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Chronic Kidney Disease: A New Classification and Staging System

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Chronic kidney disease (CKD) is a growing health problem in the United States. Several recently published studies emphasize that CKD is underdiagnosed and undertreated.[1–4] It therefore cannot be overstated that recognition of this chronic condition is crucial to facilitate the employment of measures that can slow progression to end-stage renal disease (ESRD). Also, appropriate and timely interventions in patients with CKD would enhance therapy of comorbid conditions, reduce associated complications, and improve patient outcomes. These are certainly achievable goals, as many effective therapies for slowing the progression of CKD and correcting or reducing associated comorbidities have become available in the past few decades.[5–7] To this end, a system to classify stages of CKD is justified to permit a logical approach to diagnosis and therapy in these patients. A working group of the National Kidney Foundation (NKF) recently published clinical practice guidelines to aid physicians in diagnosing and managing CKD.[8] Based on the NKF guidelines, this article will examine the implications of CKD growth, establish a definition for CKD, describe a system to classify stages of CKD, and briefly review the prevalence of and treatment options for CKD.

SCOPE OF THE PROBLEM

The implications of rapid growth in both the incidence and prevalence of CKD are enormous. The most worrisome is that this growth will result in a huge influx of patients into the ESRD system. Based on data from the US Renal Data System, the incidence of ESRD has increased steadily for the past 15 years, rising from 142 cases per million population in 1987 to 308 cases per million population in the year 2000.[9] Expansion of the ESRD population will have a significant economic impact on the already overextended Medicare system. For example, Medicare expenditures for the ESRD program in 1996 increased 12.5% over the previous year, computing to an estimated $10.96 billion.[10] A larger impact can be predicted from the estimated growth of both the CKD and ESRD populations.

The growth of the ESRD population will also exacerbate the predicted shortfall in nephrology clinicians. The increase in both CKD and ESRD populations may overwhelm the ability of nephrologists and other health care providers to fully provide interventions that will improve both the length and quality of patients' lives if an organized approach to this problem is not in place. Hence, it became imperative that the CKD epidemic be addressed in a comprehensive fashion. The NKF took the challenge and created the CKD Work Group to achieve this goal.

DEFINING CKD AND DEVELOPING A STAGING SYSTEM

Several terms have been used to describe the period between the initial diagnosis of kidney disease and the institution of renal replacement therapy (ie, dialysis or transplantation). Such terms have included *pre-ESRD*, *chronic renal insufficiency*, *chronic renal failure*, and *chronic renal disease*. Unfortunately, none of these terms is particularly accurate and, in fact, may be confusing to nonnephrology physicians. The term *pre-ESRD* gives the impression that dialysis is an inevitable outcome of all kidney diseases and implies that no effective therapies exist to halt or slow the progression of CKD. The terms *renal insufficiency*, *chronic renal failure*, *chronic renal disease* and *pre-ESRD* have negative connotations; also, these terms include the word *renal*, which is not easily understood by patients or their families. For these reasons,

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Table 1. Staging System and Action Plan for Chronic Kidney Disease

Stage	Description	GFR (mL/min per 1.73 m²)	Action*
—	At increased risk for CKD	≥ 90 with risk factors†	Screening CKD risk reduction
1	Kidney damage‡ with normal or increased GFR	≥ 90	Diagnosis and treatment Slow progression of CKD Treat comorbidities Cardiovascular disease risk reduction
2	Mild decrease in GFR	60–89	Estimate progression
3	Moderate decrease in GFR	30–59	Evaluate and treat complications
4	Severe decrease in GFR	15–29	Prepare for renal replacement therapy
5	Kidney failure	< 15 or dialysis	Replacement if uremic

Adapted from National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39(2 Suppl 2):S65. With permission from Elsevier Science.

CKD = chronic kidney disease; GFR = glomerular filtration rate.

*Includes actions from preceding stages.

†Risk factors: hypertension, dyslipidemia, diabetes mellitus, anemia, systemic lupus erythematosus, chronic analgesic ingestion.

‡Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine, or imaging tests.

the term *chronic kidney disease* was chosen by the CKD Work Group.

The first order of business for the work group was to define and classify CKD. The glomerular filtration rate (GFR) is the best overall measure of kidney function. Factors that influence GFR include both structural (or functional) kidney disease as well as patient age. In general, the annual decline of GFR with age is approximately 1 mL/min per 1.73 m² of body surface area, beginning after the patient reaches approximately 20 to 30 years of age.[11] Although a chronic decline in GFR (a level of less than 60 mL/min per 1.73 m² for ≥ 3 months) is evidence of CKD, substantial kidney damage can exist without a decrease in GFR. In this circumstance, kidney damage is defined as a structural or functional abnormality of the kidney that can lead to impaired kidney function that persists for 3 months or more with or without a decreased GFR. Manifestations of kidney damage can include pathologic abnormalities noted on renal biopsy specimens or abnormalities revealed by blood, imaging, or urine tests. Utilizing this definition, CKD is present if the GFR is less than 60 mL/min per 1.73 m². In addition, CKD is present if the GFR is greater than or equal to 60 mL/min per 1.73 m² if other evidence of kidney damage also exists. A classification and staging system based on the level of GFR was subsequently developed by the CKD Work Group (**Table 1**).

Defining CKD using this staging system provides a common language for communication between the various health care providers. The system will allow more reliable estimates of the prevalence of earlier stages and of populations at increased risk for CKD. In addition, evaluation of factors associated with a high risk of progression can be recognized. Treatments can be more effectively examined and the development of adverse outcomes in this population can be more easily determined. Finally, a classification and staging system also facilitates the application of clinical practice guidelines, clinical performance measures and quality improvement programs.

ESTIMATION OF GFR AS AN INDEX OF KIDNEY FUNCTION

Serum creatinine is the most commonly used biochemical parameter for estimating GFR and as such has been employed as an index of renal function. However, it is not an accurate measure of GFR, and it is especially inaccurate as an estimate of GFR when the serum creatinine level is between 1 and 2 mg/dL. This is because creatinine, unlike inulin, is secreted by the renal tubules. As renal function declines, the amount of creatinine

secreted by the tubules increases and raises the amount of creatinine in the urine (not filtered by the glomerulus). The ability of the renal tubule to secrete creatinine is maximal at a serum creatinine concentration of approximately 2 mg/dL. This effect acts to falsely increase the creatinine clearance, resulting in an overestimation of GFR. The serum creatinine concentration is also affected by body mass, muscle mass, diet, drugs, and laboratory analytical methods. "Normal" ranges of serum creatinine quoted by laboratories are particularly misleading because they do not take into account the age, race, sex, or body size of the individual. As an example, consider the following patients, both of whom have a serum creatinine level of 1.3 mg/dL. "Patient A" is a 20-year-old, 80-kg man. "Patient B" is an 80-year-old, 60-kg woman. Using the Cockcroft-Gault equation, patient A's GFR is estimated at 102 mL/min per 1.73 m^2, which is within the normal range, whereas patient B's GFR is estimated at 32 mL/min per 1.73 m^2. Patient B's GFR is clearly reduced and suggests the presence of significant CKD. Unfortunately, patients such as patient B are often thought of as having relatively normal kidney function and will receive medications that are not properly dosed for their levels of kidney function. In addition, prophylaxis for exposure to nephrotoxins such as radiocontrast media may be overlooked because the renal function is assumed to be normal.

Nephrologists have known for decades that inulin clearance is the gold standard test for measuring GFR. Unfortunately, this test is cumbersome and relatively expensive, and it is not widely available for clinical use. Iothalamate (^{125}I-iothalamate) clearance is used at some centers to estimate GFR and is a reasonably accurate substitute for the inulin clearance method. This method is also expensive and somewhat cumbersome to perform as a routine clinical test. A 24-hour urine collection for creatinine clearance is the accepted alternative measure of GFR because it is widely available and is a test that is familiar to most clinicians. However, this test is often difficult for patients to carry out and perform correctly, and it is less accurate than either inulin or iothalamate clearance.

To simplify estimation of renal function in patients, GFR estimates from prediction equations are utilized. These formulas take into account serum creatinine level, age, gender, race, and body size, and they are better estimates of GFR than serum creatinine concentration alone. The formulas used are sufficiently accurate and, as a result, are recommended by most nephrologists. The two most widely used are the Cockcroft-Gault and the Modification of Diet in Renal Disease Study (MDRD) equations.

The Cockcroft-Gault equation ([140 – age in years] × weight in kg/[72 × serum creatinine], with the result for females multiplied by 0.85) was originally developed to estimate creatinine clearance.[12] Although it provides an adequate estimate of GFR, the MDRD equations are more accurate.[13] MDRD equation 7 is the preferred formula, but it requires measurement of blood urea nitrogen (BUN) and serum albumin. The formula is $(170 \times [\text{serum creatinine (mg/dL)}]^{-0.999} \times [\text{age (years)}]^{-0.176} \times [0.762 \text{ if female}] \times [1.18 \text{ if African American}] \times [\text{BUN (mg/dL)}]^{-0.170} \times [\text{albumin (g/dL)}]^{+0.318})$. An abbreviated form of the MDRD equation that does not require BUN or albumin measurement was also developed and is: $(186 \times [\text{serum creatinine (mg/dL)}]^{-1.154} \times [\text{age (years)}]^{-0.203} \times [0.742 \text{ if female}] \times [1.21 \text{ if African American}])$ and maintains reasonably good accuracy. Links to calculators for these equations can be found at http://www.kidney.org/professionals/doqi/index.cfm.

The MDRD equation was tested in a large sample of patients (N = 558) with a range of kidney diseases and ethnicities (European Americans and African Americans).[13] GFR values were validated in the sample group using urinary clearance of ^{125}I-iothalamate as the gold standard. It is important to recognize that certain patient groups were not well represented in the MDRD study sample. Groups not evaluated include patients at extremes of age and body size; the severely malnourished or obese; patients with skeletal muscle diseases, paraplegia, or quadriplegia; vegetarians; those with rapidly changing kidney function; and patients prior to dosing drugs with significant toxicity that are excreted by the kidneys. Therefore, clearance measurements are still required in groups who were underrepresented in the MDRD sample to fully validate the formula for all patients.

PREVALENCE OF CKD STAGES

The next goal of the CKD Work Group was to obtain prevalence estimates for each stage of CKD. Prevalence estimates were obtained by utilizing a reference group comprised of patients evaluated in the Third National Health and Nutrition Examination Survey (NHANES III).[8] Between 1988 and 1994, NHANES III enrolled 33,994 Americans aged 2 months and older. In this sample of patients, the MDRD equation was used to estimate GFR. In addition to abnormal GFR levels, the presence of micro- or macroalbuminuria on spot urine specimens was considered sufficient evidence of kidney damage. The prevalence of each GFR category was subsequently determined (**Table 2**). The level of albuminuria was used to estimate the prevalence of the first 2 stages. (The ratio of albumin [and protein] to creatinine in spot

urine samples has been documented to reliably correlate with 24-hour urine measurements for albumin and protein.[14])

Stage 1 and 2 estimates are based on a single measurement of albuminuria. As one might suspect, overestimation of prevalence for these stages may result from this approach—microalbuminuria was persistent in only 61% of a subset of 1241 patients that were retested.[8] However, this overestimation may be balanced by the exclusion of other patients with kidney disease not manifested by albuminuria. For example, kidney damage may also manifest as hematuria, pyuria, or abnormal imaging tests. These important kidney parameters were not evaluated in the NHANES III population.

A staging system based on severity of disease is justified from several perspectives. Adverse outcomes of CKD are directly related to the prevailing level of kidney function. Furthermore, CKD tends to worsen over time, and the risk for adverse outcomes increases over time with disease severity. In addition, it is well documented that as GFR declines, the prevalence of hypertension, anemia, elevated parathyroid hormone level, hyperphosphatemia, hypocalcemia, and hypoalbuminemia increases.[15,16]

APPROACH TO PATIENTS WITH CKD

The approach to the patient involves establishing the presence of CKD, determining the stage of disease, and enacting an action plan based on the stage. The management of CKD patients requires a multidisciplinary approach involving primary care physicians, nephrologists, endocrinologists, cardiologists, vascular surgeons, physician assistants, nurse practitioners, dietitians, and social workers. The goals of this interdisciplinary approach are to identify patients either with or at increased risk for CKD, to slow the progression of CKD to ESRD, to identify and treat comorbid conditions, to identify and prevent complications of CKD, and to prepare patients mentally and physically for renal replacement therapy. As seen in Table 1, the action taken increases from simple screening maneuvers and risk reduction to more complex disease management.

The initial evaluation of patients with established CKD should include an assessment of comorbid conditions and a thorough review of medications. Medications should be adjusted for the level of renal function. Blood pressure monitoring is essential to diagnose hypertension and facilitate optimal blood pressure control to reduce ongoing kidney damage. Laboratory tests that should be performed include serum creatinine concentration to allow estimation of GFR, protein- or albumin-to-creatinine ratios in spot urine samples to assess for kidney damage, and urinalysis. Finally, imaging of the kidney by ultrasonography is warranted in most CKD patients.

Table 2. US Prevalence of Chronic Kidney Disease by Stage

Stage	Description	GFR (mL/min per 1.73 m²)	Prevalence*	
			N (1000s)	%
1	Kidney damage† with normal or increased GFR	≥ 90	5900	3.3
2	Mild decrease in GFR	60–89	5300	3.0
3	Moderate decrease in GFR	30–59	7600	4.3
4	Severe decrease in GFR	15–29	400	0.2
5	Kidney failure	< 15 or dialysis	300	0.1

Adapted from National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39(2 Suppl 2):S50. With permission from Elsevier Science.

GFR = glomerular filtration rate.

*Prevalence based on population of 177 million adults age ≥ 20 years.

†Kidney damage as manifested by abnormalities noted on renal pathology, blood, urine, or imaging tests.

The approach is implemented in a step-wise fashion and will vary for the individual patient based on the severity of the impairment of the GFR. In a patient with a normal GFR (≥ 90 mL/min per 1.73 m²) or a mildly impaired GFR (> 60 mL/min per 1.73 m²) the focus will be on delaying progression and treating comorbid conditions. Progression is best predicted by plotting the reciprocal of the serum creatinine level over time. The Walter Reed Army Medical Center Section of Nephrology Web site is an excellent resource for this purpose (http://www.wramc.amedd.army.mil/departments/medicine/nephrology/tools/index.html). This plot will predict a date when the GFR will reach target levels that are approved by the Center for Medicare and Medicaid Services for the initiation of renal replacement therapy. In general, the cut-off values are 15 mL/min per 1.73 m² for diabetic patients and 10 mL/min per 1.73 m² for nondiabetic patients.

In the past decade, several treatments have been shown to slow the progression of CKD. In diabetic patients these include tight glucose control and normalization of blood pressure.[5,6] Strict blood pressure control (< 125/75 mm Hg) in diabetic patients and in nondiabetic patients with proteinuria is associated with a slower rate of decline of GFR.[16–18] ACE inhibitors and angiotensin-receptor blockers may slow progression by mechanisms other than blood pressure lowering.[19,20] Other potentially important therapies include dietary protein restriction, lipid control with statins, smoking cessation, and correction of anemia. These aspects will be discussed more fully in a future article addressing the therapies employed to reduce progression of CKD.

In patients with moderate impairment (GFR of 30–60 mL/min per 1.73 m^2), a search for uremic complications (eg, anemia, abnormalities in mineral metabolism) should be undertaken. In addition, treatment of these processes should be initiated. In contrast, the focus of care for patients with severe impairment (GFR of 15–30 mL/min per 1.73 m^2) should be on appropriate preparation for renal replacement therapy. Electrolyte and acid-base disturbances such as hyperkalemia and metabolic acidosis need to be monitored and treated aggressively. Nutritional state should be assessed and dietary counseling undertaken to optimize protein intake without inducing hyperphosphatemia, hyperkalemia, or metabolic acidosis. Also, correction of anemia and mineral metabolism disturbances should continue during this late stage.

In addition to those patients who already have CKD, there is an even larger group of patients who are at risk for the development of CKD. This group includes patients with diabetes mellitus, hypertension, and systemic lupus erythematosus, as well as chronic analgesic drug users. In addition, African Americans appear to be at higher risk for kidney damage than other racial groups. As part of the initial evaluation of high-risk patients, the CKD Work Group advised measurement of blood pressure, serum creatinine level (to estimate GFR), and protein- or albumin-to-creatinine ratio in a spot urine specimen to assess for kidney damage. Other selected tests, such as renal ultrasonography, computed tomography or magnetic resonance imaging of the kidneys, serum electrolyte levels, and urinalysis may be indicated in specific clinical situations.

CONCLUSION

The rising incidence and prevalence of CKD in the United States has mandated a unified approach to its evaluation and classification. The approach put forth by the NKF's CKD Work Group stratifies patients with CKD into stages according to estimated GFR and the presence or absence of kidney damage and proposes a stage-based clinical action plan. The complete K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification can be found at the Web site address http://www.kidney.org/professionals/doqi/kdoqi/toc.htm. In addition, a CKD Web site for primary care practitioners was developed by the Yale University Nephrology Section and can be found at http://kidney.med.yale.edu.ckd.

The next article in this series will review available interventions for slowing the progression of CKD. Future articles will address anemia and mineral metabolism disturbances associated with CKD, cardiovascular disease in patients with CKD, and the preparation of patients for renal replacement therapy. **HP**

REFERENCES

1. Obrador GT, Ruthazer R, Arora P, et al. Prevalence of and factors associated with suboptimal care before initiation of dialysis in the United States. J Am Soc Nephrol 1999;10:1793–800.
2. Kausz AT, Khan SS, Abichandani R, et al. Management of patients with chronic renal insufficiency in the Northeastern United States. J Am Soc Nephrol 2001;12:1501–7.
3. Duncan L, Heathcote J, Djurdjev O, Levin A. Screening for renal disease using serum creatinine: who are we missing? Nephrol Dial Transplant 2001;16:1042–6.
4. Nissenson AR, Collins AJ, Hurley J, et al. Opportunities for improving the care of patients with chronic renal insufficiency: current practice patterns. J Am Soc Nephrol 2001;12:1713–20.
5. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group [published erratum appears in N Engl J Med 1993;330:152]. N Engl J Med 1993;329:1456–62.
6. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med 1993;329:977–86.
7. Giatras I, Lau J, Levey AS. Effect of angiotensin-converting enzyme inhibitors on the progression of nondiabetic renal disease: a meta-analysis of randomized trials. Angiotensin-Converting-Enzyme Inhibition and Progressive Renal Disease Study Group. Ann Intern Med 1997;127:337–45.
8. National Kidney Foundation (NKF) Kidney Disease Outcome Quality Initiative (K/DOQI) Advisory Board. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. Am J Kidney Dis 2002;39(2 Suppl 2):S1–246.
9. US Renal Data System. USRDS 2001 annual data report. Bethesda (MD): National Institutes of Health, National

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Institute of Diabetes and Digestive and Kidney Diseases; 2001. Also available at http://www.usrds.org/adr_2001.htm. Accessed 4 Feb 2003.
10. Healthy people 2010: chronic kidney disease. Bethesda (MD): National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2000.
11. Davies DF, Shock NW. Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. J Clin Invest 1950;29:496–507.
12. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16:31–41.
13. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: a new prediction equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med 1999;130:461–70.
14. Ginsberg JM, Chang BS, Matarese RA, Garella S. Use of single voided urine samples to estimate quantitative proteinuria. N Engl J Med 1983;309:1543–6.
15. Hsu CY, Bates DW, Kuperman GJ, Curhan GC. Relationship between hematocrit and renal function in men and women. Kidney Int 2001;59:725–31.
16. Buckalew VM Jr, Berg RL, Wang SR, et al. Prevalence of hypertension in 1,795 subjects with chronic renal disease: the modification of diet in renal disease study baseline cohort. Modification of Diet in Renal Disease Study Group. Am J Kidney Dis 1996;28:811–21.
17. Lazarus JM, Bourgoignie JJ, Buckalew VM, et al. Achievement and safety of a low blood pressure goal in chronic renal disease. The Modification of Diet in Renal Disease Study Group. Hypertension 1997;29:641–50.
18. Brenner BM, Cooper ME, de Zeeuw D, et al. RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med 2001;345:861–9.
19. Lewis EJ, Hunsicker LG, Clarke WR, et al. Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. N Engl J Med 2001;345:851–60.
20. Ravid M, Savin H, Jutrin I, et al. Long-term stabilizing effect of angiotensin-converting enzyme inhibition on plasma creatinine and on proteinuria in normotensive type II diabetic patients. Ann Intern Med 1993;118:577–81.