Chronic Kidney Disease in the General Population

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End-stage kidney disease (ESKD), defined as the need for dialysis, receipt of a transplant, or death from chronic kidney failure, generally affects fewer than 1% of the population. However ESKD is the end result of chronic kidney disease (CKD), a widely prevalent but often silent condition with elevated risks of cardiovascular morbidity and mortality and a range of metabolic complications. A recently devised classification of CKD has facilitated prevalence estimates that reveal an "iceberg" of CKD in the community, of which dialysis and transplant patients are the tip. Hypertension, smoking, hypercholesterolemia, and obesity, currently among the World Health Organization's (WHO's) top 10 global health risks, are strongly associated with CKD. The factors, together with increasing diabetes prevalence and an aging population, will result in significant global increases in CKD and ESKD patients. Treatments now available effectively reduce the rate of progression of CKD and the extent of comorbid conditions and complications. The challenges are (1) to intervene effectively to reduce the excess burden of cardiovascular morbidity and mortality associated with CKD, (2) to identify those at greatest risk for ESKD and intervene effectively to prevent progression of early CKD, and (3) to ultimately introduce cost-effective primary prevention to reduce the overall burden of CKD. The vast majority of the global CKD burden will be in developing countries, and policy responses must be both practical and sustainable in these settings.

Index Words: Chronic kidney disease; end-stage kidney disease; epidemiology; screening; global burden of disease

Dialysis and transplantation, required for end-stage kidney disease (ESKD) management, are the most obvious and burdensome manifestations of kidney disease. The vast majority of ESKD cases result from progressive kidney damage caused by chronic kidney disease (CKD). Although ESKD affects fewer than 1% of the population, CKD is widespread.[1,2] As populations age and prevalence of type 2 diabetes rises, global increases in the incidence and prevalence of CKD and ESKD can be expected. In addition CKD increases the risks of cardiovascular mortality and morbidity and other complications of reduced kidney function. We present our current understanding of CKD in the general population and identify the key challenges to reducing the burden of disease.

The Classification of CKD

A general lack of agreement on the definition and stages of progression of CKD and lack of uniformity in diagnostic tests has been suggested to be largely responsible for widespread underdiagnosis, undertreatment, and underreferral.[3] The recently constructed Kidney Disease Outcomes Quality Initiative (K/DOQI) Classification of CKD provides a framework for understanding and managing CKD in the general population.[4] The K/DOQI classification recognizes the key manifestations of kidney damage, which are albuminuria, hematuria, abnormal kidney structure, and reduction in glomerular filtration rate (GFR). It provides a staging process consistent with current concepts of the progressive nature of CKD and outlines an intervention action plan for each stage. This classification has facilitated more accurate estimates of the prevalence of CKD,[1,2] and revealed an "iceberg" of CKD in the community, of which ESKD is only the tip (Figure 1). This classification will provide a valuable tool, particularly for primary care practitioners who carry the greater burden of CKD diagnosis and initial management.

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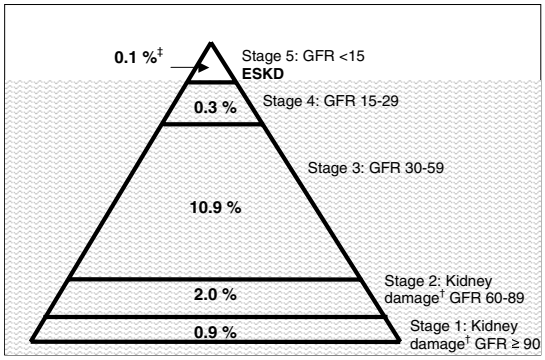

Figure 1. The "iceberg" of CKD in the general population, percentages from the AusDiab study and ANZDATA‡. Kidney damage† is defined as structural or functional abnormalities, manifest as either pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies. Data from Chadban et al,[2] K/DOQI,[4] and McDonald and Russ[42].

Natural History of CKD in the General Population

Recent cross-sectional studies have estimated the CKD prevalence in the adult populations of the United States and Australia stratified by K/DOQI stages. In the United States, among the noninstitutionalized population older than 20 years, the proportions with stage 1 to 5 CKD were 3.3%, 3.0%, 4.3%, 0.2%, and 0.2%, respectively, a total of approximately 20 million persons.[1] In Australian adults older than 25 years, the proportions with stages 1 to 5 CKD were 0.9%, 2.0%, 10.9%, 0.3%, and 0.003%, respectively.[2] Results of such surveys make clear the extent of the CKD burden in these countries.

As CKD is largely asymptomatic until its latter stages, patients usually come to medical attention once kidney damage and its complications are present. Little is known about the early course of disease, its relationship to ESKD, or the rate of decline of kidney function. The proportion of patients with CKD who will progress to ESKD, and which patients are at greatest risk, remains unclear. Although longitudinal data on the natural history of CKD in the general population are sparse, the difference in prevalence of CKD and ESKD clearly indicates that relatively few patients eventually require renal replacement therapy (RRT). In the United States for example, although 20 million adults are estimated to have CKD,[1] the prevalent number of RRT patients in 2001 was approximately 400,000.[5] Understanding how the characteristics of those individuals likely to progress to ESKD, or die of CKD-related complications before reaching ESKD, differ from the characteristics of those for whom CKD runs a benign course is crucial to understanding and addressing CKD.

Longitudinal cohort studies under way in the United States, the Netherlands, and Australia should provide more definitive information on rates of and risk factors for progression to ESKD. Data on the natural history of CKD in the general population are urgently needed to establish (1) whether the incidence of CKD is increasing, (2) the rate of CKD progression to ESKD, (3) the factors that influence progression, and (4) the implications for health-care systems worldwide. Without such information, developing effective prevention and intervention programs and planning adequately for the future burden of CKD and ESKD will be difficult, if not impossible.

Who Is at Risk?

We know that the most significant risk factors for CKD include age, sex, diabetes, hypertension, obesity, smoking, and high cholesterol and triglyceride levels.[1,2,6-8] Evidence also suggests genetic risks for ESKD, demonstrated through linkage analysis[9,10] and familial clustering of CKD and ESKD.[11-13] A US-based study of the family history of incident RRT patients found that 20% reported first-degree or second-degree relatives with ESKD; positive family history was more common among patients whose cause of ESKD was diabetes or glomerulonephritis.[13]

The prevalence of ESKD is high among many ethnic groups. For example, African-American males have nearly double the risk of all-cause ESKD than do White American men.[14] Indigenous Australians experience ESKD at a rate approximately 9 times higher than does the general population[15]; the rate of ESKD in remote communities rises to 20 to 30 times the national incidence.[16] Similarly, New Zealand Maori and Pacific Islanders living in Australia and New Zealand are at increased risk for ESKD.[17,18] Indigenous Australian and

New Zealander ESKD patients tend to be younger than their nonindigenous counterparts, have an excess of comorbidities, particularly diabetes, and have a much higher mortality rate.[19] Other ethnic groups at increased risk for ESKD include Native Americans and North American Hispanics[5], as well as indigenous peoples of South America (eg, Goajiro Indians [20]) and Canada.[21]

CKD and Mortality

The contribution of kidney disease to mortality, on either a national or global level, is not widely appreciated. Analysis of data from the Australian Bureau of Statistics regarding deaths reported during 1997 to 1999 shows approximately 1 in 10 Australian death certificates listed kidney disease as the underlying or as an associated cause of death.[22] Mortality from CKD has been underestimated, largely as a consequence of historical reporting of only a single underlying cause of death. Such reporting is inappropriate for chronic diseases, which are associated with numerous complications, plus chronic and acute comorbidities. An additional obstacle to identifying all deaths associated with kidney disease is the ICD-10 classification, whereby kidney diseases are divided across "chapters."[23] This classification results in hypertensive kidney disease and diabetic kidney disease being coded outside the genitourinary chapter. As a result, almost 1 in 4 deaths attributable to kidney disease may not be identified as such in published statistics.

Recent longitudinal cohort studies have investigated the risk of mortality, cardiovascular morbidity, and progression to ESKD associated with CK.[24,25] With each increasing stage of severity of CKD, an associated increased risk of progression to ESKD was found. However, at every CKD stage, death was far more likely than progression to ESKD.[24] A study of more than one million community-based patients of Kaiser Permanente in California demonstrated an independent, graded association between reduced GFR and the risk of cardiovascular events and hospitalization.[25] CKD has significant implications for clinical and public health in terms of morbidity and mortality, above and beyond the inherent risk of progression to ESKD.

Progression of CKD to ESKD or Death Might Be Preventable

Treatments are available that reduce the rate of progression of both CKD and associated comorbid conditions and complications. For example, early detection of CKD and prescription of angiotensin-converting enzyme (ACE) inhibitors might not only slow the progression of kidney disease but also reduce the high rate of cardiovascular disease.[26] Meta-analyses of randomized controlled trials indicate that ACE inhibitors slow the progression of diabetic and nondiabetic kidney disease, decrease blood pressure and proteinuria, slow increases in serum creatinine, and reduce the incidence of ESKD.[27-29] Compared with either drug alone, ACE-inhibitor therapy combined with angiotensin receptor–antagonist (ARA) therapy has superior benefits in reducing progression to ESKD in patients with proteinuric nephropathies.[30-32] Control of diabetes also retards progression of kidney damage and reduces vascular risk.[33] Some evidence suggests that lipid-lowering drugs have a similar effect,[34] although a large-scale trial of cholesterol-lowering therapy in CKD patients is necessary to definitively demonstrate the benefit of cholesterol reduction in this group of patients.[35] Although smoking reduces kidney function[36] and increases the risk of kidney damage,[37] these risks are diminished in former smokers.[37] Finally, CKD outcomes might be improved through an appropriately monitored low-protein diet,[38] although concerns about possible malnutrition mean that protein restriction is not universally recommended for CKD management.

In addition to preventing ESKD, therapeutic intervention can reduce the rate of complications, associated comorbidities, and death. Many known complications of impaired kidney function are already apparent in the early stages of CKD.[39] Complications are so common that management of its associated comorbidities is more expensive than management of CKD itself.[40] Despite availability of treatment for most of the cardiovascular risks attributable to progressive kidney disease,

cardiovascular diseases remain the leading cause of mortality for ESKD patients.[41] and a leading cause of premature morbidity and mortality across all stages of CKD.[24] Early detection and treatment of complications and comorbidities will improve long-term patient outcomes as well as dialysis outcomes.

Targeted Screening Might Be Viable

With diabetes and hypertension as two of the most significant underlying causes of ESKD,[5,42] and the prospect of a substantive reduction in these diseases unlikely in the short term,[43] ESKD incidence has been suggested to be most successfully reduced by interventions slowing the rate of progression of CKD.[44] This procedure necessitates early detection by screening, followed by intervention. Data from population-based studies have demonstrated the value of proteinuria[45] and albuminuria [7] as predictors of progressive kidney function loss. A longitudinal study of the prognostic significance of abnormal findings by dipstick urinalysis in Okinawa, Japan, [45] found proteinuria was associated with a 15-fold increase in the risk of developing ESKD over a 10-year period. Furthermore, the PREVEND study group in the Netherlands has found albuminuria is independently predictive of a decline to moderately or severely reduced GFR.[7]

A limited number of studies have evaluated the feasibility of mass screening for CKD; however, randomized controlled trials have not yet addressed this question. Models indicate that, because of the enormous number of people who would need to be screened to prevent a single ESKD case, mass screening of the general population for CKD is not cost-effective.[46,47] Diabetic patients are a high-risk group for whom targeted screening is cost-effective.[47] Added to blood-pressure lowering and antiproteinuric therapies, intensive glucose control can reduce the incidence and progression of diabetic nephropathy.[33,48] Hence, screening of diabetic individuals and early intervention are likely to improve outcomes. The global increase in diabetes will mean parallel increases in ESKD attributable to diabetic nephropathy. Diabetes is already responsible for approximately half of all ESKD cases in the United States, New Zealand, and Singapore and is the fastest growing cause of ESKD in European countries.[49]

Hypertension is extremely common; for example it is present in nearly one-third of the Australian population older than 25 years,[2,50] and frequently undermanaged.[51] Hypertension is a critical factor in the progression of kidney disease; it is almost pathognomonic for advanced CKD. It is a leading cause of ESKD in both Australia[42] and the United States,[5] and proteinuria is approximately 5 times more common in hypertensive persons than in normotensive persons.[2] Despite the large size of the hypertensive population, screening for proteinuria in hypertensive persons as young as 30 years has also been demonstrated to be cost-effective.[47]

Current clinical practice guidelines in the US, Canada, and Australia support screening for CKD in persons with diabetes[52-54]and, in the US and Australia, persons with hypertension and family members of persons with diabetes, hypertension, or kidney disease.[53,54] Screening, however, is not rigorously carried out, despite recommendations.[55,56] Even more concerning, underdetection and undertreatment of diabetes and hypertension is extremely common, and many people are unaware that they fall into a high-risk category for CKD. In Australia, for example, approximately half of those with hypertension or diabetes are estimated to be unaware of their condition,[51,57] while fewer than a third of Australian diabetic patients have their blood glucose measured at the minimal recommended frequency.[58]

Assessment of the feasibility of CKD screening also requires consideration of potential harms, such as unnecessary kidney biopsies, adverse effects of treatment, and psychological stress. Side effects of ACE-inhibitor or ARA therapy include a dry cough,[59] an acute elevation of serum creatinine (which, in most cases, stabilizes and does not affect the long-term benefits of ACE-inhibitor therapy),[60] and, more seriously, angioneurotic edema[59] and reversible acute kidney failure in patients with renovascular hypertension.[61] ACE inhibitors also increase levels of an endogenous inhibitor of red cell production[62]; given the detrimental association between

anemia and cardiovascular disease, further research into the effect of ACE inhibitors on erythropoiesis is warranted.

Where screening programs are implemented, resources must be available for adequate follow-up, care, and therapeutic intervention.[63] Moreover, nephrologist training and workforce planning will need to take into account the current and future number of CKD and ESKD patients, lest widespread screening and referral overwhelm the health system. Because early referral will not result in improved outcomes for all patients, we must identify those who will benefit most.[64] At the same time, we need to educate primary care physicians to manage CKD. The quality of available primary care, highly variable between countries, is strongly related to health outcomes.[65] An effective primary care system will be a vital component of CKD prevention strategies.

Effective intervention may also be precluded on the basis of factors other than availability of resources. Certain high-risk groups, particularly ethnic minorities, marginalized groups, or the socioeconomically disadvantaged, might have difficulties in accessing regular and adequate health care for reasons of geography, finance, cultural or linguistic barriers, issues of prejudice or stereotyping, or patient mistrust.[66,67]

Projected Global Health Burden of CKD

Hypertension, smoking, hypercholesterolemia, and obesity are among the WHOs top 10 risks to health,[43] accounting for a large proportion of the global burden of disease. These factors are also strongly associated with CKD. Although few estimates of the future burden of CKD and ESKD are available, one forecast estimates growth in new ESKD patients between 1998 and 2010 to be at least 4.1% per annum in the United States.[68] Projections made by the USRDS indicate the prevalent ESKD population will grow to 1.3 million Americans by 2030.[5] In other developed countries, projected increases are even larger. The forecasted annual increase in ESKD prevalence in Canada is 5.8% [69]; in Europe, it is approximately 8%.[70] Registry data from developing countries indicate increases in ESKD prevalence of a magnitude at least equal to developed countries. For example in Malaysia, prevalent RRT cases increased approximately 11% per annum between 1999 and 2003.[71] However, because of limitations to RRT services, these figures, where available, are likely to greatly underestimate the true ESKD burden in these populations.

Factors influencing ESKD incidence and prevalence include improved survival with other diseases, particularly cardiovascular disease[72] and type 2 diabetes.[73,74] The worldwide epidemic of type 2 diabetes[75] is largely explained by sedentary lifestyle, overly rich nutrition, and resultant obesity.[74] Globally increasing rates of type 2 diabetes in children is also of serious concern.[74] Better treatment means that affected patients live longer with their disease and are more likely to develop its complications, which includes CKD and ESKD.[76]

Because chronic diseases are predominantly diseases of old age, global aging is likely to deliver an increase in the prevalence and incidence of CKD and ESKD. By 2050, largely driven by falling mortality in Asia, 1 in 5 persons is projected to be over the age of 60 years, compared with 1 in 10 persons in 2000.[77]

Conclusion

CKD is likely to be a much greater problem than previously anticipated. On the grounds of trends alone, costs of ESKD will become prohibitive. Developed countries face a likely scenario of RRT rationing within a few years,[78] whereas in developing countries, rationing is already often the norm. Longitudinal studies could provide data essential for accurate cost projections and, more importantly, for the design of rational approaches to early detection and intervention in CKD. Potential benefits include both prevention of ESKD and of CKD-associated complications and mortality. The availability and efficacy of treatments to slow CKD progression and reduce complications add weight to the feasibility of targeted screening programs. Treatment of CKD to slow the progression of, and ideally prevent, ESKD is also associated with signifi-

cant economic benefits. In patients with a GFR of 60 mL/min/1.73 m^2 or less, modeling a reduction in the rate of GFR decline of only 10% showed cumulative direct health-care savings to 2010 of US$18.6 billion.[44] Additional indirect savings from prolonged personal productivity are also likely to be significant.

The "risk transition" accompanying globalization and lifestyle changes in the developing world has brought alarming rises in the prevalence of obesity, diabetes, hypercholesterolemia and hypertension.[43] These problems correspond to an observed rapid escalation of noncommunicable disease, which now accounts for more deaths than communicable disease on every continent except Africa.[79] Currently, low-income and middle-income countries (gross national income of less than US$9,206 per capita as of 2003; total population approximately 5 billion) suffer 85% of the global burden of noncommunicable disease.[80] Prevention of kidney disease is a vital objective in the developing world; the relevant resources and personnel are not, and will not be, available to deal with the current and potential future burden of ESKD.[78] Currently 10% of those receiving RRT reside in developing countries; a direct relationship exists between gross national product (GNP) and availability of RRT.[81] The best prospect for curbing mortality from ESKD in these countries is early detection of those at risk, followed by intervention or primary prevention of CKD. One such screening and intervention program for CKD has been found to be feasible in Bolivia.[82]

Besides the limited availability of RRT in many developing countries, the substantial burden of cardiovascular disease that accompanies CKD is an issue of major public health importance. Moreover, many countries will have to cope with a dual burden of escalating chronic disease alongside undiminished rates of communicable diseases, in particular HIV/AIDS.[43] Not only do developing countries not have the economic resources to deal with the impending burden of chronic disease but most of this burden will fall on people of working age and reduce overall prospects for economic growth. As noted in a recent WHO report, the overall health status of a country plays an important part in the degree of economic growth that the country experiences.[83] The growing burden of CKD and related chronic diseases is both a key global health imperative and a social and economic imperative that we must now address.

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