Chronic kidney disease – the silent epidemic

Chronic kidney disease brings a huge burden of premature death.

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Professor Davids received his undergraduate training at UCT and postgraduate training in internal medicine and nephrology at Stellenbosch University. He was awarded an International Society of Nephrology Fellowship that allowed him to spend a year in Toronto (2000 - 2001) with Professor Mitchell Halperin, focusing on electrolyte and acid-base disorders. This remains his main area of interest, together with the teaching of renal physiology, and also the use of technology in teaching.

The World Health Organization (WHO) estimated that of the approximately 58 million deaths in 2005, 35 million (60%) were caused by chronic diseases.[1] Middle- and low-income countries account for 80% of these deaths (Fig.1). While we are all concerned about the spectre of the diabetes epidemic looming large on the horizon, it is much less well appreciated that this will be accompanied by a silent shadow, an epidemic of chronic kidney disease (CKD), which brings with it a huge burden of cardiovascular disease (CVD) and end-stage renal disease (ESRD), and premature death.

Definition and classification of CKD

CKD is defined as the presence of kidney damage or a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 for 3 months or more.[2] Markers of kidney damage include the presence of proteinuria or albuminuria, haematuria (after exclusion of other causes), or structural abnormalities confirmed on renal imaging.

The diagnosis of CKD does not require 24-hour urine collections. GFR should be estimated from serum creatinine using prediction equations like the Cockcroft-Gault formula or the Modification of Diet in Renal Disease (MDRD) equation. Proteinuria can be quantified by measuring the protein/creatinine ratio or albumin/creatinine ratio on random urine samples.

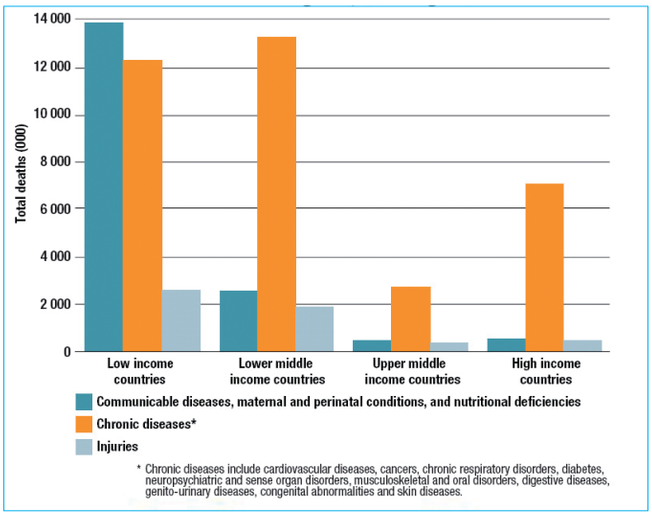

Fig. 1. Projected deaths by major cause and income group (all ages) (WHO report, 2004[1]).

CKD is defined as the presence of kidney damage or a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 for 3 months or more.

Patients are classified according to GFR (Table I), ranging from stages 1 and 2 where there are persistent urinary abnormalities but preserved renal function, to stages 4 and 5 that represent advanced CKD and ESRD. In the early stages the emphasis is on detection and prevention of progression, while during the later stages the focus includes management of the complications of CKD and preparation for renal replacement therapy.

Most pathology laboratories in South Africa now routinely report estimated GFR, using the MDRD equation. There is no additional cost for this calculation and it offers a more accurate measurement of renal function than serum creatinine only. A serum creatinine of 130 µmol/l in a 65-year-old white woman would reflect a GFR of 37.9 ml/min/1.73 m^2 (stage 3 CKD), while the same creatinine level in a 40-year-old black man reflects a GFR of 68.4 ml/min/1.73 m^2 (stage 2 CKD).

These formulas should be applied only to patients with stable CKD; they are not suitable for use in the setting of acute renal failure. The formulas are also unreliable in pregnancy, in patients with normal renal function, and in ESRD. In these settings a 24-hour collection for creatinine clearance is still useful.

Global epidemic of CKD

Population studies in various countries indicate that CKD affects as many as 1 in 10 adults, or over 500 million people worldwide.[3] Approximately one-quarter to one-third of diabetics will develop diabetic nephropathy, making it one of the leading causes of CKD and ESRD. It is estimated that the number of people with diabetes will rise from 171 million in 2000 to 366 million in 2030, resulting in millions of new cases of CKD. The largest relative increases will occur in the Middle East, sub-Saharan Africa and India (Fig. 2). In absolute numbers the countries with the largest projected number of cases in 2030 will be India (79.4 million), China (42.3 million) and the USA (30.3 million).[4]

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Table I. Definition and classification of chronic kidney disease*

Stage	Description	GFR in ml/min/1.73m²
1	Kidney damage† with normal or increased GFR	≥ 90
2	Kidney damage with mild decrease in GFR	60 - 89
3	Moderate decrease in GFR	30 -59
4	Severe decrease in GFR	15 -29
5	Kidney failure	< 15 or dialysis

* Requires the presence of kidney damage or a decrease in GFR for ≥ 3 months.
† Indicated by the presence of abnormalities of the composition of blood or urine (e.g. proteinuria, albuminuria, haematuria), or structural abnormalities. Patients found to have a GFR of 60 - 89 ml/min/1.73 m² without one of these markers should not be considered to have CKD and need not be subjected to further investigation.

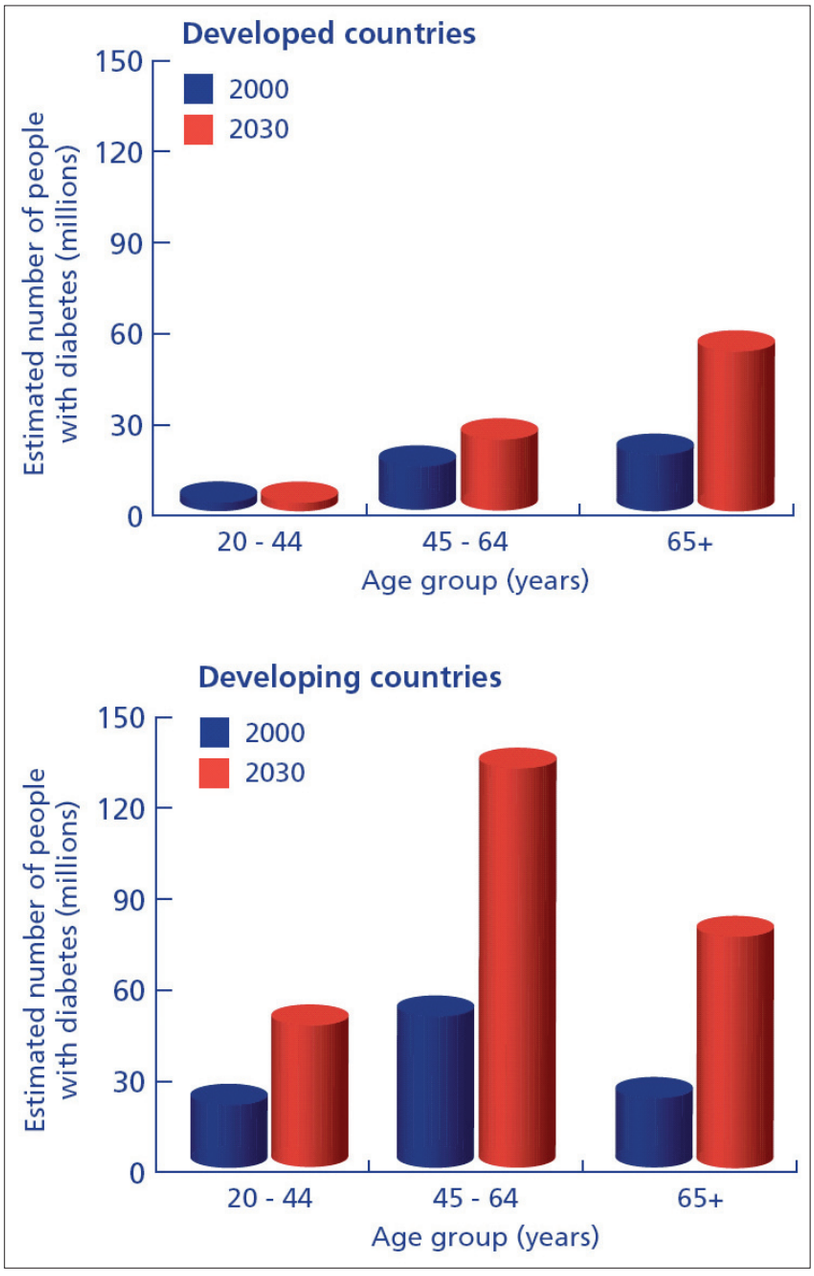

Fig. 2. Projected numbers of adult diabetics – 2000 and 2030 (WHO report, 2004[1]).

Among indigenous populations diabetes and its complications have produced a health crisis and the incidence of end-stage kidney disease has reached epidemic levels.[5] In Canada, for example, rates for diabetes among indigenous people are up to 10 times those for non-indigenous people, depending on the province. A change to a more 'Western' diet and the rising rates of obesity along with genetic predisposition are all hypothesised as potential aetiologies. In addition, a greater likelihood of social disadvantage, with consequent problems such as intrauterine growth retardation and frequent infections, may also contribute to this increased risk of chronic disease.

In developing countries chronic glomerulonephritis and interstitial nephritis cause most cases of CKD because of the high prevalence of infections. Streptococcal infections are common in Africa while tuberculosis is a particular problem in causing CKD in the Middle East and India. In Africa the hepatitis B and C viruses, and increasingly HIV, are important causes of CKD. Parasitic infections may cause ureteric obstruction, interstitial nephritis and glomerulonephritis.[6]

Because treating ESRD is simply unaffordable for many countries, the emphasis must be on prevention of CKD, and detection and slowing of progression of the early stages of CKD to ESRD with its serious and costly complications.

CVD as a complication of CKD

Patients with CKD have a greatly increased risk of death from heart and cerebrovascular disease. Go *et al.*[7] followed up over 1 million people in a community setting, finding an independent, graded association between reduced GFR and the risk of death, cardiovascular events, and hospitalisation (Fig. 3). The Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure (JNC VII) and the American Heart Association have acknowledged CKD as an independent risk factor for CVD events.[8,9] CKD places patients in the highest-risk group, with JNC VII including CKD as a 'compelling' indication for optimal blood pressure control, justifying lower target blood pressure and treatment with specific antihypertensive agents. The US National Kidney Foundation and the American Heart Association recommend that patients with CKD be included in the highest-risk group for treatment of dyslipidaemia, justifying a lower target LDL cholesterol level.[9]

The relative risk of CVD increases from about 1.5 among patients with isolated

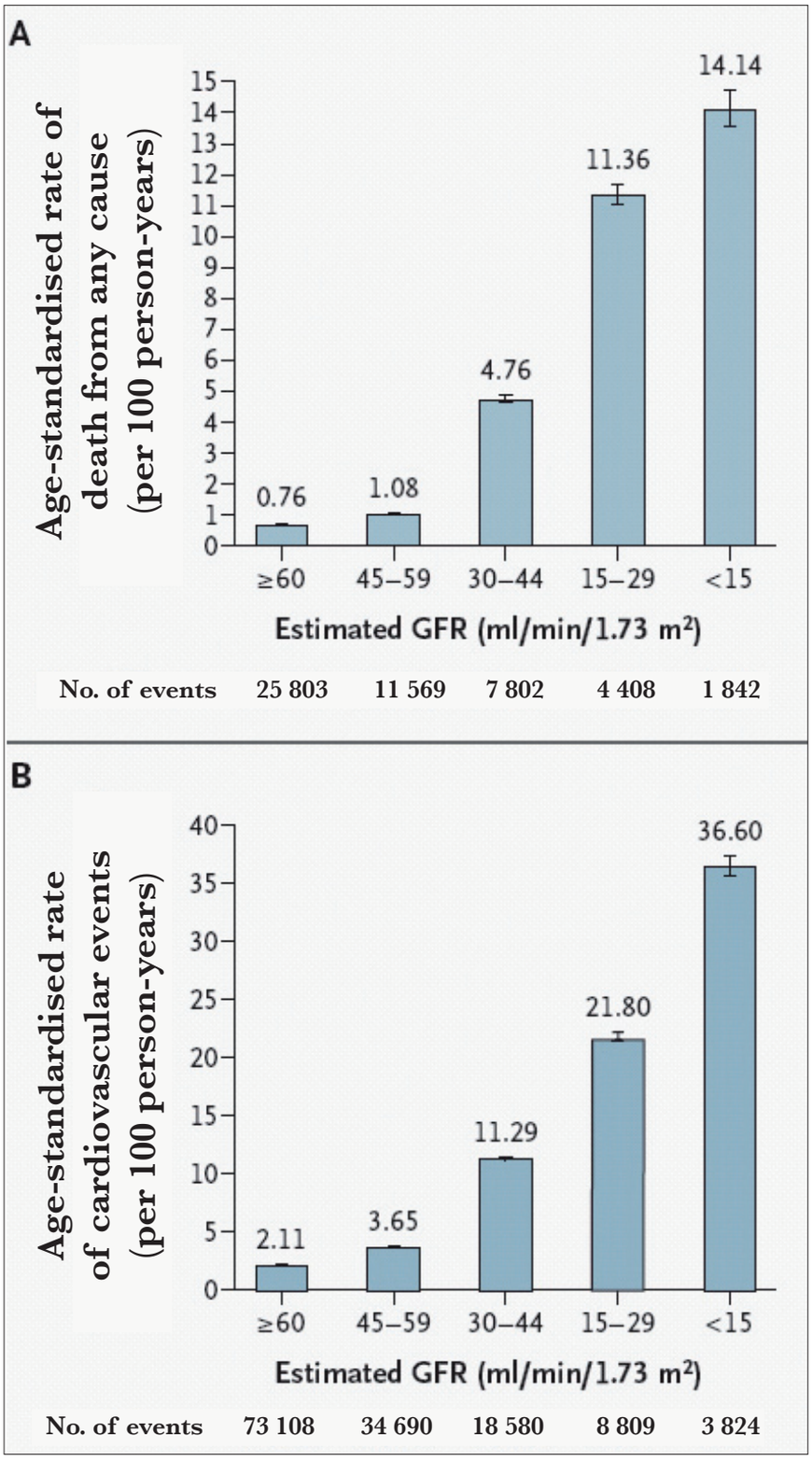

Fig. 3. Deaths and cardiovascular events by stage of CKD (Go, et al. [10]).

proteinuria to almost 500 among young patients who are dependent on regular dialysis.[6] This is attributed to the frequent presence of 'traditional' risk factors, such as hypertension and dyslipidaemia, as well as to 'non-traditional' factors such as hyperphosphataemia, hyperhomocystinaemia, malnutrition, inflammation, chronic fluid overload, and anaemia. A patient with CKD is far more likely to succumb to CVD than to progress to ESRD requiring dialysis or transplantation. In those who do reach ESRD and are included in dialysis and transplant programmes, CVD mortality is 10 - 30 times higher than in the general population.[10]

Malnutrition and inflammation are common in patients with CKD and worsen with progression toward ESRD. These are major predictors of poor clinical outcome, as reflected by the strong association between hypoalbuminaemia and CVD. Among dialysis patients, traditional indicators of overnutrition (high cholesterol or body mass index (BMI)) are associated with better outcomes, while a low BMI and low cholesterol or creatinine are risk factors for a poor outcome. These paradoxical relationships are referred to as 'reverse epidemiology'.

Worldwide there are well over 1.3 million people on maintenance dialysis, and this number is projected to exceed 2 million by 2010.

It has been suggested that inflammation is the cause of both malnutrition and CVD, and the term malnutrition-inflammation-atherosclerosis (MIA) syndrome has been coined to indicate this interaction.[11] Causes of inflammation in dialysis patients include exposure to dialysis membranes or peritoneal dialysis fluid, poor water quality, and infections.

Treatment for ESRD

If we assume a similar incidence of ESRD across most countries of the world, then the wide variation in prevalence is mainly due to differences in survival, which reflects the availability of dialysis and transplantation. Worldwide there are well over 1.3 million people on maintenance dialysis, and this number is projected to exceed 2 million by 2010.[12] Haemodialysis (89%) is much more common than peritoneal dialysis (11%) as the treatment modality. Japan has the highest prevalence rate of ESRD in the world, at 1 857 per million population (pmp) in 2004, followed by Taiwan with 1 706 and the USA with 1 542.[13]

Given the costs of treatment, it is not surprising that most of the world's dialysis patients are being treated in high-income countries, with 52% from just 4 countries: the USA, Japan, Brazil and Germany. Total annual costs for ESRD in the USA have reached $32.5 billion. Based on the USA average of around $66 000 per patient per annum, it is estimated that 1 trillion dollars would be needed to care for ESRD patients worldwide from 2001 to 2010.[14]

Renal replacement therapy represents an

unaffordable financial burden for most poor countries.[6] Frequently, patients undergoing chronic dialysis are only partially rehabilitated, and remain unable to work. Dialysis is often inefficient because of resource limitations – essential treatments such as erythropoietin, intravenous iron, active vitamin D, and statins not being available, coexisting infections and malnutrition being common, and transportation difficulties often resulting in non-compliance.

In countries with a GDP per capita below US$10 000 there is a significant correlation between GDP and ESRD prevalence. In India and Pakistan less than 10% of patients with ESRD are offered renal replacement therapy. Treatment rates in North Africa vary from 30 to 186.5 pmp. In sub-Saharan Africa a conservative approach to therapy most often applies. Few patients can afford chronic dialysis, and renal transplantation is often not available.[15]

In South Africa, the last formal report from the South African Dialysis and Transplant Registry was in 1994 and revealed a prevalence of 99 pmp (3 399 patients), with half of these being on dialysis and half having functioning grafts.[15] Two-thirds of patients on dialysis were on haemodialysis and one-third on peritoneal dialysis. When examining estimates of prevalence in countries with similar gross national incomes per capita (GNIPC) to South Africa (GNIPC $4 960), one finds that in 2004 Malaysia had an ESRD prevalence rate pmp of 522 (13 348 patients; GNIPC $4 960), Turkey 433 (31 251 patients; GNIPC $4 710), and Thailand 243 (15 083 patients; GNIPC $2 750).[13] It would seem reasonable that the resources made available for renal replacement therapy in the public sector in South Africa be linked to the GNIPC and that currently a prevalence rate of 200 - 300 pmp could be expected.

Prevention and treatment of CKD

CKD is a progressive disease, with ongoing loss of renal function even after the initial injury is no longer present. However, complications of CKD can be prevented or delayed by effective treatment of the earlier stages of CKD by reducing proteinuria, by good blood pressure control and by blocking the renin-angiotensin system.[16] Angiotensin-converting enzyme (ACE) inhibition and the use of angiotensin-receptor blockers are protective through combined antihypertensive and anti-proteinuric effects. Aggressive risk factor reduction can normalise or even reverse the annual rate of loss of renal function, and

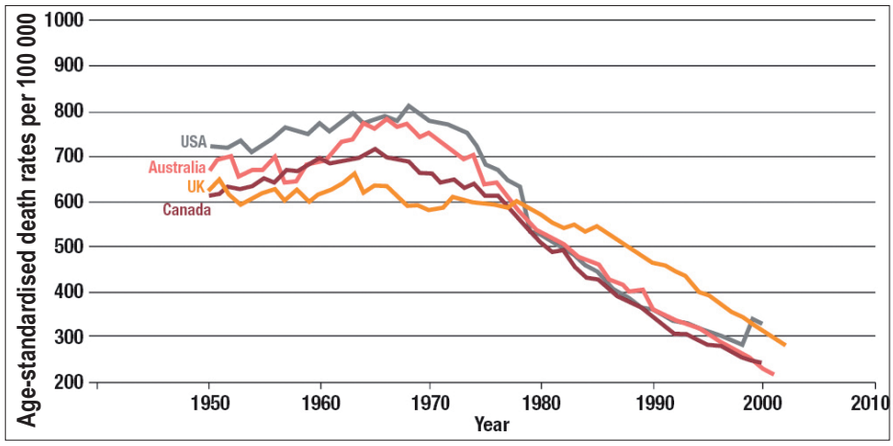

Fig. 4. Deaths from heart disease among men over 30 (1950 – 2002) (WHO report, 2004[1]).

successful intervention programmes have resulted in marked reductions in deaths from renal and cardiovascular causes.[17]

While we know how to treat CKD, there is frequently failure to reach therapeutic targets, lack of awareness of clinical practice guidelines or ineffective implementation of guidelines. In the USA, the third National Health and Nutrition Examination Surveys (NHANES III) revealed that only 27% of patients with CKD had a blood pressure < 140/90 mmHg, and a majority of patients had severe anaemia, with only one-quarter being prescribed erythropoietin despite insurance cover being available for most of them.[18] In Italy, the management of stages 3 and 4 CKD patients was examined in 26 renal clinics. The vast majority of patients received inhibitors of the renin-angiotensin system. However, diuretic treatment was underutilised, statins were not prescribed for most hypercholesterolaemic patients (78%), and erythropoietin treatment was seldom prescribed for patients with anaemia (78%).[19]

In several countries, the application of existing knowledge has led to major improvements in the life expectancy and quality of life (Fig. 4). The cumulative total of lives saved is impressive. From 1970 to 2000, an estimated 14 million CVD deaths were averted in the USA and 3 million in the UK.[1] Effective action is required at national and international levels, and co-operation across disciplines is essential. A 2004 report by the WHO on preventing chronic diseases[1] summarises the situation as follows:

'In low income countries, it is vital that supportive policies are put in place now to reduce risks and curb the epidemics before they take hold. In countries with established chronic disease programmes, additional measures are needed not only to prevent the diseases through population wide and individual risk reduction but also to manage illness and prevent complications. Taking up the challenge for chronic disease prevention and control, especially in the context of competing priorities, requires courage and ambition. On the other hand, the failure to use available knowledge about chronic disease prevention and control is unjustified, and recklessly endangers future generations. There is simply no excuse for allowing chronic diseases to continue taking millions of lives each year when the scientific understanding of how to prevent these deaths is available now. The agenda is broad and bold, but the way forward is clear.'

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In a nutshell

- Chronic kidney disease (CKD) is defined as kidney damage or a glomerular filtration rate (GFR) of < 60 ml/min/1.73 m^2 for 3 months or more.
- As many as 1 in 10 adults is affected, with diabetic nephropathy, glomerulonephritis and uncontrolled hypertension being the major causes.
- The global burden of CKD is expected to increase in parallel with the increase in diabetes – the developing world bearing the brunt of this epidemic.
- The major consequences of CKD are end-stage renal disease (ESRD) and premature death from cardiovascular disease (CVD).
- A patient with CKD is far more likely to die of CVD than to reach ESRD.
- CKD is a very strong risk factor for CVD, justifying lower targets for blood pressure and lipid control.
- The management of ESRD is extremely costly; therefore the emphasis must be on the early detection and treatment of CKD, which is very effective in preventing progression to ESRD and in decreasing the morbidity and mortality from CVD.
- Management involves maintaining a healthy weight, increasing physical activity, reducing salt intake, smoking cessation, and treating hypertension and hyperlipidaemia, including the use of drugs that block the renin-angiotensin system.
- Effective action is required at national and international levels to combat this global public health problem, and co-operation across disciplines is essential.

Single suture

Gene for autism

Another possible candidate gene for autism has been identified. Dan Arking and colleagues at Johns Hopkins University studied the DNA of 1 295 autistic children and their parents. They found a common variant of the gene CNTNAP2. This gene helps to co-ordinate interactions between cells in the nervous system and is often associated with autism.

The gene could be a good target for drugs because it is active through life, rather than only during development.

New Scientist, 26 May 2007.