BHS British Hypertension Society

Fact File *03/2006*

Estimated GFR

Introduction

The rate of filtration across the glomerular membrane, the GFR, is the initiating step in many of the homeostatic functions of the kidney and it is widely accepted as the best overall measure of kidney function.

Classification of Chronic Kidney Disease (CKD)

The internationally agreed classification of CKD is based on the GFR.

Classification of Chronic Kidney Disease, Population Prevalence and Recommended Frequency of Testing

Stage	Description	GFR (mL/min/1.73m^2)	Population prevalence (%)	Recommended Testing Frequency
1*	Kidney damage with normal or increased GFR	≥90	3.3	Annually
2*	Kidney damage and mildly decreased GFR	60-89	3.0	Annually
3	Moderately decreased GFR	30-59	4.3	6 Monthly
4	Severely reduced GFR	15-29	0.2	3 Monthly
5	Kidney failure (established renal failure)	<15	0.2	3 Monthly

* The diagnosis of stage 1 and 2 CKD requires the presence of kidney damage for ≥ 3months manifest by pathological abnormalities of the kidney or abnormalities in the composition of urine, such as haematuria or proteinuria, or abnormalities in imaging tests either with (stage 2), or without (stage 1), decreased GFR. Based on the KDIGO classification, 3rd National Health and Nutrition Examination Survey 2003, and the UK CKD Guidelines.

In the United Kingdom CKD affects about 10% of the population and is often asymptomatic until renal function is severely reduced. Mild CKD is also important as it represents a significant risk

factor for vascular disease. The cardiac and vascular changes associated with CKD begin early in the course of disease and large population based studies have demonstrated an exponential increase in vascular risk as the GFR falls below 60 mL/min/1.73 m^2. In stage 3 chronic kidney disease the 5 year mortality is 20% and the risk of progression to end stage renal failure is 1%.

Estimating the GFR Using Creatinine Based Formulae

The GFR is a measure of kidney efficiency and is defined as "the volume of plasma from which a given substance is completely cleared by glomerular filtration per unit time". For an inert substance that is freely filtered at the glomerulus and neither secreted or re-absorbed a simple formula defines its clearance.

GFR = Urinary Concentration x Urinary Volume ÷ plasma concentration

A variety of exogenous (radio isotopic and non radio isotopic) substances can be used to get a accurate assessment of GFR. Inulin infusion is considered the Gold Standard but the use of infused markers is both too labour intensive and costly for routine clinical use. Endogenous markers such as creatinine obviate the need for infusion but still require timed urine collections and since serum creatinine is secreted by the tubule it does not behave in an inert manor. In adults the intra-individual day to day co-efficient of variation for repeated measures of creatinine clearance exceeds 25%. Furthermore age, gender, ethnicity, muscle bulk and obesity affect the relationship between serum creatinine, muscle mass/body weight and GFR. Serum creatinine may remain within the reference range despite marked renal impairment in patients with low muscle mass. Similarly those with large muscle mass can have a high serum creatinine in the presence of normal renal function.

There are many formulae for estimating GFR. The two best known are the Cockcroft and Gault and the formulae derived from the Modification of Diet in Renal Disease (MDRD) study. The Cockcroft and Gault estimate requires a weight, information is not routinely available in the biochemistry laboratory. There are several MDRD equations. In the UK we have adopted the isotope dilution mass spectrometry (ID-MS) traceable version of the Modification of Diet in Renal Disease (MDRD) equation:

GFR (mL/min/1.73 $m^{2)}$ = 175 x [serum creatinine (umol/L) x 0.011312]$^{-1.154}$x [age}$^{-0.203}$ x [1.212 if black] x [0.742 if female]

Precision and accuracy of eGFR decreases as GFR increases. When eGFR exceeds 89 mL/min/1.73 m^2 it should be reported as greater than 90 mL/min/1.73 m^2 rather than as an exact number.

Inter laboratory variation in bias of serum creatinine estimation causes significant differences in estimates of GFR. The UK National External Quality Assessment Scheme (UK NEQAS) will

provide recommended correction factors for the MDRD equation to adjust for method related differences compared to the ID-MS reference method.

THIS WILL MEAN THAT A "HOME" CALCULATED EGFR IN THE CLINIC OR IN THE GP SURGERY BASED ON THE REPORTED SERUM CREATININE WILL DIFFER SLIGHTLY FROM THE EGFR REPORTED BY THE LABORATORY WHICH WILL BE TRACEABLE TO THE GLOBAL ID-MS STANDARD.

Who needs an eGFR?

The NSF and the UK CKD Guidelines have made specific recommendations concerning which groups should be screened for CKD and how often. In particular, people with diabetes, vascular disease, heart failure, hypertension, urinary tract obstruction, neurogenic bladder or surgical urinary diversion, those taking diuretics, angiotensin converting enzyme inhibitors or angiotensin II receptor blockers and people with a family history or genetic risk of kidney disease should undergo regular surveillance.

There is a decline in the eGFR as people age, which is predominantly related to disease. The association of eGFR with mortality is weaker in the elderly than in younger age groups.

Limitations and Cautions

The MDRD formula should not be used in children. When required eGFR can be calculated using the Schwartz formula but eGFR will not be routinely reported in those under the age of 18 years. eGFR is also not of value in acute renal failure and caution in interpretation should be used in pregnancy, oedematous states, muscle wasting diseases, amputees and the malnourished. Where precise knowledge of GFR is important e.g. dosing in cancer chemotherapy where there is a narrow therapeutic margin or assessment of a potential living related kidney donor, formula based estimates of GFR should be avoided.

What do we know: Further Questions and Areas for Research

The adoption or formula based estimates of GFR has focused attention on the limitations of creatinine as a filtration marker, on the inaccuracies in the currently used assays for creatinine and on the variation in creatinine production rates in different disease states and in different ethnic groups.

The MDRD formula was validated in patients with known CKD, but performs less well in those with near normal renal function. Even if the formula were perfect the reciprocal relationship between GFR and serum creatinine leads to inaccuracies in measurement of serum creatinine having a proportionally larger effect on the estimated GFR when serum creatinine concentration is at the lower end of the reference range than when it is abnormal. This reciprocal relationship holds for any endogenous filtration marker such as Cystatin C which offers some advantages over creatinine but may not be cost effective. This limits the value of estimated GFR in for instance those with hyperfiltration due to diabetes.

By convention GFR is normalised to body surface area. Estimated GFR reporting using the MDRD formula, which avoids body weight, reinforces this practice. However are complications of CKD better correlated or predicted by normalised or actual GFR? Which is better for drug dosing? Which BSA formula should be used? What is the influence of race, body shape and obesity? Validation is urgently required in south Asians and Chinese who have high rates of CKD.

In patients with CKD rate of change of renal function can be accurately assessed using repeated eGFR. However intra individual variation in serum creatinine over time can be as high as 10%. In clinical practice the impact of illness, particularly sepsis and/or drugs (e.g. NSAIDS) on renal function and the interference with the creatinine assay by certain drugs (e.g. antibiotics) further complicates interpretation.

eGFR isn't Everything

Despite its many limitations eGFR does equate to percentage kidney function and produces a platform to demystify CKD. Early identification of CKD facilitates the optimisation of cardiovascular risk strategies in this high risk population. However eGFR is only part of the clinical and laboratory assessment of kidney disease. Proteinuria and blood pressure control are key determinants of both vascular and renal outcomes.

References and Research

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Renal Association - eGFR

http://www.renal.org/eGFR/index.html

National Kidney Federation

http://www.kidney.org.uk/books/help-igotKF.html