

# Glomerular filtration rate (GFR) and estimation of the GFR (eGFR) in adults

*The GFR is the best overall measure of renal function.*

**Jocelyn Naicker, BSc, MB ChB, MFGP (SA), FCPATH (SA), MMed (Chem)**

*Consultant Chemical Pathologist, National Health Laboratory Service (NHLS), Charlotte Maxeke Johannesburg Academic Hospital (CMJAH)*

## Laboratory

*Jocelyn Naicker is Senior Lecturer for the Department of Chemical Pathology in the Faculty of Health Sciences at the University of the Witwatersrand Medical School. After spending 16 years practising in various disciplines of clinical medicine including family practice, she specialised in chemical pathology in 2001 and has since worked at several laboratories within the Central region of the NHLS.*

Correspondence to: Jocelyn Naicker (jocelyn.naicker@nhls.ac.za)

## Glomerular filtration rate

Glomerular filtration is an essential function of the kidney and the glomerular filtration rate (GFR) is generally accepted as the best overall measure of the functioning renal mass in both health and disease.<sup>1</sup> Measurement of the GFR is based on the plasma clearance of a substance by glomerular filtration. In order for the clearance of a substance to be the same as the GFR the clearance marker should be in a stable concentration in the plasma, eliminated from the blood only by the kidneys, freely filtered by glomeruli, not secreted, synthesised or metabolised within the kidney and not reabsorbed from the filtrate. The GFR varies according to age, gender and body size. By convention the GFR is adjusted to a standard body surface area (BSA) of 1.73 m<sup>2</sup> for adults.

## Plasma clearance markers for measured GFR (mGFR)

### Exogenous markers

Plasma clearance markers may be endogenous or exogenous. The ideal exogenous marker is inulin, and it is the gold standard. The isotopic markers <sup>51</sup>chromium ethylene-diamine-tetra-acetic acid (<sup>51</sup>Cr-EDTA), <sup>99m</sup>technetium-labelled diethylene-triamine-pentacetate (<sup>99m</sup>Tc-DTPA) and <sup>125</sup>I-iothalamate, as well as non-radioisotopically labelled markers like iohexol, produce measures of GFR that correlate well with inulin clearance. Their use, however, is considered costly and impractical for routine clinical use.

### Endogenous markers

Endogenous plasma markers include serum creatinine (S-Cr) and cystatin C (S-Cys C).

## Serum creatinine

Creatinine is derived from muscle creatine and is liberated into the blood stream at a steady state. The level of creatinine in blood is therefore proportional to muscle mass and varies with gender, age and race. S-Cr levels are also affected by diet (raised 3 hours after eating cooked meat) and muscle wasting (decreased).<sup>1,2</sup>

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## Creatinine clearance

Creatinine clearance (CrCl) has been the most widely used measure of GFR and requires the complete timed collection of urine as well as a blood sample for S-Cr (taken during the urine collection period). The formula in the box below shows how it is calculated.

$$\text{CrCl} = \frac{\text{Urine creatinine concentration}}{\text{Plasma creatinine concentration}} \times \frac{\text{Urine volume in ml}}{\text{Time of urine collection in min}}$$

The measuring units of both the urine and plasma creatinine concentrations have to be adjusted to the same units (either mmol/l or  $\mu\text{mol/l}$ ) so that the CrCl is reported in plasma volume cleared of creatinine (ml) per unit time (min).

The problem with the use of CrCl as a measure of GFR is the fact that creatinine is secreted by proximal renal tubules and small bowel and that these proportions increase with impaired kidney function. CrCl therefore overestimates the GFR by 10 - 40%.<sup>1</sup> A further problem with the measurement of CrCl is poor patient compliance with regard to the collection of a complete urine sample. Frequently the sample volume for the stated time is incorrect and this adds error to the final result.

## Standardisation of creatinine assays

There were unacceptable differences related to S-Cr results between clinical laboratories. In order to reduce inter-laboratory variation and improve accuracy, diagnostic companies had to have their creatinine assays re-standardised so that they were traceable to an Isotope Dilution Mass Spectrometry (IDMS) Reference that became available in 2007. By the end of 2009 all major global diagnostic manufacturers had completed this re-calibration process.

## Serum cystatin C (S-Cys C)

S-Cys C, a low-molecular weight (13.3 kDa) protein that is a cysteine protease inhibitor, is produced at a constant rate by all nucleated cells.<sup>3</sup> It does not have the same relationship with muscle mass, age and gender as serum creatinine is almost completely filtered by

glomeruli and completely reabsorbed and degraded within renal proximal tubular cells.<sup>4</sup> S-Cys C therefore appeared to be a better marker of GFR than S-Cr. Further studies have shown that S-Cys C is upregulated by certain tumours, is raised in thyroid disorders and during corticosteroid therapy.<sup>4</sup>

The use of S-Cys C has been hampered by its relatively greater cost (than S-Cr) and by analytical issues related to standardisation. Reference material for standardisation has recently become available and will enable measurement of more comparable inter-laboratory S-Cys C levels.

### Clinical monitoring of impaired kidney function in chronic kidney disease (CKD)

In chronic disorders like hypertension and diabetes mellitus, progressive kidney damage can occur with loss of kidney function. A decline in GFR in these patients is often not reflected by the level of S-Cr. Only 40% of patients with a reduced GFR have normal S-Cr levels.<sup>5</sup>

The Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guideline for patients with CKD from the National Kidney Foundation (NKF) has provided a definition and classification of CKD that is used by nephrologists both locally and internationally (Table 1). CKD is defined as either kidney damage or GFR < 60 ml/min/1.73 m<sup>2</sup> existing for at least 3 months.<sup>1</sup>

Clinical uses of GFR measurement include assessment of the renal function, staging of CKD, timing of renal replacement therapy, use in calculating the correct dose adjustment of drugs (especially drugs excreted by

kidneys) administered to CKD patients and identification of patients in whom to avoid administration of contrast media (for imaging procedures).

### GFR prediction equations to estimate GFR

Estimation of GFR (eGFR) using mathematical equations has helped to overcome the existing practical problems encountered with the use of exogenous markers for mGFR and the collection of timed urine specimens for measurement of CrCl. Most of the equations available are based on S-Cr levels because it is routinely measured in laboratories. Standardisation of creatinine assays has improved the inter-laboratory comparisons. Some equations using S-Cys C are also available, used either alone or in combination with S-Cr. It remains to be seen whether the standardisation of S-Cys C improves the performance of eGFR prediction equations. The eGFR equations using S-Cr are only valid under steady state conditions.

### Cockcroft-Gault (CG) equation

In 1976 the original Cockcroft-Gault (CG) equation estimated the creatinine clearance (not mGFR using a gold standard method).<sup>6</sup> The study population only included white male patients and a factor was used to estimate the CrCl for females (it was assumed that female lean body mass was approx 15% lower).<sup>6</sup> The equation was derived using an unstandardised creatinine assay. It is not surprising to find that the CG equation, like the CrCl it estimates, also overestimates the GFR (by approximately 23%).<sup>7</sup>

The CG equation has been used over many years in pharmacokinetic studies to determine the dose adjustment required

with various levels of kidney function. As the samples from the original CG study were no longer available for re-analysis using IDMS-standardised creatinine assays there is a possibility that dosing guidelines may be incorrect when using standardised creatinine test results. The US food and Drug Administration (FDA) currently recommends that new pharmacokinetic studies should base their dosing guidelines on the newer prediction formulae for eGFR.

### Modification of diet in renal disease (MDRD) study equation

The MDRD study equation was developed in the USA using data from patients with CKD and there have been several versions of the equation. In 1999 the 4 variable (4-v) equation was devised using unstandardised S-Cr measurements.<sup>7</sup> This was then re-expressed in 2005 using an IDMS standardised creatinine assay (Fig. 1).<sup>8</sup>

The MDRD study demonstrated that the eGFR correlated well with mGFR determined by urinary clearance of <sup>125</sup>I-iothalamate in the CKD patients in the lower eGFR <60 ml/min/1.73 m<sup>2</sup> range. However, in the upper eGFR >60 ml/min/1.73 m<sup>2</sup> range there was significant underestimation of mGFR (increased false positive diagnoses of CKD). This is the reason for laboratories not reporting actual MDRD eGFR values in the >60 ml/min/1.73 m<sup>2</sup> range.

In 2002 the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation (NKF) recommended the use of the MDRD prediction equation for estimation of GFR as part of management of patients with CKD.<sup>1</sup> Several Internet web sites have eGFR calculators.

**Table 1. NKF-KDOQI stages of chronic kidney disease. NKF-KDOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification<sup>1</sup>**

| Stage | Description                                | eGFR (ml/min/1.73 m <sup>2</sup> ) |
|-------|--|------------------------------------|
| 1     | Kidney damage with normal or increased GFR | >90                                |
| 2     | Kidney damage with mildly decreased GFR    | 60 - 89                            |
| 3     | Moderately decreased GFR                   | 30 - 59                            |
| 4     | Severely decreased GFR                     | 15 - 29                            |
| 5     | Kidney failure                             | <15                                |

Limitations to the use of the MDRD-derived eGFR include age <18 years and >70 years, pregnancy, oedematous conditions, extremes of body size, mass and nutritional status (vegetarianism, high-protein diet, creatine or amino acid supplementation), conditions affecting skeletal muscle (muscle wasting, cachexia, paraplegics, amputees), patients on dialysis or patients with acute changes in kidney function (acute kidney injury).<sup>1</sup>

The CrCl does not offer greater value than the MDRD eGFR and may be useful in patients in whom the use of MDRD eGFR is contraindicated.

An MDRD eGFR study on black South African CKD patients at Chris Hani Baragwanath Hospital in Soweto, Johannesburg, used a standardised creatinine assay and showed an overall eGFR median positive bias of 27% when applying the prescribed African-American ethnicity factor (4th variable) of the MDRD equation.<sup>9</sup> When the factor was not applied, the overall median positive bias decreased to 5%.<sup>9</sup> For this reason, MDRD eGFR calculated by the National Health Laboratory Service (NHLS) laboratories uses the same MDRD formula for both black and white patients (i.e. the ethnicity factor is not used).

In a retrospective study of stable CKD renal clinic patients at the King Edward VIII Hospital in KwaZulu-Natal, MDRD eGFR was calculated using unstandardised creatinine assays. In their black African patients in the eGFR <60 ml/min/1.73 m<sup>2</sup> group there was an overestimation of mGFR by 17.1% which decreased to 5.3% when the ethnicity factor was removed.<sup>10</sup> In the eGFR >60 ml/min/1.73 m<sup>2</sup> group the overestimation of mGFR was 38% which decreased to 19.3% without the ethnicity factor.

This suggests that in Africa the MDRD 4-v rev can be used to estimate GFR in CKD patients with GFR <60 ml/min/1.73 m<sup>2</sup> provided the African-American ethnicity factor is not used.

### Chronic Kidney Disease Epidemiology Collaboration Study (CKD-EPI)

New prediction formulae were sought because of the inability of the MDRD formula to detect early deterioration of kidney function in patients with GFR >60 ml/min/1.73 m<sup>2</sup>.

The CKD-EPI study group was established by the National Institute of Diabetes & Digestive & Kidney diseases (NIDDK). Their study included patients with and without kidney disease and a standardised S-Cr-based equation was developed and validated.<sup>11</sup> The researchers found that the equation yielded eGFR results that were as accurate as MDRD-derived eGFR results in patients in the eGFR <60 ml/min/1.73m<sup>2</sup> range and more accurate results at eGFR >60 ml/min/1.73m<sup>2</sup> range.

Limitations of the CKD-EPI study were that the database was not representative of the demographics of the general population and lacked sufficient numbers of subjects from ethnic minorities.

When the CKD-EPI equation was applied to the South African CHB CKD dataset, all levels of mGFR were found to be overestimated (to a lesser degree at ranges >60 ml/min/1.73m<sup>2</sup>). This was contrary to the findings in USA and European black subjects. The CKD-EPI equation produced less bias when the black ethnic coefficient was not used.

Similar findings of overestimation of GFR were obtained when using both MDRD and

CKD-EPI prediction equations in an eGFR study in a rural community in Ghana.<sup>12</sup> Although a standardised IDMS standardised creatinine assay was used, researchers were only able to compare their eGFR values with creatinine clearance due to the rural setting of the study. eGFR performance (using both equations) here again showed less positive bias when the ethnicity factor was not used.

There is little convincing evidence that the CKD-EPI equation in its present form can be used as an improved method of estimating mGFR in African populations with GFR >60 ml/min/1.73m<sup>2</sup> using existing coefficients for black subjects derived outside Africa. This is probably related to leaner body composition (relative to African-Americans) and possibly factors relating to extrarenal creatinine excretion. Additional local trials need to be conducted using present-day IDMS-standardised creatinine assays within the various ethnic groups of the South African population.

References available at [www.cmej.org.za](http://www.cmej.org.za)

### IN A NUTSHELL

- The GFR is the best overall measure of renal function.
- Clearance markers for the measurement of GFR (mGFR) can be exogenous or endogenous.
- Creatinine clearance (CrCl) overestimates the mGFR.
- The Cockcroft-Gault equation estimates the CrCl and therefore overestimates the mGFR.
- The Cockcroft-Gault equation was derived using unstandardised creatinine values.
- Chronic kidney disease (CKD) is defined as impaired kidney function with a GFR <60 ml/min/1.73m<sup>2</sup>.
- The MDRD equation is recommended for estimation of the GFR (eGFR) in patients with CKD.
- The African-American ethnicity factor used in the MDRD eGFR causes an overestimation of the GFR in South African black patients and is therefore not used in NHLS laboratories.
- The MDRD eGFR is unreliable in patients with GFR >60 ml/min/1.73m<sup>2</sup>.
- The CKD-EPI equation that estimates GFR was developed for use in patients with GFR >60 ml/min/1.73m<sup>2</sup>.

$$\text{eGFR (ml/min/1.73m}^2\text{)} = 175 \times [\text{Standardised S-Cr } (\mu\text{mol/l)} / 88.4]^{-1.154} \\ \times [\text{age (yr)}]^{-0.203} \\ \times [0.742 \text{ if patient is female}] \\ \times [1.212 \text{ if patient is African-American}]$$

Fig. 1. MDRD study equation 4-v revised (re-expressed for use with IDMS standardised creatinine) for estimation of glomerular filtration rate (eGFR) in patients with chronic kidney disease.<sup>8</sup> S-Cr serum creatinine; \* multiplied by.