The Chronic Kidney Disease Epidemic: Stepping Back and Looking Forward

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Estimating the prevalence of chronic kidney disease (CKD) is no simple task. The overall prevalence is relatively low but may be higher in select populations that are not accessible to surveys (e.g., certain ethnic groups, the sick or elderly). Moreover, the tests that define CKD lack precision and transportability to healthy populations. During the past decade, it is not clear that CKD has grown substantially. Some epidemiologic factors that are associated with CKD (obesity and diabetes) are increasing, whereas others (uncontrolled hypertension and smoking) are decreasing. Reasons for the discrepancy between a stable CKD population and ongoing ESRD growth remain speculative. There is evidence that ESRD rates may be stabilizing and that efforts to reduce progression in high-risk groups may be starting to show benefit. Expanding the definition of CKD and increasing detection may be required to reduce overall CKD prevalence. One concern is that many of the well-defined high-risk patient groups (diabetes and black) are still undertreated. Increasing the investigation and treatment of low-risk patients may not be the answer. Clinical inertia (failure to initiate or change therapy) may be a more significant and modifiable barrier toward reducing ESRD, and this deserves increased attention. Furthermore, reducing CKD prevalence will require controlling the precipitating causes. The incremental benefit of detecting CKD in low-risk patients, use of expensive therapies in CKD, or new strategies such as the treatment of prehypertension require solid evidence, not only of the variety that shows benefit (hard end points) but also to whom, when, and at what cost.

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millions of citizens. Simply put, the “epidemic” of CKD is all in how you define disease.

A recent review documented the overwhelming evidence that supports albuminuria as a risk factor for cardiac and renal disease (12). The guidelines also define CKD in patients with higher GFR and albuminuria (2,3). The proponents argue that patients with diabetes and albuminuria have diabetic nephropathy, and most patients with glomerulopathy will have albuminuria. Even if a specific renal lesion is absent, albuminuria reflects endothelial dysfunction/atherosclerosis and is a strong independent epidemiologic risk for CVD. However, estimation of CKD prevalence on the basis of albuminuria in the population requires reading the fine print. Because albuminuria above a specified cut point is not present on repeat sampling in 25 to 50% of surveyed patients, the population estimates are reduced accordingly (13). However, any degree of albuminuria may be abnormal and associated with significant CVD risk (14). Albuminuria is seen in 12 to 14% of adolescent teens, suggesting that the assumptions about CKD and atherosclerosis be taken in the context of age (15). Albuminuria detection rates may be threefold greater with more sensitive testing methods (16). The distribution of albuminuria and low GFR in the general population suggests these tests may identify different segments (17). Albuminuria is not seen in many patients with and without diabetes and significantly impaired kidney function (17). In some ethnic groups, albuminuria may not confer the same increase in cardiovascular risk (18). Taken together, the prevalence of albuminuria and therefore CKD in the general population could have much higher estimates than presently conceded, could approach or exceed 15% of the adult and adolescent population, and may not truly reflect kidney damage in many. Although this discussion may seem overly process driven, the outcome of this debate may have important health care delivery implications. Using the arguments above, all if not most primary hypertension also should be labeled as CKD. The epidemic just got larger. A more conservative and possibly defensible approach in population studies would be to include albuminuria in conjunction with hypertension, diabet es, or hematuria with higher levels of GFR as CKD.

Is the CKD Epidemic Growing?

The undeniable epidemic has been a marked increase in ESRD treatment. Presently, the lifetime risks for ESRD using previously described methods and updated with current 2003 incidence rates are 8.0, 7.8, 3.0, and 2.2% for black women, black men, white men, and white women, respectively (Figure 1) (19). Although most point out that the morbidity and the mortality are high for those who are on dialysis, the mortality is higher without ESRD treatment. The ESRD estimates still do not account for patients who are not referred, are denied, or refuse ESRD therapy. Quantifying nonreferral is difficult, and knowing the extent of attitude change over the past decade is more elusive (20). Nonetheless, nonreferral and nonacceptance still do exist. Although overall ESRD incidence rates in the United States have been relatively stable at 332, 340, and 338 per million population in the past 3 successive years (2001 through 2003 inclusive), the true risk for ESRD before death still remains an underestimation, at present inaccessible, and the absolute burden of ESRD is likely to see continued growth (21). ESRD prevalence will stabilize only when incidence rates (inflow) fall below ESRD mortality rates (outflow). Under these circumstances, projected individual lifetime risks for ESRD could stabilize even though ESRD prevalence counts could increase for some time (establish new equilibrium).

What has been harder to demonstrate is whether there has been an equally large increase in CKD by any definition in the past decade. The only true population-based studies have been the National Health and Nutrition Examination Survey (NHANES) I, II, and III and 1999 through 2000 cross-section, complex stratified sample studies of the US population. These cohorts, although extremely, large do not include the institutionalized and the sick or adequately sample other high-risk populations (Hispanic) (13,22). Given the relatively low incidence of low-GFR CKD in the general population, especially in younger adults, accurate estimates are not possible. Not only could CKD prevalence be underestimated with these surveys, but also significant changes in CKD prevalence will be missed (low power to detect a difference). The study by Hsu et al. (23) suggested that there was a 25% increase in CKD as defined by an MDRD GFR of <60 ml/min per 1.73 m² from 1978 to 1991, which appears largely in the population with diabetes. The recent study of Coresh et al. (13) suggested that there has been no further increase in CKD from the 1988 through 1994 survey to the 1999 through 2000 evaluation. The relatively low estimates of CKD in the adult population do not readily convey that most of the CKD is in the older age population. The estimate by Hsu et al. of the population with GFR <60 ml/min per 1.73 m² is only 2.46% from NHANES III, whereas the estimate by Coresh et al. for the same data is almost double at 4.4%. Hsu et al. (23) confined the population to 20- to 74-yr-olds, whereas the study by Coresh et al. (13) had no upper age limit. Therefore, the 1.94% discrepancy (44% of the population with low-GFR CKD) can be explained by the inclusion of patients who are aged 75+, who have a very high prevalence of low GFR. Both studies would have missed patients in long-term care facilities, in whom the prevalence of CKD is extremely high (22).

If CKD prevalence has not increased substantially, then the
question raised is why have the ESRD rates continued to climb? There are several factors in addition to some growth in CKD. Two studies have argued against better patient survival in high-risk patients as the proximate reason for more ESRD (24,25). Some have concluded that there must be a greater risk for disease progression to account for this discrepancy (25). However, there may be a greater willingness of patient and provider to accept treatment especially in the older segments of the population. In the past decade, the mean age of incident ESRD therapy has increased by 4.5 yr for men and 2.5 for women and 3.6 for white and 2.6 for black populations (21). That CKD has the highest prevalence in the oldest segment of the population (>75) but ESRD rates have only recently outstripped those in the 60- to 74-yr-old group can be explained by higher competing mortality and nonacceptance in the past (21). Although the increase in life expectancy has been modest at 0.5, 1.9, and 1.7 yr in the white female, white male, and black female populations, the increase for black men has been 3.8 yr (26). Longer life expectations increase the cumulative risks for ESRD. Earlier initiation of dialysis therapy also has played a role and is a factor that may be difficult to quantify. The estimated GFR of patients who start dialysis has increased steadily in the past decade from 7.4 to 10 ml/min per 1.73 m² (21). Patients who start dialysis with higher GFR are older and have more comorbidity. These factors could explain a significant increase in ESRD without a significant detectable change in CKD prevalence or rate of disease progression.

**Will the CKD Epidemic Grow?**

It is possible that despite the best attempts to control progression by nephrologists, there may be factors that are accelerating progression in the late and unreferral population. In this case, the prevalence of CKD may remain relatively stable, but transitions into CKD and exit to ESRD and death may be higher. Several studies pointed out that the risk factors for CVD and CKD are the same (27,28). Fox et al. (28) reported that hypertension, diabetes, obesity, and smoking were associated with development of CKD and could be accelerating transition through to ESRD.

Overall mortality rates for CVD have dropped dramatically in the past 25 yr (29). Both early treatment of cardiovascular risk factors and lower case fatality rates have contributed to this decline. If the CVD and CKD are linked through common risk factors, then higher rates of progression would seem unlikely, unless the benefits of CVD disease prevention outweigh the benefits of CKD progression. Surprising, one report projected a potential decline in life expectancy if trends in obesity continue (30). Although some would argue that it is not the obesity *per se* but rather the associated diseases (hypertension and diabetes), other, more subtle influences, such as obesity-related inflammation/oxidative stress, also may contribute (31). Figure 2 shows trends for hypertension (>140/90 mmHg), high cholesterol (>240 mg/dl), smoking, diabetes (total and undiagnosed), CKD, and microalbuminuria from the National Health Examination Survey (NHES); NHANES I, II, III; and 1999 through 2000 national surveys (32–35). Diabetes and obesity have increased, whereas other risks such as hyperlipidemia, smoking, and hypertension have declined. The lack of any significant change in CKD may be the result of countervailing forces. Alternatively, the adverse effects of diabetes and obesity simply may take another decade to manifest. Finally, there may be other unrecognized accelerators of disease progression. An example may be over-the-counter drugs such as nonsteroidal anti-inflammatory drugs (36). It is not clear whether greater use of these medications, especially in the elderly, contributes significantly to progression.

Predicting trends in CKD also will require knowledge of age and ethnicity population shifts. Longer life expectancies undoubtedly will increase both CKD and ESRD. Increases in populations with high rates of developing ESRD (black individuals) or diabetes (Hispanic, American Native, and other ethnic groups) will contribute to ESRD and may not be portrayed accurately in future population CKD surveys because of the limited ability to examine accurately underrepresented populations.

The black population is an important area of concern. Despite having a prevalence of CKD that is no different from that of the white population, the risk for developing ESRD is three- to fourfold higher in black individuals. To explain this phenomenon, transition from normal levels of renal function to modest CKD and eventually ESRD must be considerably higher in black individuals. Calculating transition rates from different levels of function are hampered by lack of accurate CKD prevalence estimates at incremental ages. Modeling analysis suggests that a very high rate of progression from mild to moderate kidney impairment occurs in black individuals between the ages of 40 and 60 and probably earlier and that transition rates from moderate CKD to ESRD are threefold higher than that seen in white individuals (37). A longitudinal, observational, community-based study observed high rates of progression (threefold higher) (38). This study also suggested that much (80%) of this increase could be explained by potentially modifiable factors, such as lower socioeconomic status, suboptimal health behaviors, suboptimal control of glucose level, and BP.

Studies show that some of the discrepancy between BP control...
for black and white individuals is diminished when access is equal (39,40).

There is hope that these transition or progression rates can be controlled. Although the African American Study of Kidney Disease and Hypertension (AASK) study failed to show an effect of tight BP control to reduce progression, controlling BP and use of angiotensin-converting enzyme (ACE) inhibitors reduced mean rates of GFR loss to <2.5 ml/min per 1.73 m² per year (41). What is required is access to the population that is most at risk and the resources to ensure that targets are achieved and maintained. Examination of the NHANES III data also shows that the oldest age group (>75) of black individuals tend to have better kidney function than their white counterparts (37). Family clustering of ESRD especially in black individuals has been observed, and studies that are designed to detect genetic determinants are under way (42,43). Both observations are supportive of a relatively strong genetic predisposition (although environmental factors cannot be ruled out) whereby patients who are at risk progress rapidly, leaving a protected subgroup with preserved kidney function. This area is ripe for genetic studies that identify the subset that are most at risk and should be targeted early. However, even this information will not help until effective models of health care delivery are implemented.

Failure of Therapy and Future of CKD

The recent findings that the cumulative risk for ESRD in type 1 diabetes abroad and the ESRD incidence rates for all diabetes in the United States actually are declining is very encouraging (44,45). The age-adjusted incidence of ESRD from diabetes fell from 305 per 100,000 people with diabetes in 1996 to 232 per 100,000 in 2002 (45). Treatment strategies with lower BP goals and early ACE inhibition and angiotensin receptor blocker use may be working. Supporting this argument are the findings of better BP and cholesterol control in the segments of the population with obesity and diabetes (33,46). ACE inhibition/angiotensin receptor blocker use has nearly doubled in the CKD (with and without diabetes) populations from the NHANES III (1988 through 1994) to the 1999 through 2002 survey and has increased nearly as great in incident ESRD patients in the past few years (21). Nonetheless, many of these patients are far from under optimal control, and this represents the real challenge (47). Diabetes represents 53% of incident ESRD patients. Innovative financing of treatments as well as the availability of multidisciplinary care clinics may be needed to achieve targets fully (48). The role of computerized clinical decision support systems requires further study (49). One could argue that if we simply were better at treating patients with diabetes (achieving blood sugar, cholesterol, and BP targets) and treating patients with hypertension to goal with appropriate and prompt therapy, then we would reduce not only the risk for CKD and ESRD but also the mortality that is associated with these states. Although there is evidence of improvement, clinical inertia (failure of health care providers to initiate or intensify therapy) may be the largest barrier to achieving treatment targets (50,51). In a recent large hypertension cohort, Okonofua et al. (52) found that changes in antihypertensive therapy were made at only 13.1% of the visits in patients with uncontrolled hypertension (≥140/90 mmHg). Primary care physicians are not alone in demonstrating significant clinical inertia in the treatment of hypertension in CKD (53).

One of the fundamental tensions in medical care is whether to affect health by intensely treating a smaller diseased segment of the population of patients who are at risk or a more global approach to disease prevention (hypertension and diabetes prevention). A second dilemma is determining the best cut point to define a disease or risk factor compared with normal. BP, albuminuria, GFR, lipids, glucose, and all other current inflammatory measures suffer the consequences and controversy of being dichotomized (or staged), whereas their impact on CVD and CKD likely is continuous (within reason) (14). Although much is being written about how every level of GFR reduction and increase in proteinuria is associated with adverse outcomes, we are left with the need to define operationally a strategy in the context of our population. Redefining and enlarging the CKD population may seem to be more convenient and efficient conceptually for identification and treatment from a nephrology or epidemiologic perspective. Broadening the definition of CKD may not be as effective as hoped if the issues of access and inadequate therapy are not addressed or if this strategy simply identifies lower risk populations. The risks, incremental benefits, and incremental costs of intervention strategies over present interventions must be addressed.

Several areas of uncertainty should be discussed. Increased referral for kidney evaluation and monitoring and treatment in multidisciplinary CKD should greatly benefit those who are at high risk for progressive renal disease. It is unclear what the impact will be if milder degrees of CKD or of isolated albuminuria are referred with much less risk for progression. Will the incremental benefits be worth the costs? Screening for renal disease in patients with hypertension and kidney disease is strongly supported. Will ongoing monitoring of albuminuria in patients with hypertension and diabetes be necessary if BP is not controlled? Could the costs of monitoring be better spent on therapy? It also is not clear that unselected screening for isolated proteinuria/albuminuria (in the absence of hypertension, diabetes, or low GFR), performing additional renal investigations, and treating with antihypertensive therapy will be cost-effective (54). It also is not clear the extent that unselected referral of the very old (≥75) with asymptomatic CKD (stages 1 through 3) will change overall outcomes substantially. This group constitutes a significant proportion of the population with low-GFR CKD and albuminuria as currently defined and has high competing risks for death. Mortality risks are not uniform across all age groups for any given GFR and are not greatly elevated in older patients until GFR falls to <30 to 40 ml/min per 1.73 m² (55,56). A large percentage of the patients with a GFR <60 ml/min per 1.73 m² are older and have a GFR between 50 and 59 ml/min per 1.73 m² (56). Cumulative risks for ESRD also are very low in this elderly population (57). This is an area where guidelines for action may have been promoted before the evidence. Along these lines, even several cancer screening strategies have limits in the very old despite remaining at high risk for disease (58). This is not to suggest that this
segment of the population be denied effective antihypertensive and lipid-lowering therapy but that the need to investigate CKD stages 1 through 3 may not lead to a substantial improvement in outcomes.

Reducing the development of CKD in the community is an alternative but possibly more elusive strategy. One could argue that the increase in risk for CVD and ESRD is already present by the time CKD is established, and treatments are not likely to be curative at any time point. Defining CKD at a specific GFR or albuminuria cut point by itself will not reduce numbers of patients who develop CKD. Alternative or additional options to reduce the prevalence of CKD include lifestyle modification programs and possibly pharmacologic interventions in patients who are at high risk for diabetes (59,60). Routine ACE inhibition in patients with diabetes before albuminuria may prevent nephropathy and be cost-effective/saving (62,63). More widespread use of ACE inhibition in the general hypertensive population over the longer run actually may prevent or at least delay new-onset diabetes (64). Younger black individuals who currently have low-normal GFR (60 to 80 ml/min per 1.73 m²) especially with genetic/family risk and are identified through high-yield screening approaches may be critical to improving outcomes in this population (65). The use of age-referenced GFR may help devise a more effective and efficient plan of action. The costs and benefits or redefining hypertension to lower levels in the global population also should be addressed but may be a significant challenge on many fronts (66). These strategies actually would reduce the prevalence of CKD but would require further study before widespread implementation.

The purpose of this article was not to discount the important efforts of many to increase the awareness of CKD in the community with the hope of improving outcomes in this population. It was to forecast changes in the epidemic with the more recent data and to look critically at our current and possibly future strategies. As definitions of hypertension and diabetes have changed, so will those of CKD. The extent of the “CKD epidemic” in turn will change. Definition aside, CKD growth is not inevitable, as witnessed by an analysis of the more recent population surveys, will be subject to counterbalancing stresses, and is not likely to be reduced without a significant new strategy. The effect of ESRD is more difficult to predict. There are signs that incidence rates of ESRD are stabilizing, but the overall effect on ESRD will be less than desired and far less than the potential. Achieving current treatment goals in all at-risk patients could reduce rates further and eventually stabilize ESRD prevalence. Nonetheless, there are known (diabetes and obesity) and possibly unknown factors that could undermine future success. Research into mechanisms and more novel treatments are welcomed to prevent and treat atherosclerosis and progressive renal scarring. It is easy to say that we must be more aggressive, do everything, and have newer treatments. However, we should not lose sight of the fact that frontier research should include innovative strategies that improve access to care, achieve treatment goals by eliminating if not reducing clinical inertia, and identify those who are most at risk. As with any intervention, there will be need of evidence not only of the variety that shows benefit but also to whom, when, and at what cost.

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