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Review article

MEASUREMENT OF GLOMERULAR FILTRATION RATE BY EXOGENOUS AND ENDOGENOUS FILTRATION MARKERS

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ABSTRACT: The National Kidney Foundation (NKF), through its Kidney Disease Outcomes Quality Initiative (K/DOQI), and other National institutions proposed glomerular filtration rate (GFR) to describe, classify, screen and examine chronic kidney disease (CKD). GFR is the standard measure of renal function but cannot be practically measured for clinical and research purposes, so serum creatinine (Scr) is used to calculate estimated GFR (eGFR) which is affected by age, weight, muscle mass, race, various medications and extra-glomerular elimination. To overcome this Cystatin C (CysC) is new and reliable marker for renal function due to its low molecular weight it is freely filtered through glomerulus, completely reabsorbed and catabolized, but not secreted, by tubular cells. Various equations used for GFR estimation such as the Modification of Diet in Renal Disease (MDRD) Study equation, Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Cockcroft–Gault (CG) equation based on Scr , Grubb and Hoek equation based on CysC and Stevens equation based on both SCr and CysC are used. CKD–EPI is preferred for identifying patients with CKD and for staging the disease. The risk of underestimation of kidney function with MDRD is highest when the GFR is 30 mL/minute/1.73 m^2 so GFR is calculated by CKD–EPI equation for these persons. CKD–EPI is recommended for diagnosis and staging when the addition of appropriate prophylactic drugs or avoidance of certain nephrotoxic drugs should occur.

The aim of this review is to evaluate from recent literature available different exogenous and endogenous markers used for the determination of GFR and which marker found suitable for the determination of GFR according to literature available on PubMed and determine their reliability in the detection and monitoring of CKD and its stages.

Key words: Glomerular filtration rate, chronic kidney disease, Creatinine, Cystatin C, Measurement of GFR

Abbreviations - Glomerular filtration rate (GFR), chronic kidney disease (CKD), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), Cockcroft–Gault (CG), Serum creatinine (Scr), serum cystatin C (CysC), National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI), Cardiovascular disease (CVD), Food and drug administration (FDA), Diethylene triamine pentaacetic acid (DTPA), Ethylene diamine tetra acetic acid (EDTA)

INTRODUCTION

The GFR is the best indicator of renal function (Grubb *et al*., 2005). By definition, GFR is the rate at which substances are filtered from the blood, of the glomeruli into Bowman's capsules of the nephrons. Early stages of renal function impairment are clinically silent and are diagnosed only by measuring GFR by external filtration markers (measured GFR, mGFR) (Coresh *et al*., 2005) When GFR <60, functional impairments is detected by internal filtration markers and calculated eGFR (Stevens *et al*., 2008). The complications of CKD increase with decreasing GFR and may progress from gradual reduction in renal function to end-stage renal disease (ESRD). Low GFR is risk factor for cardiovascular disease (CVD) mortality (Matsushita *et al*., 2010; Levey *et al*., 2011). Appropriate dosing of drugs excreted by the kidney is usually based on GFR so GFR is the best marker for assessing the overall function of the kidney (Toto *et al*., 1995)

Measurement of Glomerular Filteration Rate

GFR cannot be measured directly in humans. It has to be determined indirectly by measuring the clearance of an ideal filtration marker. Such marker has to be freely filtered at the level of the glomerulus so the molecular weight of such a marker has to be low and the compound must not bind to plasma proteins. The ideal marker must be able to achieve a stable plasma concentration, should not be reabsorbed, secreted or metabolized by the kidney, should be physiologically inert and should not alter renal function. Several methods used to measure GFR involve the measurement of ability of the kidney to clear an exogenous or endogenous marker.

Renal clearance of a substance is defined as the volume of plasma from which the substance is completely cleared by the kidneys per unit of time. Depicted as GFR = (US ×V) /PS, where GFR = the flow rate in milliliters per minute of plasma through the glomerular membranes. *US* = Urinary concentration of the substance, *V* = Volumetric flow rate of urine in milliliters per minute, *PS* = Plasma concentration of the substance

Renal clearance techniques involve measuring blood and urine concentrations of either endogenous or exogenous substances. GFR is best determined under standardized conditions, which include discontinuation of medication, prior fasting, sufficient water loading to maintain a urine flow rate >1 mL/min, and complete bladder emptying because GFR deviate from normal values for age from various influences including diet, postural changes, alterations in renal nervous tone, hormones, prostaglandins, atrial natriuretic peptide, drugs, pregnancy, and renal diseases. Determination of mGFR and eGFR is useful to measure renal function in patients with high prevalence of GFR <60, staging of CKD into stages I–V and the usefulness of function-preserving treatment measures.

EXOGENOUS FILTRATION MARKERS (m GFR) -

Radio isotopic Markers-

These markers include ^{51}Cr-ethylenediaminetetraacetic acid (EDTA) (Askergren *et al*., 1981; Blake *et al*., 1997; Brochner-Mortensen *et al*., 1969; Chantler *et al*., 1972). ^{99}mTc, diethylenetriaminepentaacetic acid (DTPA), and ^{125}Iiothalamate. ^{51}Cr-EDTA is best marker as compare to ^{99}mTc-DTPA and ^{125}I-iothalamate because its clearance is closest to inulin clearance (Brochner-Mortensen *et al*., 1969 ; Blaufox *et al*., 1996). When GFR is measured using urinary or plasma clearance methods, it is essential that renal tubular secretion or reabsorption does not contribute to elimination of the compound, plasma protein binding of the radioisotopic markers is negligible, and no extra-renal elimination of the marker occurs. In patients with low GFR (<30 mL/min) and in patients with ascites or edema, best preferred method is renal clearance method (Blaufox *et al*.,1996).

Non radiosotopic Markers

Nonradioactive compounds inulin and iohexol (Effersoe *et al*., 1990) is used to measure GFR. Inulin clearance used as gold standard measure of GFR (Van Rossum *et al*., 2003) because it is freely filtered by the glomerulus, not reabsorbed, secreted, or metabolized by the renal tubule, not bound to plasma proteins, nontoxic, and physiologically inert, but it requires continuous intravenous infusion; multiple timed urine collections and its measurement is expensive so it is only used in research studies when very accurate estimation of renal function is required.

In Iohexol Clearance non radio labelled iodinated contrast agent, iohexol is used and measured by HPLC with reversed-phase separation and UV detection, following prior deproteinization with perchloric acid (Krutzen *et al*., 1984). This method is again very expensive and time consuming (Brown *et al*., 1991; Gaspari *et al*., 1998; Arvidsson *et al*., 1990 ; Krutzen *et al*., 1984). So a new technique is proposed based on X-ray fluorescence, but this method is less sensitive than HPLC and requires administration of significantly larger doses of iohexol, leading to higher risk of nephrotoxicity and adverse reactions (Brown *et al*., 1991; Gaspari *et al*., 1998; Rocco *et al*., 1996).

Endogenous filtration markers

Creatinine and low molecular weight proteins cystatin C have been used as endogenous markers of GFR. Most widely used endogenous markers of GFR is Creatinine expressed as its serum concentration or as renal clearance (Rehberg *et al*., 1926) based on the renal clearance of exogenously administered creatinine. In 1937 the use of endogenous creatinine clearance was developed. (Popper *et al*., 1937)

Creatinine

GFR is determined by measuring Scr which is freely filtered at the glomerulus and its concentration is inversely proportional to the GFR, so that each halving of the GFR results in a doubling of the Scr concentration (Kassirer *et al*., 1971). Creatinine having molecular mass 113 Da, is a near perfect filteration marker and this is measured by standardized method based on modified jaffe's reaction which is able to separate Creatinine from non-creatinine chromogens (e.g. acetic acid, acetone, pyruvate, glucose, ascorbic acid, bilirubin) (Tomlinson *et al*., 1969 ; Horber *et al*., 1985). The ratio of creatinine clearance to inulin clearance ranges from 1.1 to 1.4 (Smith, 1951; Shannon, 1935; Dodge *et al*., 1928; Shemesh *et al*., 1985; Levey *et al*., 1988). In severe renal insufficiency patients the ratio may reach 2.5, indicates as much as 60% of urinary creatinine is derived from tubular secretion. GFR will deviate from normal value which is 130 mL/mm/1.73 m^2 of body surface area in men and 120 mL/min/1.73 m^2 in women under the age of 30 years and declines with age there after (Wesson, 1969; Matsushita *et al.,* 2010).

Creatinine Clearance.

Creatinine is endogenously produced and released into body fluids at a constant rate, its clearance can be measured and is an indicator of GFR (Perrone *et al.,* 1992). Creatinine clearance in the past has been seen as more sensitive for detection of renal dysfunction than serum creatinine measurement but it requires timed urine collection, which is laborious and inconvient (Goldberg *et al.,* 1987; Payne, 1986; Ricos *et al*., 1994) Also Creatinine clearance provide only crude index of GFR.

CrCl (mL/min) = [Urinary creatinine (mg/dL) x urine volume (mL/ min)] / [S_{Cr} (mg/dL)]

Cystatin C and other low molecular weight protein-

Several low molecular weight proteins of <30 KDa like α2-microglobulin, RBP (Retinol binding protein), α1-microglobulin, β-trace protein, (Priem *et al*., 1999) and CysC are freely filtered from circulation by renal filteration, then reabsorbed in the proximal tubule or excreted into the urine so these are used as a marker of GFR. But their serum concentrations are influenced by other, non renal factors such as inflammation (α2-microglobulin) and liver disease (RBP, α1-microglobulin) (Ayatse *et al*., 1991).

Several groups explained CysC as more sensitive and specific means of monitoring changes in GFR than SCr. (Finney *et al*., 1997; Grubb, 1992; Kyhse-Andersen *et al*., 1994 ; Newman *et al*., 1995) CysC is a low molecular weight (12.8 kD) nonglycocylated cationic basic protein consisting of 120 amino acids synthesized by all nucleated cells belongs to the cystatin superfamily of endogenous cysteine proteinase inhibitors (Pucci *et al*., 2007; Shlipak *et al*., 2005; Risch *et al*., 2001; Bokenkamp *et al*., 2002) CysC have small size and high isoelectric point (pI 9.2), which enable this to freely filtered than other proteins at the glomerulus (Grubb, 1992). Serum concentration of CysC is unaffected by race, inflammatory conditions, gender, body composition, and age (after 12 months) (Finney *et al*., 2000; Bokenkamp *et al*., 1998) clearance from the circulation occurs only by glomerular filtration (Grubb, 1992; Jacobsson *et al*., 1995; Tenstad *et al*., 1996) .

Cys C can be measured by immunodiffusion or rocket electro immunoassay, but these are insensitive methods. Most practical methods using an automated particle-enhanced turbidimetric immunoassay (PETIA) or nephelometric immunoassay (PENIA) to measure the formation of antigen-antibody complexes and its reciprocal is highly correlated with GFR. Several commercial CysC methods are available including automated applications. CysC was proposed as a marker of GFR potentially superior to Scr (Dharnidharka *et al*., 2002). A meta-analysis of 46 cross-sectional studies including adults and children shows the correlation of GFR with CysC is superior than creatitine based equation in the estimation of GFR (Brzin *et al*., 1984). CysC was found to be the best predictor of kidney failure and death from cardiovascular disease in a longitudinal cohort study of 4637 older people (Simonsen *et al*., 1985).

Newman and colleagues found that, in a group of patients with a range of GFRs, the CysC concentration increased earlier than creatinine as GFR decreased to about 80 mL/min/1.73 m^2 compared with about 40 mL/min/1.73 m^2 for serum creatinine (Newman *et al*., 1995). CysC was found to be useful to detect mild to moderate impairment of kidney function (Bostom *et al*., 2000, Coll *et al*., 2000).

Advantages and limitations of Cystatin C

Serum concentrations of CysC were found to be unaffected by muscle mass, diet, or gender (Kyhse-Andersen *et al*., 1994). Though large doses of glucocorticoids (500 mg methylprednisolone) increased serum CysC concentration, (Grubb, 1992) low or medium doses of glucocorticoids (20 to 60 mg/day prednisone) have no effect on its concentration (Bokenkamp *et al.,* 2002). Several publications suggest influence of thyroid hormone (Den Hollander *et al*., 2003; Fricker *et al*., 2003; Jayagopal *et al*., 2003). CysC levels are lower in the hypothyroid and higher in the hyperthyroid state as compared with the euthyroid state (Fricker *et al*., 2003).

Creatinine-based eGFR

Equations for estimating GFR

Various equations used for GFR estimation include the Modification of Diet in Renal Disease (MDRD) (Cockcroft *et al*., 1976), the Cockcroft–Gault (CG) (Levey *et al*., 1999), and the Chronic Kidney Disease Epidemiology Collaboration (CKD–EPI) (Levey *et al*., 2009) for adults. In children Schwartz formula was used (Schwartz *et al*., 1976).

The CG equation was the first of these three equations developed, which was determined by studying hospitalized adult male patients (Dharnidharka *et al*.,, 2002).The CG equation underestimates GFR in the aged group and is less accurate in patients which have normal kidney function.

The MDRD equation was the second equation developed in 1999 in chronic renal insufficiency study in which 1,628 men and women were enrolled. This equation was adjusted for 4 variables - body-surface area, race, gender, and age. GFR is expressed as mL/min/1.73m^2 and race is categorized as either black or not black.

In the Practice Guidelines for CKD, published in 2002 by the Kidney Disease Outcomes Quality Initiative of the National Kidney Foundation (K/DOQI) and the more recent Kidney Disease: Improving Global Outcomes (KDIGO) guidelines simplified MDRD equation has been included as the primary GFR marker and staging of CKD (Levey *et al*., 2005; *Levey et al., 2011)*. Most studies confirmed that the MDRD equation provides a more accurate assessment of GFR than the CG equation (Froissart *et al*., 2005; Poggio *et al*., 2005) including among diabetic patients with moderate to severe CKD (Rigalleau *et al*., 2005). Limitations of MDRD equation is that at higher values of GFR, it shows significant negative bias (Poggio *et al*., 2005 ; Rule *et al*., 2004) and poor precision (Poggio *et al*., 2005). New CKD-EPI equation was developed in 2009 from data of 8254 people with and without CKD in 10 studies and authenticated in 3896 people in 16 separate populations (Levey *et al*., 2009). In younger people, whites and women the CKD-EPI equation gives higher values of eGFR compared with the MDRD equation, at this range the CKD-EPI equation was more accurate than the MDRD equation (Rule *et al*., 2004; Levey *et al*., 2009).

The CKD–EPI equation is standardize for race, Body Surface Area, age and sex and is expressed as mL/min/1.73 m^2. In 2002 the National Kidney Foundation's KDOQI classified CKD on the basis of eGFR. According to this CKD occurs when eGFR<60 mL/min/1.73m^2 for ≥3 months. CKD stages are classified into Stages I–V according to the eGFR as follows-Stage 1 GFR >90 ml/min/1.73 m^2, Stage 2 GFR 60–89 ml/min/1.73m^2, Stage 3 GFR 30–59 ml/min/1.73 m^2, Stage 4 GFR 15–29 ml/min/1.73m^2 and Stage 5 GFR <15 ml/ min/1.73 m^2.

Table -1 Classification of stages of chronic kidney disease according to K/DOQI guidelines.

Stages of kidney disease	GFR(mL/min/1.73 m^2)	Description	Related abnormalities
Normal	> 90	Healthy kidney	
Stage 1	> 90	Normal kidney function	Albuminuria, proteinuria, hematuria
Stage 2	89-60	Mildly reduced kidney function	Albuminuria, proteinuria, hematuria
Stage 3 A 3 B	59-45 44-30	Moderately reduced kidney function	Proteinuria, hematuria, anemia, hypocalcemia,hyperphosphatemia
Stage 4	29-15	Severely reduced kidney function	Proteinuria, hematuria, anemia, acidosis,hypocalcemia, hyperphosphatemia
Stage 5	<15 or dialysis	Very severe or end stage kidney failure	Uremia, anaemia, malnutrition, hyperparathyroidism, high B.P., swelling in hands/legs eyes/lower back, shortness of breath

Table-2 Creatinine- and Cystatin C-based equations for calculation of eGFR

Children	
	Creatinine-based
Pediatric Schwartz equation (Schwartz *et al*.,1976)	GFR (ml/min/1.73 m^2) = (0.41× height, cm)/ (serum creatinine, mg/dl).
Counahan-Barratt equation (Counahan *et al*., 1976)	eGFR (mL /min) = 0.43 × height (cm) × $(S_{Cr}$ mg/dL$])^{-1}$
Equation according to Grubb *et al*. (Grubb *et al*., 2005)	Cystatin C-based eGFR (mL /min/1.73 m^2) = 84.69 × $(S_{cystatin\ C}$ [mg / L$])^{-1.68}$ × 1.384 (in children <14 years)
Adults	
Cockcroft-Gault equation (Levey *et al*., 1999)	Creatinine-based C_{Cr} (mL / min) = (140 – age [years]) × $(S_{Cr}$ [mg / dL$])^{-1}$ × (BW [kg] × $[72]^{-1}$) Correction factor: for women × 0.85
MDRD equation (Stevens *et al.,* 2008)	Creatinine-based eGFR (mL / min/ 1.73 m^2) = 175 × $(S_{Cr}$ standardized [mg / dL$])^{-1.154}$ × (age [years]$)^{-0.203}$ Correction factor: for women × 0.742 for blacks × 1.18
eGFR_CKDEPI (Levey *et al.*,2009)	Serum Creatinine [S_{cr}] in mg/dl based **Female** If Serum Creatinine ≤0.7mg/dl GFR =166 × $(S_{cr}/0.7)^{0.329}$ × $(0.993)^{Age}$ If Serum Creatinine ≥0.7mg/dl GFR =166 × $(S_{cr}/0.7)^{1.209}$ × $(0.993)^{Age}$ **Male** If Serum Creatinine ≤0.9mg/dl GFR =163 × $(S_{cr}/0.9)^{0.411}$ × $(0.993)^{Age}$ If Serum Creatinine ≥0.9mg/dl GFR =163 × $(S_{cr}/0.9)^{1.209}$ × $(0.993)^{Age}$
Equation according to Hoek *et al*., (2003)	Cystatin C-based eGFR (mL/min/1.73 m^2) = 80.35 × $(S_{cystatin\ C}$ [mg / L] – 4$)^{-1.68}$
Stevens *et al* .,(2008)	GFR = 177.6 x $SCr^{-0.65}$ x $CysC^{-0.57}$ x $age^{-0.20}$ x 0.82 (if female) x 1.11 (if black)

Estimating GFR for medication adjustment

NKF and the American College of Cardiology (ACC)/American Heart Association (AHA) (Braunwald *et al*., 2002) approved CG equation for dose-adjusting medications based on kidney function. NKF recommends that MDRD unadjusted for BSA (not multiplying MDRD by the patient's BSA) is a method for adjusting medication doses based on kidney function. In 1998 FDA Guidance for Industry document suggest CG for drug labelling recommendations. A study of 5,000 subjects found that MDRD adjusted for BSA correctly identified dose reductions 88% of the times, and the CG equation accurately calculated the renal dose adjustments 85% and 82% of the times, using actual and ideal body weights, respectively (Stevens *et al*., 2009).

Benefits and limitations of the MDRD equation

Advantages of the MDRD equation when compared with nuclear medicine techniques, which are considered as the gold standard for kidney function measurement, creatinine or urea clearance is that the formula was more accurate and this equation does not require 24-hour urine collection, which is inconvenient for patients yielding false positives for CKD. Limitations of this equation is that it cannot evaluated in persons <18 years and >75 years of age, pregnant women, extremes in body size and races other than Caucasian and African American. MDRD equation was not suitable in normal renal function type I diabetes, elderly, and kidney transplant recipients (Norden *et al*., 1987; Waz *et al*., 1993 ; Stoves *et al*., 2002).

Table-3 Standard Markers of Glomerular Filtration Rate

Standard	Markers	Advantages	Disadvantages
Gold standard	Inulin continuous-infusion urinary clearance method	Gold standard	Exogenous, time-consuming (Estelberger *et al*., 1995). requires timed urine collection Poor specificity of analysis
Silver standard	Inulin single-bolus plasma clearance method		Exogenous, Time-consuming (Estelberger *et al*., 1995). Poor specificity of analysis
	51Cr-EDTA (Rehling *et al*., 1984) 99mTc-TPA (Effersoe *et al*., 1990), 125 I-iothalamate	Radioisotopic	Exogenous, Radioisotopic. Time-consuming
	Iohexol	Nonradioisotopic	Exogenous
Bronze standard	Creatinine	Endogenous, Inexpensive Can be used to estimate GFR from equations (e.g., MDRD,CKD-EPI)	Poor sensitivity and specificity
	Cystatin C	Not secreted and reabsorbed and more sensitive and specific than creatinine	Influence of thyroid function (Den Hollander *et al*., 2003; Fricker *et al*., 2003 ; Jayagopal *et al*., 2003)
Other markers	Creatinine clearance and Urea	Endogenous and Inexpensive	Requires timed urine collection Inaccurate, Poor sensitivity and specificity
	Retinol binding protein (RBP) and α1-Microglobulin	Endogenous Not secreted/reabsorbed	Non renal influences on production rate

Cystatin C-based eGFR

Several groups have recently developed equations to calculate GFR from serum CysC. In comparison with the MDRD equation, which was calculated from a large population in a multicenter study, CysC based equations were created and validated in smaller samples using different gold standard measurements for GFR. CysC based equation for children according to Grubb (Grubb *et al*., 2005) has proved more reliable than the Counahan-Barratt equation (Counahan *et al*., 1976) and for adults Hoek equation (Hoek *et al*., 2003) is more sensitive than the MDRD equation. In older age groups the physiological decrease in GFR from year to year is listed more sensitively with CysC based eGFR than GFR estimated by the MDRD equation (Shlipak *et al*., 2009), and GFR >3 is associated with a higher successive risk of mortality (Rifkin *et al*., 2008).

Recently, (Stevens *et al*., 2008) developed an equation to estimate eGFR which include both SCr and CysC. Age, gender and race better than earlier equation based on SCr and CysC regarding to bias, precision and accuracy (Rigalleau *et al*., 2007; Ma *et al*., 2007, Tidman *et al*., 2007)

Advantages of Cystatin C based eGFR

CysC based eGFR sensitive for acute as well as chronic kidney disease and this eGFR estimation is independent of age, sex, race, lean muscle mass and diet. In patients having potentially nephrotoxic medications such as contrast media cancer therapeutics or antibiotics in cardiovascular disease patient's early detection of kidney damage is possible which improves patient's outcome in renal disease.

CONCLUSIONS

The goal of GFR determination is to diagnose chronic kidney disease in early stages to enable clinicians to slow its progress. GFR is determined by various exogenous and endogenous markers. Exogenous marker such as inulin is gold standard marker of GFR but it is time consuming and required timed urine collection to avoid these endogenous markers based GFR equation introduced which is based on SCr, CysC and both SCr, CysC. Most research studies shows that CKD–EPI is the most accurate method for diagnosis and staging of CKD and CG for drug-dosing decisions. The FDA recommends that CG and MDRD both incorporated into the drug label.

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