THE PROS AND CONS OF STAGING CHRONIC KIDNEY DISEASE

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Background and Objectives: In 2002 the National Kidney Foundation Kidney Disease Outcomes Quality Initiative presented a new definition and classification for chronic kidney disease (CKD), which was revised in 2004 to the current CKD staging system. This significantly increased awareness and understanding of CKD-related issues and promoted the use of evidence-based clinical practice principles. Due to the wealth of knowledge that has been acquired, the accuracy and appropriateness of CKD staging system has now been questioned, prompting a timely and comprehensive evaluation of the current atmosphere surrounding CKD staging. Here, we discuss the benefits and limitations of the current CKD staging system and provide suggestions for improvement.

Methods: A review of journals in PubMed and other databases surrounding the issues of CKD staging was performed. A minimum of 40 reviews and original works were examined and the most significant articles were chosen for this review.

Results: Several important facts were highlighted. The prevalence of CKD has risen between the periods 1988–1994 and 1998–2004. There are numerous limitations to the estimated glomerular filtration fraction (eGFR) measure of renal function. Albuminuria, which impacts cardiovascular risk as well as CKD progression, should be combined with eGFR. The approach of adding albuminuria into staging has been shown in large scale studies to correlate more strongly with renal outcomes and optimally predict CKD prognosis. Recommendations for primary prevention, secondary prevention and tertiary prevention of CKD as well as appropriate referrals to a nephrologist were provided.

Conclusions: There is great support for revising the current CKD definition and classification system. (*Ethn Dis.* 2010;20:77–81)

Key Words: Chronic Kidney Disease, Staging, Albuminuria, Estimated Glomerular Filtration Rate, Primary, Secondary, Tertiary Prevention, Referral to a Nephrologist

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INTRODUCTION

In 2002 it was widely recognized that chronic kidney disease (CKD) was under-recognized and inadequately treated, and that the number of persons dying from CKD complications and cardiovascular disease was rapidly increasing. One reason for the poor outcomes was ascribed to the wide variability in diagnosis and treatment due to lack of agreement on the definition and classification of CKD.[1] As a result, the National Kidney Foundation Kidney (NKF) Disease Outcomes Quality Initiative (KDOQI) published the first classification and standardization of CKD based on the presence of kidney damage or reduced renal function. This was later revised in 2004 by the NKF Kidney Disease Improving Global Outcomes (KDIGO) program which was established to develop and implement worldwide clinical practice guidelines to improve the care and outcomes of kidney disease patients by promoting coordination, collaboration and integration of initiatives. Thus, the current staging system was modified to include the presence of albuminuria or proteinuria, renal tubular syndromes and transplantation. This led to significant progress and expansion in our understanding of issues surrounding CKD. In the face of these advancements, the accuracy of the current definition and classification have been questioned and subjected to intense scrutiny. Here, we present a review and analysis of the arguments for and against the current CKD staging system and suggestions for its enhancement.

METHODS

An electronic search of MEDLINE/PubMed and other databases was conducted using terms relevant to the topic of CKD staging. All pertinent articles in English were retrieved and additional searches were performed based on references cited within the retrieved articles. All original articles were peer-reviewed, and some articles were invited literature reviews. Only the most significant articles were selected for this study. The tables were either retrieved from the references cited or derived from several relevant papers on the specific topic.

RESULTS

Current Definition and Staging of CKD

Chronic kidney disease is defined by either structural or functional pathological evidence of glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, in the presence or absence of kidney damage. Pathological abnormalities refer to: 1) structural damage by biopsy; 2) defects on imaging studies; 3) defects in the blood (such as renal tubular disease); 4) defects in the urine (proteinuria/albuminuria); or 5) kidney transplant. The measurement of eGFR

Table 1. Current CKD classification based on severity and treatment

Stage	Description	GFR (mL/min/1.73 m^2)	Treatment
1	Kidney damage with normal or ↑ GFR	≥90	1–5 T if kidney
2	Kidney damage with mild ↓ GFR	60–89	transplant
3	Moderate ↓ GFR	30–59	
4	Severe ↓ GFR	15–29	
5	Kidney failure	<15 or dialysis	5 D if HD/PD

GFR: glomerular filtration rate; T: transplant; D: dialysis; HD: hemodialysis; PD: peritoneal dialysis.

has allowed for CKD to be classified into 1 of 5 stages. Subsequent improvement in this classification system added the presence of renal replacement therapy by either dialysis (D) or transplantation (T) as shown in Table 1. Currently, both the KDIGO/KDOQI and the American Diabetes Association promote annual screening for CKD by spot urine determination of an albumin to creatinine ratio (ACR), and simple blood testing for creatinine and calculation of eGFR. In addition, it is recommended that all patients with CKD be educated on the importance of avoiding medications and diagnostic procedures that may potentially worsen their kidney function.

Pros of the Current CKD Staging System

The current CKD staging system has provided common language for universal communication and more accurate identification of the incidence and prevalence of CKD. It has also facilitated the application of clinical practice guidelines and clinical performance measures. Importantly, the current staging system has increased awareness of CKD by the medical community at large and led to the observation that CKD prevalence has risen. Specifically, in 2007, Coresh et al reported an increase from 10% between 1988 and 1994 to 13% between 1999–2004.[2] In addition, it has become apparent that some patient populations are at greater risk for developing early CKD, and still others at advanced stages of CKD are more likely to die than progress to end stage renal disease (ESRD). In fact, the United States Renal Data System has reported that African Americans are 4 times more likely than Whites to have CKD. Additional analyses of the National Health and Nutrition Examination Survey (NHANES) of individuals aged >20 years uncovered several details regarding the epidemiology of CKD recorded between 1999 and 2006. Namely, the presence of diabetes, hypertension and smoking were more prevalent in African Americans at all CKD stages; there was a higher incidence of hypertension and hyperlipidemia in patients with CKD stages 3 and 4 than in patients with CKD stages 1 and 2; and there is lack of awareness of the presence of CKD.[1]

The universal language of the current CKD staging system has promoted considerable research activities and facilitated relevant study comparisons of variables such as educational intervention and nutritional management. The resulting expansion in kidney-related databases and funding support from various organizations have improved health policies in this regard and contributed to the support of appropriate CKD management. These maneuvers will undoubtedly lead to optimal evidence-based management principles that will fully benefit CKD patients.

Unequivocally, eGFR is the measure of kidney function that has provided the foundation for classifying CKD staging. Although serum creatinine has been widely used to assess renal function, it may be affected by age, race, dietary intake and body size. Notably, eGFR adjusts for the majority of these parameters and is a better overall index of kidney function. Several formulas have been developed to calculate eGFR,[3] but the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) Equations are most commonly used. The Cockcroft-Gault Equation was developed in 1973 from a sampling of 249 men with known kidney disease and GFR 30–130 mL/min. The MDRD equation was then developed in 1999 from a larger and more diverse population of 1638 patients also with known CKD.[4] Of these, the MDRD is considered the more accurate formula, and in addition eliminates the difficulties and inconvenience of 24-hour urine collections required for determination of creatinine clearance. It is now customary to report the eGFR thresholds <60 mL/min/1.73 m^2.

Limitations of the Current CKD Staging System

Although the MDRD formula has been widely accepted, it may underestimate eGFR >60 mL/min/1.73 m^2. In addition, the MDRD study population was limited to Caucasian and African American adults aged 18–70 years with CKD while relatively healthy individuals and others aged <18 and >70 years were not studied.[5] The importance of the demographics of the study population used to generate the eGFR formula was recently demonstrated by Rule et al.[6] Specifically, inclusion of healthy persons may lead to greater risk of eGFR >60 mL/min/1.73 m^2 in men vs women, whereas a formula developed from patients with clinical CKD may lead to greater risk of eGFR >60 mL/min/1.73 m^2 in women vs men. As a result, equations that model the non-GFR determinants of serum creatinine in patients with clinical evidence of CKD may not be transferable to the general population. This suggests that a single equation for both the general population and nephrology clinics may not exist. Due to this variable accuracy of earlier stages of CKD defined by the current MDRD formula, it may be

prudent to compress CKD 1, 2 into a single stage (CKD 1).

There are other limitations to the MDRD formula. The original MDRD formula was developed using the Beckman CX-3 method for creatinine measurement, which was not traceable to the isotope dilution mass spectrometry (IDMS) reference measurements. In addition, the values founded on this system may not be applicable to whole blood creatinine measurements. Further, the calibration commutability may be only valid for serum-based determinations. Thus, implementation of a revised calibration from the IDMS-traceable MDRD equation may provide a more accurate measure of eGFR.

The current CKD staging system does not reflect prognostic factors and does not include specific measurements of albuminuria or proteinuria, which may itself impact disease outcomes. This is particularly true in the later stages of CKD.[7] Patients with dipstick-positive proteinuria in CKD 1, 2 may have a greater risk of reaching ESRD compared to patients with dipstick-negative proteinuria and later CKD stages. For example, the risk of reaching ESRD at CKD 3 without proteinuria is increased 2.4-fold compared to a 33-fold risk for a CKD 3 patient with dipstick-positive proteinuria. Of greater interest is the 12-fold increase in reaching ESRD for patients who have dipstick-positive proteinuria at CKD 1, 2, which is also more significant than for dipstick-negative proteinuria patients at CKD 3. Thus, the presence of albuminuria/proteinuria should not be ignored in staging CKD patients.

Albuminuria has long been associated with an increase in cardiovascular events. The age and gender-adjusted hazard ratios for cardiovascular events were not noted to be statistically elevated for CKD 3 in the absence of albuminuria. In contrast, patients with CKD 1–3 and microalbuminuria have a significantly elevated (1.5–2.5-fold) risk for developing a cardiovascular event, which also increases proportionately with the severity of albuminuria.[8] It would be of considerable benefit to provide endpoints for predicting renal outcomes, as is presently available with the Framingham assessment for cardiovascular disease. This lack of outcome predictability precludes evaluation of cost effectiveness for CKD staging. The average age of CKD patients is 70 years and the likelihood of death in this age group is 25 times more common than progression to renal failure.[2,9] NHANES reported that eGFR <60 mL/min/1.73 m^2 was present in 30% of elderly individuals, yet progression to ESRD is not routinely observed in many patients with early CKD.[10–13] Therefore, the current CKD staging may be too general and may contribute to both over-diagnosis and misdiagnosis of some individuals with early CKD 1, 2. It is clear that the prevalence of CKD far exceeds the incidence rate for progression to ESRD. Therefore, it is possible that a new staging system that includes evidenced-based risks for renal outcomes may be more appropriate.

Germane to the argument of including albuminuria in CKD staging is the need for standardization of testing for both albuminuria and proteinuria. Currently, these parameters may be determined by several methods including qualitative spot urine dipsticks, spot urine ACR, spot urine protein to creatinine ratio and 24-hour urine collections for protein quantification. Each of these measurements is described by its own relevant range of normal values and units (Table 2). Elimination of these variable definitions would enhance homogeneity and consistency in reporting.

Table 2. Definitions of proteinuria and albuminuria[4]

	Urine Collection	Normal	Microalbuminuria	Macroalbuminuria/ Clinical Proteinuria
Total protein	24-hr excretion	<300 mg/day	N/A	>300 mg/day
	Spot urine dipstick	<30 mg/dL	N/A	>30 mg/dL
	Spot PCR	<200 mg/g	N/A	>200 mg/g
Albuminuria	24 hr excretion	<30 mg/day	30–300 mg/day	>300 mg/day
	Spot urine albumin			
	Specific dipstick	<3 mg/dL	>3 mg/dL	N/A
	Spot urine ACR M	<17 mg/g	17–250 mg/g	>250 mg/g
	Spot urine ACR F	<25 mg/g	25–350 mg/g	>350 mg/g

N/A: not applicable; PCR: protein to creatinine ratio; ACR: albumin to creatinine ratio; M: male; F: female.

Can the Current Staging of CKD Be Improved?

There are several ways in which the current staging system might be improved. It is well-recognized that the cause of CKD and the rate of disease progression strongly influence management and complications. Therefore, an initial consideration would be to have a complete understanding of the natural course of CKD and to relate the natural course to specific outcome measures.

Indeed, it may be counterproductive to radically change the current CKD staging system to incorporate excessive clinical variables that may detract from the simplicity and familiarity of the current definition and classification. However, there is substantial support for incorporating albuminuria into CKD staging particularly in view of the profound influence of albuminuria on disease progression and cardiovascular disease risk.

Of utmost importance is the need for linking CKD staging with widespread institution of applicable and relevant interventions specifically directed at primary care physicians. Appropriate and timely referral to a nephrologist is essential at the first point of care

Table 3. Recommendations of when to refer to a nephrologist

Blood pressure (BP) control
-When BP is difficult to control despite 3 drugs, incl. diuretic
-Diabetic nephropathy progression
-in absence of retinopathy
-in absence of albuminuria (without retinopathy)
-in absence of active sediment
-worsening albuminuria despite good glycemic and BP control
-Rapid deterioration of renal function (>1 mL/min/y without acute injury)
-Presence of signs/symptoms of systemic disease
-eGFR approaching 30 mL/min/1.73 m^2
-Acute decline in eGFR >30% within 4 months without explanation
-Lack of comfort with complications
-Secondary hyperparathyroidism anemia, fluid retention, hyperkalemia

eGFR: estimated glomerular filtration rate.

for every CKD stage (Table 3) in order to accurately identify and manage underlying co-morbidities.

Measures for aggressive primary, secondary and tertiary CKD prevention strategies should be introduced. Primary prevention should be directed at education (such as the National Kidney Disease Education Program),[14] early detection by general screening (such as the Kidney Early Evaluation Program),[15] and risk factor reduction of high-risk individuals. Secondary prevention should be aimed at evaluation, management and improving outcomes for patients with CKD 1–4. Tertiary prevention should be directed at improving outcomes at CKD 5 with specific emphasis on managing anticipated complications and co-morbidities. Adherence to this type of algorithm may significantly reduce the existing fragmentation in renal care and provide opportunities for a team approach including, but not limited to, pharmacists, nutritionists, cardiologists and endocrinologists, all of whom are essential to reduce and eliminate poor renal outcomes.

There is evidence that modifications in the current CKD staging system may enhance clinical management of CKD. Rutkowski et al of the Kaiser Permanente system departed from the current KDOQI/KDIGO definition of CKD 1, 2 by requiring the inclusion of macroalbuminuria (>300 mg/g), rather than microalbuminuria (30–300 mg/g), since appropriate interventions for patients with diabetes and microalbuminuria were already in place.[1,16] CKD 3 was sub-divided into a "chronic stage 3" group, which included those with chronically reduced GFR stage 3 and a "CKD 3 modified" group with a higher risk for progression to renal replacement therapy. The "CKD 3 modified" group had at least 1 of several additional risk factors: proteinuria, diabetes, and eGFR (either 45–59 or 30–44 mL/min/1.73 m^2) + age <85 years. Appropriate nephrology referrals were made for advanced CKD 4, 5, and CKD 1–3 patients with proteinuria >1000 mg/day, refractory hypertension, unexplained acute decrease in eGFR>25% or an unclear diagnosis. This novel modification of CKD staging and management guidelines resulted in only a small 4% increase in nephrology outpatient visits over 5 years. Thus, it is possible to amend current CKD staging to a plan that may significantly impact diagnosis and refine referrals to high-risk individuals without increasing the burden for the limited cohort of nephrologists, and ultimately have a positive influence on overall mortality rates.

A similar study was performed by Hallan et al of the Nord-Trøndelaq Health (HUNT) Study in which albuminuria and eGFR were independently and strongly associated with progression to ESRD, despite the presence of classic cardiovascular risk factors.[17] As a result, a larger percentage of the CKD population expected to progress to ESRD (65.6%) could be detected, thus significantly increasing the predictive power of the new CKD staging on clinical prognosis. Both of these real-life studies provide support for inclusion of albuminuria in a new CKD staging system.

CONCLUSION

There are important arguments both for and against the current CKD staging system. The major increase in our knowledge of issues around CKD has prompted a re-evaluation of the appropriateness and accuracy of its current definition and classification with the primary objective of improving renal outcomes related to disease progression, acute kidney injury and cardiovascular disease. It is anticipated that several pertinent factors will be addressed at subsequent Annual KDIGO Controversies Conferences.[18] Such topics may include: the accuracy of eGFR formulas; standardization of albuminuria testing; and key factors (particularly albumin and eGFR) that determine prognosis and the potential need for additional factors. The documentation and implementation of positive results from these discussions are ardently anticipated.

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