Commentary

New results from the Modification of Diet in Renal Disease study: the importance of clinical outcomes in test strategies for early chronic kidney disease

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Summary

A formula derived from the Modification of Diet in Renal Disease (MDRD) study in chronic renal disease is widely used to estimate glomerular filtration rate (GFR). Recently a ten-year follow-up of MDRD participants evaluated four tests of kidney function measured at baseline as predictors of important long-term clinical outcomes.

Surprisingly, neither formula-estimated GFR nor reference method GFR showed a clear advantage over simple creatinine measurement whereas another test, cystatin C, looked more promising. This raises important points of principle in terms of how the usefulness of test strategies should be assessed. Data on clinical outcomes are an essential ingredient in this process.

Introduction

Recent years have seen the widespread adoption of formula estimates of glomerular filtration rate (eGFR), often calculated from serum creatinine by a method derived from the Modification of Diet in Renal Disease (MDRD) Study.1 Routine reporting of eGFR is advocated in several countries. In Great Britain it is required by the National Service Framework for Renal Services2 and general practitioners have now been asked to establish registers of patients with eGFR of 60 ml/min/1.73 m² or worse.3 MDRD formula estimations are undoubtedly valuable for managing patients with proven chronic kidney disease (CKD), for example in staging and monitoring progress. Estimates of kidney function by another calculation, the Cockcroft–Gault formula, are used for adjusting drug dosages.4 However, more controversial is the use of eGFR to test patients without previously recognized CKD. Further discussion of this is timely following the publication in 2007 of a 10-year follow-up study of participants in the MDRD trial.5

Is eGFR being used as a screening test?

In 2002 Grimes and Schulz reviewed the principles of screening, which they described as ‘a double-edged sword, sometimes wielded clumsily by the well-intended.’6 They distinguished between case
finding (seeking additional conditions in those with known predisposing conditions) and screening. Where eGFR is used selectively in patients with conditions predisposing to CKD (such as diabetes or hypertension) its application can be described as case finding. However, if eGFR is provided with every new creatinine result issued by laboratories, and if general practitioners’ computers apply the MDRD formula retrospectively to old creatinine results then testing can be described as opportunistic screening. This is particularly true since most creatinine assays are performed within broad test profiles without specific CKD questions being formulated in advance.

Grimes and Schulz emphasized on the importance of four characteristics commonly used to describe the performance of screening tests: sensitivity, specificity and the predictive values of positive and negative test results. The prevalence of disease in the tested population has a profound effect on the predictive value of abnormal test results: in populations with low disease prevalence even tests with very good specificity produce significant numbers of false positives.

**Controversies around eGFR**

Routine eGFR reporting has divided opinion. Enthusiasts highlight the poor sensitivity of serum creatinine in early CKD: in some individuals GFR may halve before serum creatinine rises above the population reference range. Sceptics underline the MDRD formula’s inaccuracy in people with normal or near-normal renal function, where there is underestimation of GFR relative to reference methods, compounded by wide variation in the size of error between individuals. In effect, sensitivity for early CKD has been enhanced at the expense of specificity; some healthy subjects will be wrongly identified as having CKD by eGFR testing. The number of individuals misclassified will increase as testing becomes more widespread: less selective testing will reduce the prevalence of CKD in the tested population and thereby reduce the predictive value of abnormal tests, increasing the false positive rate. In addition, in some patients discrepant estimates of renal function are obtained through the two most widely used formulas, MDRD and Cockcroft–Gault, with implications for drug dose adjustment in renal disease.

Some errors in eGFR will be reduced by improved standardization of creatinine assays and by controlling the conditions under which blood samples are obtained to reduce the influence of dietary factors on serum creatinine levels. However, there are issues with eGFR beyond these methodological points.

One problem is that creatinine itself is imperfect as a glomerular filtration marker. Numerous non-filtration factors, including variations in patients’ metabolic state and medications, affect serum creatinine results. Inevitably these effects will translate into errors in estimates of GFR calculated with any creatinine-based formula.

**Kidney function tests as predictors of clinical outcome**

The recent publication of a follow-up study on participants in the original MDRD trial raises a different type of issue with eGFR screening and this concerns our purpose in trying to detect CKD earlier. The objective is to permit earlier identification of individuals at increased risk of adverse clinical events so that we might have better opportunity to improve their outcomes through treatment. Patients with CKD are at risk of progressing to renal failure and of succumbing to cardiovascular disease (CVD), which is the major cause of death in these patients. Implicit in the current strategy is the expectation that by estimating GFR early in the development of CKD it might be possible to identify risk more effectively than is possible by simple creatinine measurement. It is in this regard that the long-term follow-up of MDRD participants is especially interesting. The authors compared four indices of renal dysfunction measured at baseline (serum creatinine, MDRD formula-estimated GFR, GFR measured by the iothalamate reference-method and cystatin C) as risk factors for adverse outcomes. Cystatin C is a serum component less affected than creatinine by non-renal factors, including muscle mass, and easily assayed. Although previous investigations have compared cystatin C with other markers of glomerular function, no previous study has directly compared cystatin C and serum creatinine as risk factors for outcomes in CKD patients and no study has previously compared measured GFR with cystatin C in terms of clinical outcomes. In one sense the results were disappointing in that the reference-method GFR, formula-estimated GFR and serum creatinine did not differ significantly from each other in the strength of their associations with either all-cause mortality or cardiovascular death (Figure 1). We cannot therefore assume that the extension of formula-estimation of GFR to patients with more normal renal function than the original participants in the MDRD study will improve capacity to predict cardiovascular risk.
in the way that might have been hoped. On the other hand the authors suggested that the other renal marker evaluated, cystatin C, may provide cardiovascular prognostic information in CKD beyond its role as an index of GFR. The confidence intervals were wide in the MDRD follow-up study so that the results regarding cystatin C were not decisive, but the possible prognostic value of cystatin C has been indicated by several other studies, particularly among the elderly.\(^{14–16}\) This is important because a high proportion of patients found to have reduced eGFR are elderly and the MDRD formula is itself less well validated in this age group.

### Conclusions

The new data from the MDRD study should cause reflection on testing strategies for early CKD. In judging the usefulness of testing it is not enough to assess newer tests (e.g. formula estimates of GFR) solely according to their ability to approximate to older tests (e.g. reference-method GFR). Instead we need more direct data from trials on the capacity to assess newer tests (e.g. formula estimates of GFR) to predict the adverse clinical outcomes we wish to prevent. In particular, the potential role of cystatin C in risk assessment warrants further investigation but there are other candidate tests as prognostic indicators in CKD, including B-type natriuretic peptide.\(^{17}\) Finally, it is important to appreciate that even if we had a testing strategy capable of identifying individuals with early CKD and assessing their risk of developing progressive kidney disease and/or increased cardiovascular complications, we still need proof of the effectiveness of therapeutic interventions used in such patients. Unfortunately, nephrology is characterised by a distinct scarcity of interventional trials and indeed patients with CKD have actually been excluded from many of the major trials that underpin current practice in preventative cardiology.\(^{18}\) As Sherlock Holmes once remarked to Watson: ‘It is an error to argue in front of your data. You will find yourself insensibly twisting them round to fit your theories’.

### References


