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Cystatin C to predict renal disease and cardiovascular risk

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What is cystatin C?

Cystatin C has many similarities to creatinine. It is a small molecule (13 kDa) that is filtered unchanged at the glomerulus and is measurable in the serum. Serum cystatin C (as for creatinine) can therefore be used to estimate kidney function. Creatinine is cheap, widely available, and measurement is standardised worldwide with the use of IDMS-traceable laboratory techniques. Cystatin C has been proposed as a better, more accurate biomarker for estimating kidney function: it is released by all nucleated cells and is not influenced by age, gender, ethnicity or muscle mass. However, it is less widely available, is generally more expensive than creatinine (owing to the cost of reagents and lack of widespread use), and can be elevated in inflammatory states such as cancer, thyroid disease and corticosteroid use.

Why use cystatin C to estimate kidney function?

Historically, glomerular filtration rate (GFR) was measured using either exogenous (iohexol or 51Cr-EDTA) clearance or endogenous markers, however, these markers are difficult to obtain, measurements are time-consuming and require expertise and there is substantial variability in the readings. Measuring endogenous markers (such as creatinine or cystatin C) in the urine over 24 hours is similarly cumbersome and therefore impractical and inaccurate for widespread, repeated use.

Instead, GFR is estimated from serum biomarkers using one of many equations. Of these, CKD-EPI is thought to show the greatest precision and least bias, but others include MDRD, FAS and BIS. For monitoring of changes in kidney function, estimated GFR (eGFR) is considered to be at least as good as measured GFR¹. eGFR can be calculated using

creatinine alone (eGFR_{cr}), cystatin C alone (eGFR_{cys}), or using a combination of creatinine and cystatin C (eGFR_{cr-cys})².

Under circumstances where it is desirable for eGFR to reflect renal excretory function as accurately as possible (purists may argue that this is desirable at all times), eGFR_{cr-cys} is more closely aligned to measured kidney function than eGFR_{cr} or eGFR_{cys} alone across all levels of kidney function²⁻⁴. This may be because the non-GFR determinants (biases) of both creatinine and cystatin are independent and therefore can be attenuated in an equation that combines both biomarkers.

CKD staging was generated as a simple means of planning follow-up and management, including of complications associated with kidney disease (such as cardiovascular disease (CVD), anaemia and mineral and bone disorder), and of estimating the risk of end-stage kidney disease. In the early stages, CKD is picked up more readily by eGFR_{cys} or eGFR_{cr-cys}⁵. Confirmatory testing with cystatin C-based eGFR is recommended for those with CKD stage 3a (eGFR 45-60ml/min/1.73m²)⁶, but we would recommend expanding these guidelines to those with eGFR 60-90ml/min/1.73m² too⁵, particularly if they have additional risk factors for CVD or at high risk of progressive CKD. For prediction of end-stage kidney disease (ESKD), both eGFR_{cys} and eGFR_{cr-cys} consistently outperform eGFR_{cr}^{5,7}.

How does cystatin C improve prediction of cardiovascular risk?

Only a tiny proportion of patients with CKD will progress to ESKD. Due to a combination of traditional atherosclerotic and CKD-specific risk factors, a substantial proportion of patients with CKD will experience CVD (sometimes fatal) long before needing renal replacement therapy. This risk begins early in the disease process, augments as CKD progresses, and includes atherosclerotic disease, heart failure, arrhythmia and sudden death^{5,7,8}.

eGFR_{cys} has a stronger, more linear relationship with cardiovascular outcome and mortality and is therefore able to detect an increased risk of CVD earlier than eGFR_{cr}, and before clinically significant CKD becomes apparent (Figure). eGFR_{cys} starts to detect an increased risk of CVD as soon as eGFR_{cys} falls below 90ml/min/1.73m², whereas eGFR_{cr} does not consistently recognise this increase risk until eGFR_{cr} falls below about 75ml/min/1.73m²^{5,7}. Whilst it is likely that there are some non-atherosclerotic risk factors to blame, detecting increased cardiovascular risk earlier in the disease process may allow heightened awareness for patients and clinicians, implementation of lifestyle changes and early primary prevention strategies to attenuate the risk of CVD. Once CKD is established

(especially when $\text{eGFR} < 45 \text{ ml/min/1.73m}^2$), the added risk prediction provided by eGFR_{cys} is less apparent⁵.

It is likely that eGFR_{cys} has a stronger relationship with cardiovascular risk than eGFR_{cr} in part because of non-GFR determinants. Cystatin C is elevated in some inflammatory conditions with a slightly lower eGFR_{cys} . These inflammatory conditions (themselves associated with cardiovascular risk) may be undiagnosed or are not captured routinely in risk prediction models. The lower eGFR_{cys} can fulfil some helpful confounding in identifying those at higher risk.

Implications

eGFR_{cys} or $\text{eGFR}_{\text{cr-cys}}$ outperform eGFR_{cr} for estimation of kidney function, diagnosis and staging of CKD and risk prediction of ESKD and CVD. Cystatin-based measures can also be safely used for drug dosing of potentially nephrotoxic medications⁹.

The reluctance to use these markers in clinical practice likely relates to concerns over switching from cheap, available creatinine, to a more expensive, less available biomarker, with relatively minor improvements in prediction of renal function, ESKD and CVD. The eGFR-C trial is designed to explore the accuracy, precision and cost-effectiveness of using eGFR_{cys} to monitor CKD: results are expected later in 2020¹⁰.

Whilst eGFR_{cys} / $\text{eGFR}_{\text{cr-cys}}$ should not necessarily replace eGFR_{cr} in widespread practice for routine monitoring of disease progression, earlier and more accurate detection of CKD and its associated risks could have a substantial effect on patient management and outcomes on a population scale.

Summary

These differing eGFR measures could be used in the following ways to improve accuracy and patient outcomes (Figure):

1. $\text{eGFR}_{\text{cr-cys}}$ provides the most accurate estimation of GFR, and could be used particularly when this accuracy is desirable, e.g. for drug dosing, consideration of organ donation or eligibility for clinical trials.
2. eGFR_{cys} *and* $\text{eGFR}_{\text{cr-cys}}$ in anybody with eGFR_{cr} $45\text{--}60 \text{ ml/min/1.73m}^2$ *or* $60\text{--}90 \text{ ml/min/1.73m}^2$ plus another CV risk factor to confirm diagnosis/staging of CKD. The lowest identified eGFR should be used for forward planning.

3. eGFR_{cys} should be used alongside traditional cardiovascular prediction tools to enhance risk prediction and primary prevention of CVD.
4. eGFR_{cr} for monitoring of change in kidney function, pending the outcome of cost-utility and cost-effectiveness trials

Conflict of interest statement

Text presented in this paper has not been published previously, in whole or in part. There are no new data presented in this paper. All results published previously have been referenced.

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Using **Cystatin C** alone or with creatinine provides more **accurate estimation** of **GFR**, **earlier** detection of **CKD** and risk of **cardiovascular disease**

eGFRcr-cys provides the most accurate estimation of GFR

Compared to gold-standard measured GFR

eGFRcr-cys
Greatest precision
Least bias

eGFR by CKD-EPI using creatinine alone (eGFRcr), cystatin C alone (eGFRcys) or creatinine + cystatin C (eGFRcr-cys). All eGFR measures in ml/min/1.73 m².

eGFRcys and eGFRcr-cys should confirm diagnosis of CKD

If eGFRcr 45–60 or eGFRcr 60–90 + CV risks

Measure eGFRcys and eGFRcr-cys

Use lowest eGFR to guide management

eGFRcys predicts cardiovascular disease risk earlier than eGFRcr

Compared with reference **eGFR 90**

Doubling of cardiovascular risk:

at **eGFRcys** 60–70 (early)^[5,7]

at **eGFRcr** 30–40 (later)^[5,7]