A Critique of Clinical Guidelines for Detection of Individuals with Chronic Kidney Disease

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Key Words

Chronic kidney disease • Estimated glomerular filtration rate • Clinical guidelines

Abstract

Chronic kidney disease (CKD) and its association with cardiovascular mortality is increasingly regarded as a global public health problem. International efforts to combat this 'epidemic' have led to fundamental changes not only in the way we measure renal function but also how we classify and manage CKD. Clinical guidelines have established the use of estimated glomerular filtration rate (eGFR) and Kidney Disease Outcomes Quality Initiative classification of kidney disease as the cornerstones of CKD detection. The introduction of these guidelines in routine practice has had considerable impact on the large number of patients newly labelled with a chronic disease. However, it is far from clear that these patients with low GFR have intrinsic kidney disease and the vast majority will not develop end-stage renal failure. Furthermore, there is a lack of evidence that identification of low GFR can usefully be used to screen populations either for metabolic complications of kidney disease or cardiovascular risk.

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Introduction

The relentless increase in the number of patients who will die without renal replacement therapy is an epidemic [1] with disastrous consequences for individual patients, their families and the health economy. Missed opportunities due to the failure to detect and stabilise early kidney disease coupled with the late referral of patients with progressive advanced renal disease are key factors which contribute to the poor outcome for these patients [2]. These facts underpin the ongoing national and international efforts directed towards the prevention of end-stage renal failure (<http://www.kdigo.org>). Further impetus has come from the recognition of chronic kidney disease (CKD) as an important independent risk factor for cardiovascular disease and the concept that detection can predict, and active management reduce, cardiovascular risk [3, 4].

Many countries have now adopted the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines to promote early detection and active management of patients with CKD. These strategies have involved a fundamental change in the routine reporting of renal function with the use of formula-based estimates of glomerular filtration rate, eGFR. A new disease entity, CKD, has replaced the

The at-risk population:

All guidelines

Established kidney disease
Vascular disease
Hypertension
Diabetes
Family history of CKD
Those with symptoms or at high risk of obstructive uropathy

Additional at-risk groups:

UK

Heart failure
Nephrotoxic drugs
Multisystem disease with potential renal involvement

KDOQI

All health encounters
Multisystem disease with potential renal involvement
US ethnic minority status

CARI

Aboriginal Australians
Torres Strait Islanders

Evaluation of renal function:

All guidelines

Excretory renal function

The serum creatinine alone should not be used to evaluate renal function
Clinical laboratories should routinely report estimates of GFR Equation to estimate GFR MDRD (or Cockcroft Gault¹)

Proteinuria

Dipstick analysis for proteinuria
Confirmation by spot albumin/creatinine ratio²
Confirmation by spot urine protein/creatinine ratio³
Detection of early nephropathy in at risk groups by albumin-specific dipstick or spot albumin/creatinine ratio

Haematuria

Dipstick analysis
Microscopy of urine sediment

¹ KDOQI.

² Albumin/creatinine ratio preferred unless >500 mg/g (KDOQI).

³ Early morning specimen preferred but random sample acceptable.

less obvious chronic renal failure, and there is a brand new classification and management pathway to go with it. Previous thresholds for the diagnosis of CKD have been dramatically lowered. In the USA, population-based evidence from the National Health and Nutrition Examination Study has estimated an 11% prevalence of CKD in the general population [5].

Although most CKD guidelines are targeted to specific at-risk populations, every creatinine measurement,

even if incidental to any clinical suspicion of renal disease, is now reported as an eGFR. This means that de facto, a screening programme for CKD in the general population has been established. We believe that while these developments have led to a wider appreciation of the importance and prevalence of kidney disease, they have also given rise to serious concerns about the definition of 'disease' and the implications of population screening [6]. The purpose of this review is to appraise the current guidelines for CKD, their stated goals and their effect on the clinical management of patients with CKD.

Recommended Screening Tools and Their Limitations

For many years, serum creatinine levels have been the mainstay of renal function assessment. Serum creatinine levels are determined by production, dependent on muscle mass which reflects age, sex and ethnicity, and excretion which is mostly at the glomerulus with a component of tubular secretion. Measurement of creatinine clearance with a 24-hour urine collection can be used to estimate GFR, but this test is both inaccurate and tedious. The inverse relationship of creatinine with creatinine clearance coupled with the tremendous variability of muscle mass between patients makes serum creatinine levels counter-intuitive to the non-expert, with levels at the upper limit of the 'normal range' reflecting renal function between 25 and 100% of normal depending on muscle mass.

To circumvent this problem, numerous equations have been described which estimate creatinine clearance or GFR, often focussing on particular patient groups, such as children, individuals with near normal function and the very elderly. A full review of the strengths and weaknesses of such equations is beyond the scope of this review and is fully covered in several detailed articles [7–9]. However, in the context of the recent KDOQI strategy, the most widely recommended formula is the 4-variable (age, sex, ethnicity and creatinine) MDRD eGFR equation which was first introduced for the Modification of Diet in Renal Disease (MDRD) Study and validated against iothalamate clearance (iGFR). The equation was designed and validated in patients already known to have kidney disease with mean GFR of 40 ml/min/1.73 m². The key strength of this equation is the inclusion of a variable for Afro-Americans and sub-Saharan Africans who tend to have both a higher muscle mass as well as a co-incidental increased prevalence of CKD. The MDRD formula esti-

mates the eGFR for an *average* individual of specified age, sex and ethnicity, but nevertheless it is relatively accurate in patients with CKD and is undoubtedly an excellent tool for monitoring disease progression [10, 11]. However, the formula is increasingly inaccurate as renal function approaches normal [see 16], with iGFR varying between 35 and 90 ml/min for a calculated eGFR 60 ml/min. In healthy kidney donors, the MDRD eGFR equation underestimated the measured GFR by 29% [10–12].

Should eGFR Be Used to Screen Guideline-Defined Target Populations?

The MDRD formula has not been validated as a screening tool and has significant limitations in certain target patient populations. Indeed, it is not validated in those aged less than 18 years or more than 70 years, or in patients with cachexia, severe oedema, morbid obesity, renal transplant recipients, amputees or hospitalised ill patients [13]. There are no specific data validating its use in patients with cardiac failure, vascular disease or uropathy. Hypertension and diabetes mellitus are the most common risk factors for kidney disease, but even in these patients the utility of eGFR to detect kidney disease is unproven. In type 1 diabetics enrolled in the Diabetes Control and Complications Trial, both the eGFR and estimated creatinine clearance (using Cockcroft-Gault) were significantly less than the iGFR, with only one third of estimates within $\pm 10\%$ [14]. Similar inaccuracies have been reported in patients with NIDDM with CKD stage 1 and 2, although as anticipated, eGFR was more accurate in patients with more advanced CKD [15]. A study of a cohort of hypertensives and their siblings found that CKD (as defined by eGFR) was more prevalent than when defined using serum creatinine alone. However, eGFR correlated less well than serum creatinine alone with the presence of albuminuria. It may be that most subjects with a reduced eGFR but a normal serum creatinine level do not have kidney disease. These individuals could be misclassified as having CKD because of the varying effects of protein intake and muscle mass on creatinine generation or excretion [16].

Should We Use eGFR to Screen for Cardiovascular Risk?

Epidemiological data associate CKD with an increased graded risk of cardiovascular and all-cause mortality, particularly with more advanced disease [3, 4, 17]. How-

ever, the relationship between cardiovascular disease and CKD is complex, and cardiovascular disease itself plays an important role in subsequent development of kidney disease [18]. This reciprocal relationship likely accounts for the fact that the risk of cardiovascular disease in patients with low eGFR is substantially attenuated when adjusted for traditional risk factors and that prior history of cardiovascular disease greatly outweighs the presence of CKD as a risk factor [17, 19]. Indeed, the increased risk of cardiovascular mortality in CKD may not even apply in some ethnic groups, even those with high rates of CKD [20].

There is little evidence to support screening for CKD in order to target therapies to reduce cardiovascular risk. A mechanism for increased cardiovascular disease in CKD has not been defined and may reflect abnormalities in blood pressure control, lipid abnormalities and inflammation. Although it is tempting to apply lessons learned from major interventional trials in cardiovascular disease in those without CKD, it is important to remember that patients with renal disease have been largely excluded from these studies and evidence supporting intervention is lacking [21]. As an example, even the largest database of lipid-lowering therapy in CKD with pooled analysis of several studies showed no clear benefit in those with CKD without a prior history of cardiovascular disease [22]. In fact, paradoxically, despite the strong association between CKD and cardiovascular death, traditional risk factors such as hyperlipidaemia, obesity and hypertension are associated with improved survival in patients with CKD 5 [23]. If a justification for using eGFR to screen for cardiovascular risk is made, it will also have to account for the fact that the great majority of patients with CKD detected using eGFR are elderly and in this group moderate reductions in GFR are not associated with increased mortality risk [24, 25].

Is the Diagnosis of CKD Stage 3 Relevant?

Despite the wide variability in accuracy of eGFR, the diagnostic criteria of CKD staging are rigid and fail to take into account the recognised age-related changes in renal function which suggest that GFR declines at 0.46 and 0.71 ml/year for men and women, respectively, from the age of 20 years [26, 27]. The National Health and Nutrition Examination Study observed very high rates of CKD in the elderly population [5, 28], confirmed by a recent Italian study which suggested that the prevalence of eGFR <60 ml/min/1.73 m² exceeded 30% [29]. For most of these pa-

tients, the diagnosis of CKD is irrelevant and carries the unnecessary adverse psychological burden associated with 'disease labelling' [30]. A population-based study from England showed that although the prevalence of relatively advanced kidney failure (serum creatinine >180 μM in men, >135 μM in women) was 0.55%, the majority of those patients maintained stable renal function and did not progress to ESRF [2]. Similar data from the Norwegian Nord-Trøndelag (HUNT) study demonstrated a prevalence of CKD stages 3–5 of 4.7% with the majority of affected patients older than 70 years. Progression to ESRF was rare at 0.04 (from CKD 3), 0.2 (from CKD 4), and 2.6 (from CKD5) per 100 person-years. Interestingly, the CKD prevalence observed in Norway was similar to that reported in the USA, but the relative risk of progression in US white patients was much greater. This may be due to later referral to a nephrologist and the higher prevalence of obesity and diabetes [31]. Even if patients with CKD 3 are at low risk of developing progressive renal disease, it might be argued that detection and treatment of complications of early CKD is useful. This then prompts further investigation of the patient for complications of CKD, such as anaemia and renal bone disease. However, population-based studies suggest the prevalence of clinically relevant complications is actually low in patients with CKD 3 [32].

Conclusions

Despite the introduction of strategies leading to widespread use of eGFR to detect kidney disease, its use has not been validated in target populations. While eGFR is un-

doubtedly useful in management of patients with established renal failure, eGFR levels are as variable as the serum creatinine levels from which they are calculated and must not be regarded as any form of gold-standard measurement. This is particularly important in patients with CKD stage 3 where eGFR is no more effective than serum creatinine measurement as a diagnostic tool. Widespread application of this formula may identify a small number of patients with hitherto unrecognised disease who may benefit from intervention but at the considerable expense of conferring an adverse and clinically irrelevant diagnosis on a much larger number of individuals.

Appendix

Kidney Disease Improving Global Outcomes

<http://www.kdigo.org/clinical-practice-guidelines/guideline-summaries>

The CARI Guidelines – Caring for Australians with Renal Impairment

http://www.cari.org.au/ckd_prevent_list_archives.php

Kidney Disease Outcomes Quality Initiative (KDOQI)

http://www.kidney.org/professionals/kdoqi/guidelines_ckd/toc.htm

United Kingdom Chronic Kidney Disease Guidelines (UK CKD)

<http://www.renal.org/CKDguide/ckd.html>

Canadian Society of Nephrology Guidelines

<http://www.csnsn.ca/english/home/default.asp?s=1>

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