Chronic Kidney Disease: Screening, Follow-up and Referral

Mordecai Stolk, MD, and Charles McCoy, MD

The prevalence of chronic kidney disease (CKD) and **End-stage renal disease (ESRD)** in the United States has been increasing.[1] There are more than one million people with stage 4 and 5 CKD and possibly as many as 20 million with stage 2 and 3 CKD in the United States. Evidence has been accumulating for decades that early detection and treatment of patients with CKD leads to better patient outcomes. In addition, it is believed that patients with CKD are at higher risk for cardiovascular disease. Far more people with CKD will die from cardiovascular disease than will develop ESRD. We will, therefore, attempt to answer three questions of relevance to primary care physicians caring for patients with CKD.

Which patients should be screened for kidney disease and what are the best screening tests?

There is no clinical utility to the measurement of serum creatinine other than estimating the **glomerular filtration rate (GFR)**. There are other methods to measure GFR but these methods are either too cumbersome or costly to use as screening tests. The Cockcroft-Gault equation[2] typically overestimates true GFR. In response, a National Institutes of Health-sponsored study, the **Modification of Diet in Renal Disease (MDRD)**, produced a new equation to estimate kidney function.[3] Interest in this equation was galvanized in 2002 with the publication of a classification of staging CKD by the National Kidney Foundation and the **Kidney Disease Outcomes Quality Initiative (KDOQI)** based upon the **estimated GFR (eGFR)** derived from the MDRD (Table 1).[4]

Critics of the MDRD equation have cited problems with imprecision and bias. The most clinically relevant problem with the MDRD is that it systematically underestimates "true" GFR in subjects with GFR's greater than 60ml/min/1.73m2.[5] This underestimation of GFR improves as kidney function decreases but still remains unacceptably high at a GFR range of 30-59ml/min/1.73m2.[6]

Providing early intervention and curtailing the progression to end stage renal disease is the intention behind screening for CKD in a healthy population. However, it is not entirely clear whether universal screening for CKD is more appropriate than targeted screening. Proponents of universal screening believe that because CKD is essentially asymptomatic in the early stages, implementing preventative measures early in the course of CKD can retard progression of disease. Universal reporting of eGFR with the creatinine measurement could improve recognition of CKD. This line of reasoning assumes that physicians may have difficulty inferring GFR from a serum creatinine given its nonlinear relationship to GFR thereby creating an unnecessary delay in diagnosis.[7] Additionally, all of the equations used to estimate GFR are too complex to be used routinely in a physician's busy office schedule. Opponents of universal screening state that it would be expensive, create unnecessary referrals to nephrologists, engender pharmaceutical manipulation, and, most importantly, could cause emotional and/or financial harm to patients falsely labelled as having CKD.

Screening for CKD is believed to be beneficial to identifying patients at elevated risk of cardiovascular disease. Although many observational studies have identified CKD as a risk factor for cardiovascular disease, these epidemiological studies are limited by their inherent inability to establish cause and effect or adjust for confounders such as proteinuria or other comorbidities. For instance, the **Prevention of Renal and Vascular Endstage Disease (PREVEND)** trial showed that cardiovascular events did not increase in normo-albuminuric subjects as eGFR decreased from stage 1 to 3 CKD.[8] Another study with over a million subjects reported that the hazard ratio for a cardiovascular event occurred 20% more often in subjects with an eGFR of 45 to 59ml/min/1.73m2 compared to subjects with an eGFR greater than 60ml/min/1.73m2 after adjusting for many factors including proteinuria. This increased hazard ratio was lost when adjustments for co-morbidities were taken into account. However, there was a significant increase in both all cause mortality and cardiovascular events in subjects with an eGFR less than 45ml/min/1.73m2.[9]

The issue of albuminuria in relation to and being a requirement to diagnosing CKD is relevant. Not only is albuminuria

Table 1. The Stages of Chronic Kidney Disease

Stage	Description	GFR (mL/min/1.73m^2)
	At increased risk	≥ 90 (with CKD risk factors)
1	Kidney damage with normal or ↑ GFR	≥ 90
2	Kidney damage with mild ↓ GFR	60-89
3	Moderate ↓ GFR	30-59
4	Severe ↓ GFR	15-29
5	Kidney Failure	<15 (or dialysis)

Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m^2 for ≥ 3 months.
Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease.

Adapted from: National Kidney Foundation. K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification. *Am J Kidney Dis* 39:S1-S000, 2002 (suppl 1).

a sign of kidney disease, but it can also improve diagnostic screening accuracy. Albuminuria can be a sign of kidney disease and its presence is significantly associated with increasing all cause mortality, myocardial infarctions, and progression toward ESRD at each KDOQI stage.[10] At all levels of eGFR, the presence of dipstick positive proteinuria is associated with an approximately 100 fold higher risk of ESRD than subjects without proteinuria.[11] Additionally, the MRFIT study was a longitudinal trial of men at high risk for cardiovascular disease with 25 years of follow up. The positive predictive value of patients with an eGFR of less than 60ml/min/1.73m2 without proteinuria developing ESRD was only 5.6%. However, the positive predictive value increased to 26% with the presence of both a eGFR of less than 60ml/min/1.73m2 and greater than 1+ proteinuria.[12] Lastly, the authors of a large population based study of over 65,000 patients followed for over 10 years were able to demonstrate that both eGFR and albuminuria were independently associated with progression of CKD to ESRD, and referral based on both urinary microalbumin to creatinine ratio and eGFR could improve discrimination without losing predictive power to detect patients at risk of progressing to ESRD.[13]

Given all of the literature devoted to other screening tests such as cystatin C, the best screening test remains a serum creatinine. The test is cost effective, and when used with a validated equation for eGFR such as the MDRD equation has acceptable sensitivity and specificity to decipher who may or may not have CKD. Lastly, the diagnostic accuracy of screening for CKD with a serum creatinine can be increased by either adding an urinary microalbumin to creatinine ratio or using it in the context of the patient's other co-morbid conditions.

How should patients with early stage chronic kidney disease be followed and treated?

Recommendations for patients with stage 2 and 3 CKD are complicated by the knowledge that only a small number of these patients will ever progress to ESRD. It is generally accepted that patients with hypertension, diabetes, or other diseases predisposing a patient to the development and progression of CKD should be screened yearly with a creatinine level and urinalysis. The frequency of screening healthy individuals including the elderly is controversial, but a creatinine and urine analysis should be done with any periodic examination and any hospitalization.

Patients with a eGFR >60ml/min/1.73m2 and microalbuminuria or overt albuminuria should first be evaluated for the cause of the renal disease. Persistent albuminuria on repeat evaluations over at least three months will need at least further follow-up to assess for progression. Patients with diabetes should be treated with an inhibitor of the renin angiotensin system to prevent progression to overt nephropathy,[14,15] have good control of their diabetes with a goal HgbA1c of 6.5% or less,[16] and a blood pressure goal of 130/80mmHg.[17]

Stage 3 CKD poses the greatest dilemma. Patients with diabetes should be treated in a similar way as patients with an eGFR greater than 60ml/min/1.73m2. Hypertension should always be controlled with a goal of 130/80mmHg for all patients with CKD even though the majority of these patients will have a normal urinalysis. Multiple lines of evidence substantiate that inhibitors of the renin angiotensin system are superior to other antihypertensive medications in slowing the progression of CKD.[18,19]

The diagnosis and meaning of mild to moderate CKD in the elderly is even more difficult to establish. CKD stage 1 and 2 is usually based on evidence of kidney damage either through imaging or the presence of albuminuria rather than the reported eGFR since the MDRD equation has been proven to be unreliable when the eGFR is greater than 60ml/min/1.73m2. CKD stage 3 is potentially a flawed category as it labels a significant proportion of the healthy elderly over the age of 65 years of age as having kidney disease when in fact they do not. Approximately 38% of adults over the age of 70[1] have an eGFR of less than 60ml/min/1.73m2 by the MDRD. Whether this is due to normal age related changes in GFR or true CKD is a matter of debate. Because of advanced age or low body weight, many people labeled with stage 3 CKD do not have clinically significant renal disease. Often only time will differentiate patients with progressive disease from those with a benign course. Periodic (at least yearly) reevaluation of blood pressure and serum creatinine appears to be the most prudent course of action.

When should a patient with chronic kidney disease be referred to a nephrologist?

Patients should be evaluated by a nephrologist if they have: 1) an eGFR less than 30ml/min/1.73m2 regardless of etiology, 2) eGFR greater than 45ml/min/1.73m2 with significant albuminuria or significant comorbid conditions, and 3) any eGFR in the presence of hematuria, abnormal renal imaging, or a strong family history of renal disease, 4) declining eGFR over a three to six month period of observation, and 5) CKD with uncontrolled hypertension or other complications. The KDOQI Work Group focused on improving two specific outcomes in CKD: reducing the progression of kidney failure and the progression of cardiovascular disease. As CKD progresses, interventions to prevent and treat comorbid conditions that contribute to cardiovascular disease including hypertension, anemia, mineral bone disorders, malnutrition, fluid retention, and electrolyte abnormalities make management more complicated and referral to a nephrologist may be necessary.

The KDOQI guidelines state the goals of care of patients with eGFR less than 60ml/min/1.73m2 are predicated upon diagnosis and treatment of both kidney and comorbid conditions, estimating GFR through laboratory measurement, slowing progression of kidney disease, and evaluating and treating complications.[23] Clinicians should not use the result of a serum creatinine as the only method to assess kidney function.[24] Diagnostic accuracy is limited when either the size/ethnicity of the patient and a timeframe of three months between eGFR is not used. The rationale was to scale eGFR to a standardized body surface area and exclude transient declines in kidney function and random variations due to laboratory error, diet, and hydration status. These are all pitfalls clinicians face when trying to decide whether or not to refer a patient to a nephrologist.

This point is most clearly elucidated in the elderly. There is a lack of precision to the MDRD formula which tends to underestimate true GFR, especially in the elderly. Multiple lines of epidemiological data show that the relative risk of death associated with worsening of eGFR is abrogated in the elderly.[25-27] This phenomenon was recently described[28] in a community cohort study of approximately one million

participants in which there was a relative 68% increase in nephrology consultations for CKD following automated eGFR reporting. Since elderly patients with CKD have a greater risk of cardiovascular death than ESRD[29] and accepted management of CKD did not change, referral to a nephrologist on the based on eGFR alone may not change the patient's outcome.

We must therefore challenge the development of a disease oriented model of health care and focus on a patient oriented approach to CKD. Additionally, we should remember that although there is a strong correlation between CKD and cardiovascular disease in general, the correlation between death and moderate reductions in eGFR in the elderly population is weaker. Most importantly, we also must realize that an elderly patient with an eGFR of 45ml/min/1.73m2 has a different risk profile and lower risk of progression to ESRD than a 30 year old patient with the same eGFR. Therefore, health care providers should take an individualized approach to referring to a nephrologist for CKD that centers upon the estimated likelihood of kidney disease progression. For CKD patients with eGFR less than 30ml/min/1.73m2, the decision to refer is much easier as the rate of complications of severe CKD including hypertension, anemia, and mineral bone disorders rises directly with a decreasing GFR.[24] The challenge for the medical community will be to successfully balance the proper identification and treatment of actual CKD while avoiding nephrology referrals for mislabeled CKD and its attendant costs to the health care system and patient well being.

References

1. Coresh J, Selvin E, Stevens LA, Manzi J, Kusek JW, et al. Prevalence of chronic kidney disease in the United States. *JAMA* 2007:2038-47.
2. Cockcroft DW, Gault MH. Clinical estimation of creatinine clearance from serum creatinine. *Nephron* 1976:31-41.
3. Levey AS, Bosch JP, Lewis JB, Greene T, Rogers N, Roth D. 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* 1999:461-70.
4. National Kidney Foundation. Kidney Disease Outcomes Quality Initiative. Clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis* 2002:S1-S266.
5. Stevens LA, Coresh J, Feldman HI, Greene T, Lash JP, et al. Evaluation of the modification of diet in renal disease study equation in large diverse population. *J Am Soc Nephrol* 2007:2749-57.
6. Botev R, Mallie JP, Couchoud C, Schuk O, Fauvel JP, et al. Estimating glomerular filtration rate; Cockcroft-Gault and modification of diet in renal disease formulas compared to renal inulin clearance. *Clin J Am Soc Nephrol* 2009:899-906.
7. Boulware LE, Troll MU, Jaar BG, Myers DI, Powe NP. Identification and referral of patients with progressive CKD: a national study. *Am J Kid Dis* 2006:192-204.
8. Brantsma AH, Bakker SJ, de Zeeuw D, de Jong PE, Gansevoort RT; PREVEND Study Group: Cardiovascular and renal outcomes in subjects with KDOQI stage 1-3 chronic kidney disease: The importance of urinary albumin excretion. *Nephrol Dial Transplant* 2008:3851-8.
9. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events and hospitalization. *N Engl J Med* 2004:1296-305.
10. Hemmelgarn BR, Manns BJ, Lloyd A, James MT, Klarenbach S, et al. for the Alberta Kidney Disease Network. Relation between kidney function, proteinuria and adverse outcomes. *JAMA* 2010:423-9.
11. Iseki K, Kinjo K, Iseki C, Takishita S. Relationship between predicted creatinine clearance and proteinuria and the risk of developing ESRD in Okinawa, Japan. *Am J Kidney Dis* 2004:806-14.
12. Ishani A, Grandits GA, Grimm RH, Svendsen KH, Colling AJ, et al. MRFIT Research Group: Association of single measurements of dipstick proteinuria, estimated glomerular filtration rate and hematocrit with the 25 year incidence of end-stage renal disease in the Multiple Risk Factor Intervention Trial. *J Am Soc Nephrol*: 2006:1444-52.
13. Hallan SI, Ritz E, Lydersen S, Romundstad S, Kvenild K, Orth SR. Combining GFR and albuminuria to classify CKD improves prediction of ESRD. *J Am Soc Nephrol* 2009:1069-77.
14. Ruggeneti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, et al for the Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. *N Eng J Med* 2004:1941-51.
15. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P, et al. for the Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The Effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Eng J Med* 2001:870-8.
16. Patel A, MacMahon S, Chalmers J, Neal B, Billot L, et al. for the ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008:2560-72.
17. Chobanian AV, Bakris GL, Black HR, Cushman WC Green LA, et al for Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. *Hypertension* 2003:1206-52.
18. Wright JT Jr, Bakris G, Greene T, Agodoa LY, Appel LJ, et al. Effect of blood pressure lowering and antihypertensive drug class on progression of hypertensive kidney disease: results from the AASK trial. *JAMA* 2002:2421-31.
19. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001:851-60.
20. Levey AS, Beto JA, Coronado BE, et al. Controlling the epidemic of cardiovascular disease in chronic renal disease: what do we know? What do we need to learn? Where do we go from here? National Kidney Foundation Task Force on Cardiovascular Disease. *Am J Kid Dis* 1998:853-906.
21. Sarnak MJ, Levey AS. Cardiovascular disease and chronic renal disease: a new paradigm. *Am J Kid Dis* 2000:S117-31.
22. Vanholder R, Massy Z, Argiles A, Spasovski G, Verbeke F, Lamiere N. Chronic kidney disease as a cause of cardiovascular morbidity and mortality. *Nephrol Dial Transplant* 2005:1048-56.
23. K/DOQI clinical practice guidelines for chronic kidney disease evaluation, classification, and stratification. Kidney Disease Outcome Quality Initiative. *Am J Kid Dis* 2002:S1-246.
24. Levey AS, Coresh J, Balk E, et al. National Kidney Foundation Practice guidelines for chronic kidney disease: evaluation, classification, and stratification. *Ann Int Med* 2003:137-47.
25. O'Hare AM, Bertenthal D, Covinsky KE, et al. Mortality risk stratification in chronic kidney disease: one size for all ages? *J Am Soc Nephrol* 2006:846-53.
26. Raymond NT, Zehnder D, Smith SC, Stinson JA, Lehnert H, Higgins RM. Elevated mortality risk with mild to moderate chronic kidney disease decreases with age. *Nephrol Dial Transplant* 2007:3214- 20.
27. Roderick PJ, Atkins RJ, Smeeth L, et al. CKD and mortality risk in older people: A community-based population study in the United Kingdom. *Am J Kid Dis* 2009:950-60.
28. Hemmelgram BR, Zhang J, Manns BJ, James MT, Quinn RR, et al. Nephrology visits and health care resources use before and after reporting estimated glomerular filtration rate. *JAMA* 2010:1151-8.
29. O'Hare AM, Choi AI, Bertenthal D, et al. Age affects outcomes in chronic kidney disease. *J Am Soc Nephrol* 2007:2758-65.

Mordecai Stolk, MD, is a member of Nephrology Associates.

Charles McCoy, MD, is Clinical Associate Professor of Medicine at the Warren Alpert Medical School of Brown University, and is a member of Nephrology Associates.

Disclosure of Financial Interests

The authors and/or spouses/significant others have no financial interests to disclose.

Correspondence

Charles McCoy, MD
Nephrology Associates
318 Waterman Ave.
East Providence, RI 02914
Phone: (401) 438-5950
e-mail: cmmcoy@lifespan.org