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Editorial Comments

A critical evaluation of chronic kidney disease—should isolated reduced estimated glomerular filtration rate be considered a 'disease'?

Emilio D. Poggio[1] and Andrew D. Rule[2]

[1]Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, Cleveland, OH and [2]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA

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Introduction

The definition and classification of chronic kidney disease (CKD) as adopted by the National Kidney Foundation and by the Kidney Disease: Improving Global Outcomes [1,2] has generated new interest in nephrology. A consistent classification is necessary to develop a coherent literature on the natural history, risk factors and outcomes of a disease. A primary goal with CKD classification has been to identify an earlier, often asymptomatic stage where interventions may prevent the progression to end-stage renal disease. Interventions only at late stages of disease are not desirable given the high morbidity, mortality and societal costs associated with dialysis and transplantation. The current classification of CKD is based on three fundamental components: (1) *damaged* renal parenchyma for stages 1 and 2 (e.g. proteinuria or polycystic kidneys); (2) *decreased function* as determined by glomerular filtration rate (GFR) regardless of damaged renal parenchyma for stages 3 and higher; and (3) *chronicity* to distinguish these parenchymal and functional changes from acute states. Unfortunately, recent data suggest that this classification system for CKD is not adequate as currently applied.

Serum creatinine has been pivotal for diagnosing and staging CKD because it is an inexpensive, common test in clinical practice. Unfortunately, serum creatinine is not just a marker of GFR, but also a marker of creatinine generation rate from muscle mass and dietary protein. Since direct GFR measurement is expensive and inconvenient, estimated GFR (eGFR) by the Modification of Diet in Renal Disease (MDRD) equation has been used to transform serum creatinine into a screening tool for CKD (defined by an eGFR <60 ml/min/1.73 m^2) [1]. However, using eGFR in screening for CKD has substantial drawbacks! Recent estimates of CKD claim that 26.3 million (13.1%) of adult Americans suffer from CKD [3,4]. Of these, 10 million (5.0%) are considered to have stages 1 and 2 (albuminuria and eGFR ≥ 60 ml/min/1.73 m^2), and even more, 15.5 million (7.7% of the adult American population) are considered to have stage 3 (eGFR between 30 and 59 ml/min/1.73 m^2). Recent data further show that less than a third of persons with stage 3 CKD even have albuminuria [4,5]. Why is albuminuria often absent in the majority of subjects with CKD stage 3 when albuminuria defines the earlier stages? While CKD is certainly under-recognized by clinicians, an overreaching classification system may also help explain why only ~10% of persons with stage 3 CKD are aware of their 'disease' [3] and only a few percent have diagnosis of this 'disease' in their medical record [6]. Before we 'educate' physicians and patients on CKD, perhaps we should reconsider whether there is a clinical benefit to labelling every person with an isolated eGFR <60 ml/min/1.73 m^2 with a *disease*.

When classifying disease, it should be recognized that health is a relative condition that does not have a universally accepted definition. There are generally two approaches used to define disease: the first approach is based on a 'critical value' where increased morbidity and mortality occur, while the second approach is based on 'health-associated reference values' [7]. For a critical value approach, metabolic complications (e.g. anaemia, hyperphosphataemia, acidosis) from renal disease are too uncommon to justify a threshold of 60 ml/min/1.73 m^2 [8]. Instead, it has largely been argued that an eGFR of <60 ml/min/1.73 m^2 should classify CKD because below this threshold there is increased cardiovascular morbidity, mortality and end-stage renal disease [9–11]. But a closer look at these studies does not fully support 60 ml/min/1.73 m^2 as a 'critical value'. Go *et al*. found no increased independent risk of mortality for an eGFR of 45–59 ml/min/1.73 m^2 when chronicity was established with multiple serum creatinine levels [9]. O'Hare *et al*. actually found a *decreased* independent risk of mortality in persons older than 45 years with an eGFR of 50–59 ml/min/1.73 m^2 when chronicity was established over 3–6 months. Brantsma recently showed in the PREVEND

Correspondence and offprint requests to: Emilio D. Poggio, Renal Function Laboratory, Department of Nephrology and Hypertension, Glickman Urological and Kidney Institute, Cleveland Clinic, 9500 Euclid Avenue-Desk A51, Cleveland, OH 44195, USA. Tel: +1-216-444-5383; Fax: +1-216-444-9378; E-mail: poggioe@ccf.org

Table 1. Risk of chronic kidney disease in the community by sex and by race

Method to identify CKD	Sex	Race	References
Macroalbuminuria	↑ Men	↑ Blacks	[3]
End-stage renal disease	↑ Men	↑ Blacks	[29]
Rise in serum creatinine (or decline in estimated GFR)	↑ Men	↑ Blacks	[30,31]
Elevated SCr	↑ Men	↑ Blacks	[32]
Estimated GFR <60 ml/min/1.73 m^2	↑ Women	↑ Whites	[6,33,34]
Measured GFR <60 ml/min/1.73 m^2	?	?	

study that among subjects with CKD stage 3, about two-thirds had no albuminuria and these subjects had a similar age- and sex-adjusted risk of cardiovascular events to subjects with no CKD [12]. The essential problem with this critical value approach to CKD is that a high-normal serum creatinine level is both a marker of fitness (increased muscle mass) and a marker of disease (decreased GFR).

The second approach is to define disease based on the expected range for normal subjects in good health [10]. What is the normal range for GFR or serum creatinine in a healthy 20-year-old black male or a healthy 60-year-old white female? Nephrologists have a unique resource to characterize health, our kidney donor population. Kidney donors can define a normal range for GFR and serum creatinine because they undergo extensive medical workups that include detailed histories, physical exams, comprehensive laboratory panels and radiological studies of the kidney. With kidney donors we have learned that GFR declines with normal ageing [13,14] as occurs with any organ system. Why should nephrology label the asymptomatic age-related decline in kidney function as disease? Fehrman–Ekholm *et al*. found that nearly all elderly persons (age >70 years) in good health have a measured GFR below 90 ml/min/1.73 m^2 (the lower limit of normal for a 20 year old) [15]. A pathological process may be responsible for this age-related decline, but it is unknown if this contributes to morbidity and mortality or can be prevented. Let us not forget that we routinely lower GFR in kidney donors to levels <60 ml/min/1.73 m^2 and there is rarely a return of GFR to pre-nephrectomy levels [16–18]. Importantly, there is no evidence of an increased risk of end-stage renal disease or mortality in kidney donors followed for decades after nephrectomy [19–21].

Another problem with classifying CKD stage 3 with only eGFR is that we cannot accurately estimate GFR. The lower limit of normal for eGFR [22] is ∼10–20 ml/min/1.73 m^2 lower than the lower limit of normal for the measured GFR [13,23]. This is due to two fundamental problems. First, demographics (age, sex and race) do not completely adequately model the non-GFR variability of serum creatinine. Second, the MDRD equation underestimates GFR in persons without CKD because it was developed in a CKD population [23–25]. Healthy persons are likely to have more muscle mass and better dietary protein intake (i.e. creatinine generation) than patients with CKD. Thus, an individual with a high-normal serum creatinine level has about a 50% higher GFR if they present in good health than if they present with a clinical diagnosis of CKD [23]. A third problem is that using demographics as surrogates for creatinine generation may bias the risk of CKD across demographics (Table 1). For example, who has a higher risk of CKD between a 50-year-old black male and a 50-year-old white male, both with a serum creatinine of 1.3 mg/dl? The black male may have higher creatinine generation (muscle mass) and thus a higher estimated GFR at the same creatinine level than the white male, as the estimate is modelled with the 1.21 race correction factor in the MDRD equation. At the same time, the MDRD equation was developed using only patients with clinically diagnosed CKD, and thus, this race correction factor may not account for differences in the *risk* of CKD. The black male may also be more likely to have risk factors (hypertension, diabetes, proteinuria, etc.) leading to a higher pretest probability for CKD, and thus, may have on average a lower estimated GFR than the white male for this borderline creatinine level.

Conceptually, a revised approach to CKD should include a clear differentiation between *screening* and *diagnosis* of CKD. A single elevated serum creatinine, reduced eGFR or an abnormal urinalysis should initially be viewed as a *screening* test, and a subject with suspected CKD should be considered to have an azotaemia until CKD is determined by the additional workup and clinical judgment. In addition, age- and sex-specific reference ranges for serum creatinine or eGFR should be used instead of the fixed cut-off. The upper limit of normal for males and females (95th percentile) for serum creatinine [27] has the advantage of inherent simplicity, since the age-related decline in muscle mass [28] approximately cancels out the age-related decline in GFR [13,29]. Multiple thresholds would need to be reported for eGFR [22], but eGFR has the advantage of more accurately reflecting actual GFR than serum creatinine. Concerns may be raised that these thresholds would artificially define the prevalence of CKD to 5% of the population including younger subjects, but this is not true. First, reference ranges are developed using normal subjects that have been screened to confirm health (by survey or kidney donor evaluation) not random samples of the general population. Second, reference ranges are intended for *screening* (e.g. they identify azotaemia); the *diagnosis* of CKD requires clinician input that considers additional evidence of CKD such as risk factors (e.g. hypertension and diabetes), macroalbuminuria, urine sediment, renal ultrasound and even metabolic abnormalities particularly for patients with borderline serum creatinine or eGFR levels. Third, younger healthy subjects are less likely to have a clinical indication for CKD screening and will be less likely to have serum creatinine levels checked as part of their routine clinical care. Finally, once a clinical diagnosis of CKD has been established, staging of CKD by the current MDRD equation (conveniently developed in patients with a clinical diagnosis of CKD) should follow to guide management.

This mechanism makes the system dynamic, but importantly, it incorporates clinical judgment into the interpretation of laboratory information. The primary goal should be to improve the outcomes of patients with CKD, but targeted interventions require accurate classification of CKD. The nephrology community now faces the need to improve the classification of CKD, particularly stage 3, where the clinicians' input will likely be required.

Conflict of interest statements. None declared.

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