

Mayo Clinic Proceedings

Early Referral for Chronic Kidney Disease: Good for Those Who Need It, but Who Are They?

Chronic kidney disease (CKD) is considered a common, growing, and underrecognized public health problem that affects an estimated 12% of adults in the United States.¹ From this large group, a much smaller subgroup has end-stage renal disease that requires renal replacement therapy. Who are these patients, and how can they be optimally managed to prevent disease progression and associated complications?

In 2002, the National Kidney Foundation (NKF) proposed a uniform system to classify patients with CKD² because of concerns that it is underrecognized and inadequately treated, especially due to accumulating studies suggesting the potential for specific interventions (aggressive blood pressure control and use of drugs that inhibit the renin-angiotensin-aldosterone system) to delay or retard progression.³⁻⁵ Patients are classified into 1 of 5 stages of CKD. An important component of the classification scheme is an estimation of the glomerular filtration rate (GFR). Stages 1 and 2 (mild CKD) are determined by evidence of kidney damage for 3 months or more, defined as structural or functional abnormalities of the kidney manifest on kidney biopsy, on imaging studies, or by abnormalities of the composition of the blood or urine (albuminuria), accompanied by normal or mildly reduced GFR (stage 1, GFR ≥ 90 mL/min per 1.73 m²; stage 2, GFR 60-89 mL/min per 1.73 m²). Stages 3 through 5 represent more advanced disease (moderate to severe CKD) and are determined solely by a GFR lower than 60 mL/min per 1.73 m² for 3 months or more without the requirement of other findings of kidney damage (stage 3, GFR 30-59 mL/min per 1.73 m²; stage 4, GFR 15-29 mL/min per 1.73 m²; stage 5, GFR <15 mL/min per 1.73 m²).

The validity of this classification is supported by a correlation of declining estimated GFR (eGFR) with increasing anemia, disturbances of calcium-phosphorus metabolism, cardiovascular disease (CVD), and total mortality.⁶ Indeed, most patients with reduced renal function will die of other causes before they progress to the need for renal replacement therapy. Chronic kidney disease is an independent risk factor for CVD morbidity and mortality.⁷ Increased risk relates to an excess prevalence of traditional CVD risk factors such as hypertension, diabetes, and dyslipidemia. Recent studies underscore the fact that factors specific to CKD likely play an additional and independent role, promoting vascular calcification, anemia, elevated homocysteine, and altered hemostasis.⁸⁻¹⁰ Therefore, the hope is that early identification of CKD might allow for targeted and aggressive interventions to not only prevent or delay progression to end-stage renal disease but also decrease CVD events.

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Two articles in the current issue of *Mayo Clinic Proceedings* deal with important aspects of this clinical problem. The study by Rule et al¹¹ identifies flaws in the currently recommended method to estimate GFR, an essential test for clinicians to identify and stage patients with CKD. The review by Sprangers et al¹² summarizes currently recommended interventions for patients with CKD and argues that late referral by primary care physicians may magnify mortality and complications related to CKD. The review also summarizes recent guidelines aimed to achieve effective interaction between primary care physicians and nephrologists.

A critical element of the new CKD classification scheme is estimation of the GFR. The most accurate reference standards for GFR determination are measurement of inulin or iothalamate clearance. These formal methods are expensive and generally not practical for use in routine clinical care. Measurement of serum creatinine is the most widely used method to estimate renal function but provides

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inaccurate information about the underlying GFR because its level is determined by factors unrelated to glomerular filtration.¹³ Creatinine generation is largely determined by muscle mass and dietary intake. Lower serum creatinine levels are associated with older age, female sex, chronic illness with muscle wasting, amputation, and a vegetarian diet. Higher serum creatinine levels are associated with black race, muscular body habitus, and a high-protein diet. To complicate matters further, the level of serum creatinine is influenced by renal tubular secretion, which increases as renal function declines. As a result, any given serum creatinine level can be associated with widely different values of GFR. For example, in an elderly woman with reduced muscle mass, a serum creatinine level well within the normal range can be associated with a reduced GFR. Conversely, in a young man with a muscular body habitus, a serum creatinine level in the upper end of the normal range can be associated with a normal GFR.

To more accurately predict GFR, serum creatinine has been incorporated into equations that take into account variables of age, sex, race, and body size (major determinants of variation in muscle mass) to calculate an eGFR. The Cockcroft-Gault and Modification of Diet in Renal Disease equations are most commonly used in clinical practice.^{14,15} Importantly, both equations were derived from population samples with known kidney disease. Few data address serum creatinine in healthy populations. Current NKF guidelines recommend that clinical laboratories use these equations to report eGFR when serum creatinine is measured, specifically with the goal to identify patients with CKD. Although using these tools to calculate eGFR may provide benefit, several caveats are in order. One of these derives from the fact that creatinine measurements are not standardized across laboratories.¹⁶ Serum creatinine measurements can differ by up to 0.3 mg/dL between laboratories. When incorporated into current estimating equations, such differences in measured creatinine can lead to major differences in eGFR. At a minimum, sensible application of national guidelines requires standardization of serum creatinine measurement. Also, eGFR from these equations is based on average differences in muscle mass attributable to differences in age, sex, and race. Thus, eGFR will be less accurate in patients with unusually high (underestimated true GFR) or low (overestimated true GFR) muscle mass or unusual diets (eg, vegetarian diet is associated with overestimation of true GFR). Importantly, the error in eGFR increases at higher levels of GFR. Consequently, current estimating equations do not report specific values higher than 60 mL/min per 1.73 m². Thus, clinically relevant changes in GFR occurring above this level will not be identified, and the estimating equations cannot be used to distinguish stage 1 from stage 2 CKD.

The study by Rule et al identifies another important limitation of current estimating equations. They applied previous GFR estimating equations derived separately from a CKD sample, a healthy sample, and a combined sample of CKD and healthy patients to calculate eGFR in a population-based sample of adults aged 45 years and older from Olmsted County, Minnesota. They observed that different estimating equations yielded widely different prevalence estimates for stage 3 or higher CKD, ranging from 12% with the equation derived from CKD patients to 0.2% with the equation derived from healthy patients. Previous studies by Rule and others have shown that current estimating equations derived from samples of patients with CKD underestimate GFR in healthy persons with high-normal creatinine levels.^{17,18} Thus, when applied to the general population consisting of a mixture of healthy and CKD patients, the equations overestimate CKD prevalence. As pointed out by Rule et al, this feature has important implications for estimating CKD prevalence in population studies and may lead to biased associations of risk factors for CKD. For clinical care, routine use of these equations in populations from general clinics may lead to the incorrect diagnosis of CKD in many healthy patients. Rule et al suggest that identification of CKD may be more appropriately determined by observing serum creatinine levels higher than the upper limit (97.5 percentile) of the normal range for sex and race and limiting the use of GFR estimating equations to stage patients after the diagnosis of CKD has been established. They argue that such an approach will reduce the number of healthy patients incorrectly diagnosed with CKD (high specificity), albeit at the expense of underdiagnosing CKD, particularly in older patients or those with low muscle mass for their age, sex, or race (low sensitivity). This, of course, was the original problem that led to the development of GFR estimating equations. Taken together, current data support the practice of reporting eGFR to alert the clinician to the possible presence of reduced renal function not obvious from the serum creatinine level. This practice may avoid unnecessary exposure to potential nephrotoxins or overdosing of drugs that rely on the kidney for elimination. Recognizing the importance of this clinical issue, the National Institutes of Health has sponsored a collaborative study to further develop and validate GFR estimating equations in an effort to resolve limitations associated with equations currently being applied in clinical practice and research. In the meantime, clinicians must be vigilant in their search for CKD. The measurement of serum creatinine and the reporting of eGFR should be considered in the context of a thorough history, physical examination, and assessment of the urine, including assessment for pro-

teinuria. Limitations of the application of eGFR should be understood.

As presented in the review by Sprangers et al, treatment of CKD must be timely and not delayed by limited referral patterns. The diagnosis of CKD involves consideration of reversible causes (obstruction, infection, drugs) and implementation of specific therapies designed to slow progression and lower CVD risk. Using the current classification scheme, a significant fraction of CKD occurs in older persons with stable but reduced GFR in the absence of other findings of renal injury (proteinuria). Whether these patients are at high risk for future kidney failure and would benefit from aggressive strategies to slow progression is unknown.¹⁹

The burden of caring for CKD patients will continue to rest primarily on the shoulders of primary care physicians, especially for patients with stages 1 through 3 disease. Their large numbers alone would overwhelm nephrologists in current practice. However, Sprangers et al argue that timely referral of patients with stage 4 or 5 CKD will lead to better patient outcomes. In some patients (15%-20%), kidney disease progresses rapidly and may not be evident in time to be treated optimally. However, practice reviews indicate that nearly 40% of "late referrals" (defined as failure to be seen by nephrology subspecialists until 1-6 months before the need to start dialysis) may derive from patient-related issues, and an additional 40% may relate to reluctance to refer or lack of awareness of the diagnosis on the part of physicians. The latter may be partly due to misinterpretation of serum creatinine values. In some patients (nearly 5%), Sprangers et al suggest that progression could be prevented. In many other patients, adverse outcomes including CVD complications and suboptimal planning for renal replacement therapy could be prevented. They suggest that multidisciplinary nephrology clinics that employ nurse specialists, dietitians, and social workers may provide optimum care. It is hoped that the NKF initiative will improve physician recognition of CKD and its severity, reducing the current high rates of late referral for specialist care with its resultant increase in morbidity.

Although the exact prevalence of CKD remains uncertain, it clearly is an increasingly common clinical problem. The impact of early detection and targeted treatment strategies to lessen morbidity, mortality, and progression to kidney failure is currently unknown but worthy of continued efforts to define.

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