Chronic kidney disease is common: What do we do next?

Josef Coresh¹, Lesley A. Stevens² and Andrew S. Levey²

¹Johns Hopkins Medical Institutions, Baltimore, MD and ²Division of Nephrology, Tufts-New England Medical Center, Boston, MA, USA

Introduction

Glassock and Winearls thoughtfully acknowledge some of the major gains made as a result of the standardized guidelines for the definition, evaluation, classification and stratification of chronic kidney disease (CKD) as well as point out a number of concerns [1]. We agree with the distinction between a clear epidemic rise in the number and rate of treated kidney failure [also known as end-stage renal disease (ESRD)] in the United States and other countries and much weaker data about trends in earlier stages of CKD. There is also high prevalence of earlier CKD stages 1–4 and a growing literature about associated consequences. We will briefly discuss trends in treated kidney failure, trends in earlier stages of CKD, the rationale for a single GFR cutoff for the definition of CKD, and our view of promising approaches for future research and practice in CKD. We recognize that population estimates of the full range of CKD (stages 1–5) result in dauntingly high numbers which are clearly beyond the scope of nephrologists alone. We think that the ability to make such estimates based on survey and clinical data provide important information to guide planning and to avoid thinking that all patients with CKD can or need to be seen by a nephrologist. Standardized definition and staging facilitates growth of the evidence base about prognosis and treatment that should be based not only on CKD stage, but also on the full clinical presentation, including, the cause of kidney disease, level of proteinuria, age, sex and race. It is likely that drug dosing and avoiding acute kidney injury from medications, contrast agents and procedures will largely depend on estimated GFR (eGFR) alone, but additional information will be needed for the prevention and treatment of different outcomes of CKD.

Kidney failure

Treated kidney failure is epidemic and has become common. Nearly 0.5 million patients were treated with dialysis or transplantation for kidney failure in the United States in 2005 and this number is projected to increase to 0.7 million by 2015, compared to 287 000 in 1995 and 113 000 in 1985 [2]. We agree with Drs Glassock and Winearls that the extent to which this epidemic is due to increased incidence of treatment rather than increased incidence of kidney failure is not well understood. The uniform definition of kidney failure (CKD stage 5) based on GFR <15 ml/min/1.73 m² or treatment by dialysis allows for the study of the prevalence of individuals with kidney failure who are not treated with dialysis and transplantation as included in some recent papers [3]. It is interesting to note that among US male veterans with eGFR <15 ml/min/1.73 m², the annual incidence of dialysis initiation or transplantation varies from ~80% before age 65 years to 29% after age 85 years. The range for annual mortality in the same groups was 3–9% before age 65 years and was 49% after age 85 years. In comparison, individuals with an eGFR >60 ml/min per 1.73 m² had annual rates of dialysis initiation or transplantation <0.03% for all age groups and mortality rates which varied from 0.6 to 3% before age 65 years to 12% after age 85 years. Thus, age is an important predictor of risk even within CKD stage 5.

CKD stages 1–4

eGFR is a useful first step in CKD detection, evaluation and management, but not the last step. The uniform definition of CKD is a paradigm shift and discussion of its implications is important. GFR is central to the definition and classification because it is an overall measure of kidney function and is a key determinant of concurrent complications such as hypertension, anemia and bone and mineral disorders, as well as future risk of drug toxicity, acute kidney injury, cardiovascular events and mortality. We think it is important to think separately about the risks of different complications as noted in Table 1. In addition, GFR is not the only determinant of risk. Thus, eGFR should be viewed as a necessary clinical decision tool, but a more complete clinical assessment of patients with CKD is recommended and needed. Studies that use the combination of proteinuria and eGFR to estimate risk are being published and are a first step toward this goal [4,5].

Strengths and limitations of GFR estimation. As is now well understood, GFR estimation has a number of
aim to decrease the bias in GFR estimation related to levels of kidney function. New equations should facilitating evaluation of prevalence and estimates of risk atinine or cystatin C to an interpretable metric (eGFR), serum levels of endogenous filtration markers such as cre-
limitations [6,7], but one of its strengths is translating
levels of endogenous filtration markers such as cre-
limed eGFRs in the Nijmegen study [8] cited by Glass-
reference methods. Major manufacturers have
unstandardized creatinine [11]. Major manufacturers have
set 2008 as a target for calibrating their assays to isotope
dilution mass spectrometry reference methods.

CKD prevalence in the United States is common and increasing. Overall, assessing trends over time based on laboratory data is difficult. While earlier estimates of prevalence trends from 1988 to 2000 showed only a small rise in stages 1–2 (defined as albuminuria) and a stable prevalence of CKD stages 3–4 (defined as eGFR < 60 ml/min/1.73 m²) [12,13], more recent estimates based on updated creatinine assay calibration and a much larger sample size suggest a rise in CKD prevalence from 1988 to 2004 [14]. This recent report estimates that the overall prevalence of CKD increased from 10 to 13%; the prevalence of stages 1–2 increased from 4.4 to 5.0% and the prevalence of stages 3–4 increased from 5 to 8% (P = 0.001). Aging of the US population as well as the increased prevalence of diabetes, hypertension and obesity explains all of the increase in stages 1–2 and some of the increase in the prevalence of stages 3–4. The report also points out that some of the increase is attributed to a small (0.04 mg/dl) rise in the mean serum creatinine of the population and a conservative trends analysis that removes this mean difference, reduces the size of the increase substantially (odds ratio 1.17, 95% CI 1.02–1.34, P = 0.03), and in this analysis adjustment for demographics and risk factors explains the rise in prevalence. However, the most reliable data come from the most recent surveys whose creatinine calibration was identical to standard creatinine without any statistical correction and these data result in the highest prevalence estimates. Work on NHANES surveys prior to 1988 is interesting but has unknown creatinine calibration and a high rate of missing creatinine in some of the surveys, and therefore trends over longer time intervals cannot be validly assessed. The concern that the current US CKD prevalence estimates do not incorporate the chronicity criterion is valid. Since the NHANES surveys involve only one visit, the presence of CKD as defined by reduced GFR for >3 months cannot be established directly. It is entirely plausible that of 7.7% of adults with CKD stage 3 only 5–6% will have a second repeat eGFR < 60 ml/min/1.73 m². Whether models making assumptions to simulate a hypothetical repeat visit will be more acceptable than estimates based on one visit is uncertain. Expanding the relatively limited data will tell whether CKD stages 1–4 are epidemic or merely endemic at a relatively constant but unacceptably high prevalence. In our opinion, the clear message is that there are many more patients with earlier stages of CKD than with kidney failure, and their number is higher than previously appreciated.

Do we need to change the eGFR cutoff value for the definition of CKD?

We agree with Drs Glassock and Winearls that a ‘disadvantage’-based definition is appropriate, but do not agree with the proposal to use age-specific percentiles. If the 5th percentile of creatinine or eGFR for each age, sex and race group is defined as abnormal, then the prevalence of CKD would be 5% for all groups. In our view, this would lead to far too many young people being considered to have CKD, and far too few older people. Alternatively, percentiles could be based on a ‘healthy’ elderly group, resulting in a less steep age-related increase in CKD than observed using the current cutoff level for eGFR. However, defining ‘healthy’ in older individuals is problematic. The main rationale appears to be avoiding classification of a large number of elderly people as having CKD with

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Importance of different CKD measures</th>
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<tr>
<td>Concurrent complications&lt;sup&gt;a&lt;/sup&gt;</td>
<td>CKD stage</td>
</tr>
<tr>
<td>Prognosis</td>
<td>+++</td>
</tr>
<tr>
<td>Risk of CVD or mortality</td>
<td>+++</td>
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<tr>
<td>Risk of kidney failure</td>
<td>+++</td>
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<tr>
<td>Rate of decline in GFR</td>
<td>+</td>
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<tr>
<td>AKI, drug toxicity</td>
<td>+++</td>
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</tbody>
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<sup>a</sup>Hypertension, anemia, malnutrition, bone disease, neuropathy, fatigue.
<sup>b</sup>For example, diabetic, glomerular, vascular, tubulointerstitial, & cystic kidney diseases, and kidney disease in the transplant recipient.

limited treatments options. However, it is not appropriate to define a disease based on the number of people classified as diseased or whether treatment is available. We agree that it is striking that 38% of >70-year-old individuals are classified as having CKD on the basis of decreased eGFR. However, diabetes prevalence among 65+ year olds in the United States is 22% [15] and hypertension and hypercholesterolemia are far more common. Dementia prevalence is 6% in a community sample of individuals over the age of 65, with another 16% classified as having mild cognitive impairment. Dementia prevalence is ∼33% among 80–84 year olds [16]. Inadequate treatment for common diseases should be a challenge for future research rather than a reason for changing the definition of what is normal.

The disparity between the prevalence of earlier stages of CKD and incidence of treated kidney failure across race and sex should not be taken as conclusive evidence for inaccuracies of the GFR estimating equations or inadequacy of the current GFR cutoff value. Prevalence is not incidence and prevalence over-represents cases of longer duration and slower progression. Women may have a higher prevalence at earlier stages of CKD because they progress more slowly and have a lower mortality rate. African-Americans may have a lower prevalence of CKD because they progress more rapidly and have a higher mortality. A disparity between incidence and prevalence based on duration will occur regardless of the eGFR cutoff value to define CKD. A lower cutoff for CKD in women is consistent with lower mean GFR per body surface area in young healthy women. The Framingham Heart Study for example has used the 5th percentile of creatinine in their study (64 ml/min/1.73 m² in men and 59 ml/min/1.73 m² in women) [17]. However, it is unclear that this approach will be superior to inclusion of gender with albuminuria and other clinical parameters in making decisions for individual patients.

Risk-based approaches should consider multiple risks. Different outcomes will have a different risk relationship. Let us consider the case of a 90-year-old white man with an eGFR of 50 ml/min per 1.73 m² (standardized serum creatinine 1.35 mg/dl). Is this person free of CKD? Using age-specific percentiles would suggest that he is, while using the current definition he has moderately decreased GFR and CKD stage 3. Veterans Affairs data cited by Drs Glasscock and Winearls suggest that his risk of ESRD is only 900 per million persons per year. Without a rapidly progressive course, he can be reassured that his risk of kidney failure requiring dialysis is very low. However, this low risk is nine times that of a comparably aged person with an eGFR >60 ml/min per 1.73 m² and does not include the risk of kidney failure without dialysis treatment. We think his physician and he should take the level of eGFR into account in medication dosing, avoiding drug-induced kidney toxicity, and more judicious use of radiographic contrast agents. More data is needed on the risk of these complications that are most specifically related to low GFR. Risks of other complications and hospitalizations need to be studied. Recent data suggest the risk of medical errors is higher among individuals with low eGFR [18].

Mortality is an extremely important outcome that can be ascertained simply but is not very specific to CKD. This patient’s unadjusted risk of mortality is 13.4% compared to 11.6% for similarly aged person with an eGFR of 60 ml/min/1.73 m² or greater. This is by no means a dramatic increase. However, it understates the risk since the reference group disproportionately includes individuals with high eGFR as a result of low muscle mass who have a higher mortality. In addition, large administrative databases now rely on unstandardized serum creatinine assays. Implementation of standardized serum creatinine assays will usually result in lower serum levels, higher eGFR and steeper risk gradients.

It is now acknowledged that CKD is a risk factor for cardiovascular disease. It is notable that in epidemiologic studies, adjusted CVD risk rises substantially in the elderly when eGFR based on serum creatinine is <60 ml/min/1.73 m². An elevated serum cystatin C has a much stronger relationship with CVD mortality in the elderly than eGFR based on serum creatinine. Based on this, some have argued that we should identify patients with a serum level of cystatin C >1.0 mg/l as having ‘pre-CKD.’ Interestingly, this level may correspond to an eGFR of ∼75 ml/min/1.73 m² [19]. Preliminary data from NHANES III follow-up find a similar relationship [20]. Thus, some risk analyses suggest including even more individuals than the current eGFR cutoff of 60.

GFR declines with age but how do we know if this is ‘normal’. Finally, we disagree with the presupposition that the age-related decline in GFR is normal and therefore the eGFR cutoffs for the definition of CKD should be lower in older age groups. Elevated systolic blood pressure is nearly universal in older adults and was once considered normal but its treatment reduces risk of stroke and cardiovascular disease [21]. Age-related decline in GFR occurs concomitantly with impaired concentrating ability, pathologic findings of global glomerular sclerosis, vascular sclerosis and tubular atrophy, and reduction in cortical thickness and overall kidney size [22,23]. All of these changes are considered abnormal when observed in younger individuals. The magnitude and cause of age-related decline in GFR is an important area of research. Defining it as normal because it is common threatens to dismiss the urgent need for research in this topic.

What next?
The uniform definition of CKD according to level of GFR has led to substantial understanding of the prevalence and risks associated with the full spectrum of CKD, but there is clearly much work yet to be done. We need to continue to improve accuracy of GFR estimates from serum creatinine and to go beyond creatinine to additional endogenous filtration markers and when appropriate to measured GFR. In addition, we need to develop algorithms that incorporate all salient clinical information in making different decisions. For example, the NKF-KDOQI guidelines suggest criteria for referral to a nephrologist for all patients with CKD stages 4–5, but far fewer patients with CKD stage 3 [24]. Criteria for referral, type and place of management
should be evaluated but it is likely that only a small minority of individuals with CKD stage 3 will need the care of a nephrologist. In addition to analyzing data to refine risk estimates, we need to target the most promising interventions for evaluation in clinical trials. It is logical to target treatment at the subgroup with highest risk and in which benefit is proven. However, it is premature to use the high prevalence or lack of proven treatments to define individuals with reduced eGFR as ‘healthy’.

Conflict of interest statement. None declared.

(See related article by Paul E. de Jong et al. Fact or fiction of the epidemic of chronic kidney disease—let us not squabble about estimated GFR only, but also focus on albuminuria. Nephrol Dial Transplant 2008; 23: 1092–1095.)

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