The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in the United States has been increasing. 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. In addition, it is believed that 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 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. 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). 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. This underestimation of GFR improves as kidney function decreases but still remains unacceptably high at a GFR range of 30-59ml/min/1.73m2.

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. 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.

### Table 1. The Stages of Chronic Kidney Disease

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>GFR (ml/min/1.73m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Kidney damage with normal or ↑ GFR</td>
<td>≥ 90 (with CKD risk factors)</td>
</tr>
<tr>
<td>2</td>
<td>Kidney damage with mild ↑ GFR</td>
<td>60-89</td>
</tr>
<tr>
<td>3</td>
<td>Moderate ↑ GFR</td>
<td>30-59</td>
</tr>
<tr>
<td>4</td>
<td>Severe ↑ GFR</td>
<td>15-29</td>
</tr>
<tr>
<td>5</td>
<td>Kidney Failure</td>
<td>&lt;15 (or dialysis)</td>
</tr>
</tbody>
</table>

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. 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. 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. 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. 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. have good control of their diabetes with a goal HgbA1c of 6.5% or less, and a blood pressure goal of 130/80mmHg. 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.

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 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. Clinicians should not use the result of a serum creatinine as the only method to assess kidney function. 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. This phenomenon was recently described 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 and accepted management of CKD did not change, referral to a nephrologist on the basis of 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 45 ml/m2 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 30 ml/m2, 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. 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

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