grants from AbbVie, Baxter, and Sanofi Renal, and speaker honoraria from Baxter, Fresinius Kabi, Roche Diagnostics, and Sanofi Renal. All other authors declare that they have no conflicts of interest.

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