

# GFR RESOURCE PAGE

## CYSTATIN GFR

Serum creatinine has a drawback in the measurement of glomerular filtration rate (GFR) in that it may vary according to muscle mass. Cystatin C is a 13 kilodalton protein that is filtered by the glomerulus and reabsorbed and metabolized by tubular cells. The amount that is excreted into the urine is negligible. Its production is very steady, and not dependent on muscle mass. It has been proposed as an alternate marker for estimating GFR. (coresh)

The literature is emerging, and showing that it has a benefit as a marker. Here are two formulae that might be useful in demonstrating the relationships between serum creatinine and serum cystatin C in adults. A Pediatric Cystatin GFR has been evaluated by Schwartz, et al (5)

## CYSTATIN FORMULA

DADE NEPHELOMETRY ADULT GFR =  $77.24 \times \text{cys}^{-1.2623}$

DAKO TURBIDOMETRY ADULT GFR =  $99.43 \times \text{cys}^{-1.5837}$

## SCHWARTZ CKiD PEDIATRIC FORMULA:

$\text{GFR (ml/min per } 1.73 \text{ m}^2) = 39.1 [\text{height (m)/Scr (mg/dl)}]^{0.516} * [1.8/\text{cys (mg/L)}]^{0.294} [30/\text{BUN (mg/dl)}]^{0.169} [1.099]^{\text{male}} [\text{height (m)/1.4}]^{0.188}$

cys = serum cystatin c (in mg/L)

## REDSIDE SCHWARTZ EQUATION (CREATININE):

$0.413 * \text{height(cm)}/\text{Scr(mg/dL)}$

## COUNAHAN-BARRATT EQUATION (CREATININE)

$0.43 * \text{height(cm)}/\text{Scr(mg/dL)}$

## WHAT DOES "TRACEABLE TO IDMS" MEAN?

To properly measure the GFR one must accurately measure the serum creatinine. When a laboratory calibrates their method to the single standardized serum creatinine using reference materials traceable to the primary reference material at the National Institute of Standards, we say that value is traceable to IDMS because the test is based on isotope dilution mass spectrometry (IDMS).

## REFERENCES

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# Approach to Patients with Chronic Kidney Disease, Stages 1-4

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**I. Why identify and treat patients with chronic kidney disease (CKD)?** One may find a correctible cause. By mitigating one or more risk factors, one may be able to slow progression of renal disease or reduce cardiovascular risk.

**II. Stages of CKD.** The National Kidney Foundation's (NKF) Kidney Disease Outcome Quality Initiative (KDOQI) has suggested staging CKD from stage 1 (mildest) to stage 5 (most severe) based on the level of estimated glomerular filtration rate (GFR) normalized to body surface area. The two mildest stages—stages 1 and 2, in which the GFR is still above 60 mL per minute per 1.73 m<sup>2</sup>—require evidence for kidney damage apart from reduced GFR. Kidney damage can be manifested as pathologic changes on kidney biopsy; abnormalities in the composition of the blood or urine, such as, for urine, proteinuria or changes in the urine sediment examination; or abnormalities in imaging tests. The more severe stages of CKD—stages 3, 4, and 5—are present by definition when the GFR is below 60, 30, and 15, respectively (Table 1-1).

## III. Screening for CKD

Screening should include monitoring for the presence of proteinuria and measurement of kidney function.

**A. Urinary protein measurement.** The American Diabetes Association (ADA) recommends that an evaluation for microalbuminuria be performed in all type 2 diabetics at the time of diagnosis and in all type 1 diabetics 5 years after initial evaluation. Others who should be screened include patients with hypertension or heart failure, or those with any disease known to impact kidney function.

A urine dipstick examination should be performed on a random or "spot" urine. The dipstick used should be able to detect both albumin and evidence of blood or white cells. If the urine dipstick is positive for albumin, a spot protein-to-creatinine ratio on a urine sample should be measured. If the dipstick test suggests either blood or white cell activity, then a microscopic analysis should be performed of the urinary sediment.

**B. Measuring GFR.** The recommended approach to measuring GFR is to use an estimating equation based on the serum creatinine level.

**1. Modification of Diet in Renal Disease (MDRD) equation:**  $\text{GFR} = 186 \times [\text{SCr}]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742 \text{ if patient is female}] \times [1.210 \text{ if patient is black}]$ . This equation

Table 1-1. Kidney disease outcomes quality initiative suggested stages of chronic kidney disease

Stage	Description	GFR <sup>a</sup>	Population	Prevalence
1	Kidney damage with normal or supranormal GFR	≥90	5,900,000	3.3%
2	Kidney damage with mild decrease in GFR	60–89	5,300,000	3.0%
3	Moderate decrease in GFR	30–59	7,600,000	4.3%
4	Severe decrease in GFR	15–29	400,000	0.2%
5	Kidney failure	<15	300,000	0.2%

GFR, glomerular filtration rate.  
<sup>a</sup>GFR expressed in mL per minute per 1.73 m<sup>2</sup>.

was derived from the MDRD trial and reports GFR normalized to body surface area. There are several more complex equations derived from the same study that contain additional variables, but consensus has emerged that this parsimonious equation is to be preferred. In 2006 the National Kidney Disease Education Program (NKDEP) issued guidelines for standardizing serum creatinine methods based on isotope dilution mass spectrometry (IDMS). IDMS-standardized serum creatinines are slightly different than those values that were used to derive the MDRD equation (Levey et al., 2006). For laboratories using the new IDMS-standardized serum creatinine values, the “186” term in the equation above should be set to “175” instead. When serum creatinine is measured in SI units (mmol/L), one needs to divide the creatinine value by 88.5, and then the equation with either the 186 or 175 multiplier can be used as listed. The MDRD equation differs from the previously dominant Cockcroft and Gault formula, which, in its usual form, simply predicts the creatinine clearance not normalized to body surface area. The Cockcroft and Gault formula overestimates GFR in the lower range, due to increased tubular secretion of creatinine. A number of papers have suggested alternative methods for estimating GFR, including use of equations based on serum cystatin level, which is not confounded by muscle mass or dietary creatine intake. However, the MDRD equation is the most popular validated equation in current use.

**2. Urinary clearance measurements.** There are some situations where a serum creatinine level is not reflective of GFR, and this includes patients who have markedly reduced creatinine generation rates due to muscle wasting and patients with cirrhosis (muscle wasting plus inability to determine ascites-free body weight for normalization). In such cases the serum creatinine can overestimate the GFR, and a 24-hour urine collection should be done if practical. There are difficulties with 24-hour urine creatinine measurements as well, however, and these include variations in

urine collection (i.e., incorrect collections) and variations in the tubular secretion of creatinine.

Creatinine clearance overestimates GFR because creatinine is both filtered by the glomerulus and, to a lesser degree, secreted by the proximal tubule. On the other hand, urea clearance underestimates GFR since it is both filtered and reabsorbed. For this reason one can estimate GFR as the mean value of the creatinine and urea clearances at low (<15) values of GFR.

Another approach is to measure creatinine clearance but to perform the 24-hour urine collection after oral administration of **cimetidine**, an organic cation that competitively inhibits tubular secretion of creatinine.

**C. Ultrasound and serum electrolytes.** In patients found to have CKD, one should image the kidneys, commonly by ultrasound, to look for structural abnormalities and possible obstruction and measure serum electrolytes (Na, K, Cl, HCO<sub>3</sub>) to screen for metabolic acidosis and electrolyte disorders, the presence of which may give clues to an underlying renal disease.

**IV. Mitigating risk of progression of CKD and of cardiovascular disease.** In CKD patients, risk factors for progression of renal disease are very similar to those associated with increased cardiovascular risk. One purpose of identifying CKD patients early on is to attempt to correct and/or mitigate such risk factors, in the hopes of both maintaining GFR and minimizing cardiovascular risk. The main risk factors include smoking, high blood pressure, hyperglycemia in diabetics (and perhaps in nondiabetics as well), elevated blood lipid levels, anemia, and elevated serum phosphorus levels. Urinary protein excretion and even microalbuminuria markedly increase both the risk of progression and cardiovascular complications. Levels of inflammatory mediators, notably C-reactive protein (CRP), are increased in CKD and are associated with increased atherosclerotic risk.

**A. Cessation of smoking.** Smoking is a traditional cardiovascular risk factor, and cessation of smoking is important in terms of limiting cardiovascular risk. Recent evidence suggests that smoking markedly accelerates the rate of progression of renal disease, emphasizing the importance of stopping smoking by CKD patients.

**B. Control of blood pressure and proteinuria.** The target blood pressure should be <130/80 for all patients with kidney disease, diabetics and nondiabetics, regardless of degree of proteinuria (according to the 2003 KDOQI). Whether or not hypertension is present, use of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACE-I/ARB) is recommended to slow the rate of progression in patients with diabetic kidney disease as well as in nondiabetic CKD patients with proteinuria (spot urine protein-to-creatinine ratio of ≥200 mg/g). Thiazide diuretics are the diuretic of choice for mild CKD, when  $Sc_r$  is <1.8 mg/dL (<160 mmol/L). When  $Sc_r$  is >1.8 mg/dL (>160 mmol/L), a loop diuretic (twice-a-day dosing regimen) is recommended, due to presumed reduced efficacy of thiazides under those circumstances; however, lack