Renal Function Assessment: Cockcroft-Gault vs MDRD equations, is the new one better?

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Case scenarios

- 70 yo F, 45 Kg, sCr = 0.8 mg/dL(70.7µmol/L), DM for evaluation of CKD
  CG: 55 ml/min
  MDRD: 75 m;/min/1.73m^2
- 45 yo F, 50 Kg, sCr = 0.8 mg/dL, DM for evaluation of CKD
  CG: 70 ml/min
  MDRD: 82 m;/min/1.73m^2
- 45 yo M, 52 kg, sCr = 0.8, DM for evaluation of CKD
  CG: 86 ml/min
  MDRD: 111 m;/min/1.73m^2

Renal function assessment

- Diagnosis of Chronic Kidney Disease (CKD)
  - Screening strategy
  - Staging (I-V)
  - outcome: CKD progression, risk assessment and reduction, mortality, treatment
- Drug dosing

Glomerular filtration rate (GFR)

- The ideal substance for GFR estimation should be:
  - freely filtered
  - not reabsorbed
  - not secreted
  - not metabolized
  - not synthesized

  in the renal tubules and kidney.

Inulin clearance

- Inulin, a metabolically inert sugar
- Provides good GFR estimation
- Considered the 'gold standard'
- Disadvantages:
  - non-endogenous
  - intravenous administration
  - assay availability
  - expensive

Filtration markers: exogenous

- Inulin
- Iothalamate, ^{125}I-iothalamate
- EDTA (^{51}Cr-ehtylenediaminetetraacetic acid)
- DTPA (^{99m}Tc-diethylenetriaminepentaacetic acid)
- Iohexol

Creatinine

- Amino acid derivative
- MW = 133 D
- Creatinine is produced from creatine, in muscle as an end-product of metabolism
- Filtered in glomerulus secreted in proximal tubules
- CrCl > GFR
- Secretion depends on GFR
- Cimetidine, trimethoprim → ↑ sCr, no change in GFR

Factors Affecting Creatinine Generation

Factor	Effect on Serum Creatinine
Aging	Decreased
Female sex	Decreased
Race or ethnic group†	
Black	Increased
Hispanic	Decreased
Asian	Decreased
Body habitus	
Muscular	Increased
Amputation	Decreased
Obesity	No change
Chronic illness	
Malnutrition, inflammation, deconditioning (e.g., cancer, severe cardiovascular disease, hospitalized patients)	Decreased
Neuromuscular diseases	Decreased
Diet	
Vegetarian diet	Decreased
Ingestion of cooked meat	Increased

* Variation in muscle mass accounts for the predominant proportion of creatinine generation.
† White race served as the reference group.

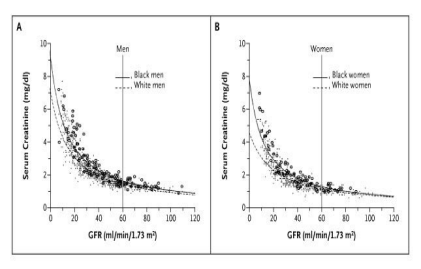
Relationship between sCr and GFR varies:

- among individuals
- overtime

Stevens L et al. N Engl J Med 2006;354:2473-2483

Relationship of Serum Creatinine Level to Measured GFR in the Modification of Diet in Renal Disease Study

GFR = 60 ml/min/1.73m²
sCr =
WM 1.3 – 1.5
BM 1.4 – 1.8
WF 1.0 – 1.2
BF 1.1 – 1.4



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Creatinine clearance (CrCl)

$$CrCl\ (ml/min) = \frac{U \quad V}{P}$$

U = urinary creatinine concentration (mg %)
V = volume of urine collection (ml)
P = serum creatinine concentration (mg%)

Creatinine Clearance estimation from sCr

Cockcroft and Gault method:

$$CrCl\ (male) = \frac{(140\text{-age}) \times wt}{sCr \times 72}$$

$$CrCl\ (female) = CrCl\ (male) \times 0.85$$

age = age (years)
wt = weight (Kg)
sCr = serum creatinine concentration (mg%)

(Cockcroft DW, Gault MH. Nephron 1976; 16:31-41)

Cockcroft and Gault equation

- Developed in 1973
- Data from 249 men, 96% men, in Montreal
- Cl_{Cr}: 30-130 ml/min
- Calculated value:
  - An estimate of Cl_{Cr}, not GFR
  - > GFR (tubular secretion)
  - Not adjusted for BSA
  - Arbitrary 85% adjustment for female

Limitations of Cockcroft and Gault method (I):

- Muscle diseases
- Malnourished patients
  (Lau A, Berk S, Prosser T, et. al. Clin Pharm. 1988; 7: 62-5)
- Advanced renal failure
- Liver disease
  (Hull JH, Hak LJ, Koch GG, et. al. Clin Pharmacol Ther. 1981; 29: 516-521)
  (Lam N, Sperelakis R, Kuk J, Seegar JD, Lau A. Dig Dis Sci., 1999;44:1222)

Limitations of Cockcroft and Gault method (II):

- Obese patients
  (Dionne et. al. Am J Hosp Pharm. 1981;38:841)
- Critically-ill patients
  (Chrymko et. al. Am J Hosp Pharm. 1981;38:837)
- Unstable renal function
  (Bjornsson. Clin Pharmacokinet. 1979;4:200)
  (Jeliffe & Jeliffe. Math Biosci. 1972; 14:17)
  (Chiou & Hsu. Res Com Chem Path Pharmacol. 1975; 10:315)

MDRD equation

- Developed in 1999
- For the Modification of Diet in Renal Disease study
- Data from 1628 CKD patients
  - 94% non-DM, 6% DM
  - 60% male
  - 88% white, 12 % black
- eGFR is adjusted for BSA
- GFR measured by iothalamate assay
- Mean GFR = 39.8 ml/min/1.73m^2
- sCr by alkaline picrate reaction assay (most commonly used)

MDRD equations

- eGFR = 170 x (Plcr) $^{-0.999}$ x [Age] $^{-0.176}$ x [0.762 if patient is female] x [1.180 if patient is black] x [SUN] $^{-0.170}$ x [Alb] $^{0.318}$

  Plcr = plasma creatinine
  SUN = serum urea nitrogen concentration
  Alb = serum albumin concentration

  eGFR as ml/min/1.73m^2

Modified MDRD equation (4-variable version):

- eGFR = 186 x (Plcr) $^{-1.154}$ x [Age] $^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is black]

(Modification of Diet in Renal Disease Study Group. A More Accurate Method To Estimate Glomerular Filtration Rate from Serum Creatinine: A New Prediction Equation. Ann Intern Med. 1999; 130: 461-471)

MDRD equations

Re-expressed MDRD equation using standardized Cr concentrations (2005):

- 5% lower sCr values
- eGFR = 175 x (StdsCr) $^{-1.154}$ x [Age] $^{-0.203}$
  x [0.742 if patient is female]
  x [1.212 if patient is black]

  StdsCr = standardized serum creatinine

Conversion to SI units

- CG equation:

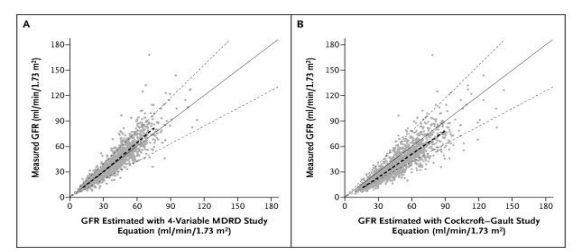
  $$\text{CrCl (male)} = \frac{(140-\text{age}) \times \text{wt}}{\text{sCr} \times 0.82}$$

- MDRD equation:

  eGFR = 32,788 x (Plcr) $^{-1.154}$ x [Age] $^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is black]
  Re-expressed (2005):
  eGFR = 30,849 x (StdScr) $^{-1.154}$ x [Age] $^{-0.203}$ x [0.742 if patient is female] x [1.212 if patient is black]

[Stevens LA et al. New Engl J Med. 2006; 354:2473]

Relation of Estimated GFR to Measured GFR in Participants of the MDRD Study



R^2 = 0.88 R^2 = 0.83

Stevens L et al. N Engl J Med 2006;354:2473-2483

MDRD equation: limitations

- The equation was originally derived from in the following patients:
  - stable CKD (GFR < 90 ml/min)
  - non-diabetic (mostly)
  - Caucasian (mostly)
- Accuracy is not established in patients, such as:
  - Pediatrics
  - Elderly
  - Hospitalized
  - Other ethnic origins, geographic locations

MDRD equation: 'healthy' adults

Significantly underestimated GFR in:

- Potential kidney donors (Poggio et al., Rule et al.)
- Type I DM with normal kidney function (Veroort et al)
  - Classification of CKD:
    - 2095 European adults, median GFR 59.8 ml/min/1.73m²
    - 32.4% misclassified
  - Accuracy improved by Cr assay calibration

MDRD equation: elderly

- 87 Caucasian patients, 50% > 65 yo
- GFR by ^{51}Cr-EDTA, mean = 22.2 ml/min/1.73m²
- MDRD and CG equations significantly underestimated GFR in patients:
  - >65 yo
  - with Cr production < 900 mg/day

[Fontsere et al. Nephron Clin Pract 2006; 104:c160-168]

MDRD equation: Diabetes mellitus

Chudleigh RA et al. (Diab Care 2007; 30:300)

- 292 newly diagnosed, non-albuminuric, type 2 patients
- GFR measured by ^{51}Cr-EDTA
- GFR >90ml/min/1.73m², significantly underestimation by CG and MDRD equations
- GFR <90ml/min/1.73m², slight underestimation by CG and MDRD equations

Ibrahim H et al. (JASN 2005; 16: 1051)

- 1286 patients with type 1 DM
- Mean GFR (^{125}I-iothalamate): 122±23 ml/min/1.73m², mean sCr = 0.85±0.14 mg/dL
- MDRD equation underestimated GFR
- CG equation underestimated GFR <120, overestimated GFR >130

→ premature flagging of early decline in renal function

MDRD equation: diabetes mellitus

Rigalleau V et al. (Diab Care 2005; 28:838)

- 160 patients (50 type 1, 110 type 2)
- GFR measured by ^{51}Cr-EDTA
- GFR groups: <60ml/min/1.73m², <30ml/min/1.73m²
- eGFRs from both CG and MDRD equations correlated well with measured GFRs. (r=0.57, 0.78 respectively)

MDRD equation: hospitalized patients

Poggio et al., (AJKD 2005; 46:242)
- 107 acutely ill hospitalized patients
- Mean GFR (^{125}I-iothalamate): 17.1 ml/min/1.73m^2, mean sCr = 3.5 mg/dL
- Both CG and MDRD equations overestimated (>25%) true GFR in >65% patients
- Performance is worse in patients with BUN/sCr ratio > 20

Hoste et al., (NDT 2005; 20:747)
- 28 adult newly admitted ICU patients, sCr < 1.5 mg/dL
  - Renal function: 1-hr urinary CrCl
  - 13 patients: CrCl < 80 ml/min/1.73m^2
  - 8 patients: CrCl < 60 ml/min/1.73m^2
- Neither CG nor MDRD equation was useful
  - Urinary Cr excretion was low, especially those with ↓ sCr
  - Low Cr production because of low muscle mass

MDRD equation: African-Americans

- 1703 subjects in AASK study (African Americans study of hypertension and Kidney Disease)
- Evaluated the effects of antihypertensives on 2 levels of BP control
- Subjects had greater body weight and higher sCr than MDRD subjects
- GFR was determined by ^{125}I-iothalamate
  - Overestimated by 24 hr Clcr
  - Underestimated by CG equation
  - MDRD equation was most accurate

[Lewis J et al. AJKD 2001; 38:744]

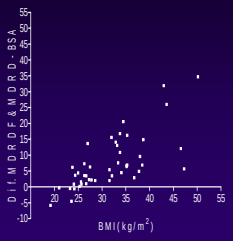
MDRD equation: Chinese

- 454 CKD patients (51% male), from 9 university hospitals in different geographic regions in China
- GFR measured by ^{99m}Tc-DTPA
  Mean = 55.1 ml/min/1.73m^2
  Patients with all 5 stages of CKD
  Weight=64.5±12.4 kg, Height=164.7±8.3cm
- Cr assay: Jaffe's kinetic method, calibrated with lab for MDRD study (Cleveland Clinic)
- eGFR = 170 x (Plcr)$^{-0.999}$ x [Age]$^{-0.176}$ x [0.762 if female] x [1.211 if Chinese] x [SUN]$^{-0.170}$ x [Alb]$^{0.318}$
  eGFR = 186 x (Plcr)$^{-1.154}$ x [Age]$^{-0.203}$ x [0.742 if female] x [1.233 if Chinese]

[Ma et al. J Am Soc Nephrol. 2006; 17:2937]

MDRD equation: Obese patients

- 46 patients (M/F:22/24)
- Wt=93±25kg, BMI=31.6±7.2kg/m^2
- sCr=2.4±1.0mg/dL
  BSA=2.1±2.1m^2
- Estimates from MDRD adjusted for BSA resembles values from CG



Which one is better? CG or MDRD

- Issues to considered for performance evaluation:

Performance of estimation equations

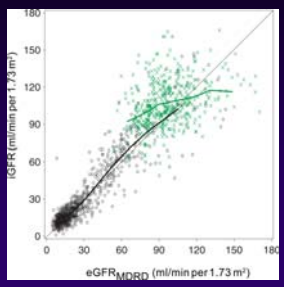
Methodoloigical issues (Cr related):
- SCr affected by:
  - Glomerular filtration
  - Cr generation
  - Cr degradation
- Assumption that Cr:
  - is stable
  - reflects renal function
- Variation of GFR over short periods of time
  - Diurnal variations

Performance of estimation equations

Fixed relationships between sCr and GFR at various GFR levels, as assumed by CG and MRDR equations

Reference GFR ('gold standard'):

- Cl_{Cr} vs GFR
  - (inulin or ^{125}I-iothalamate)
- Measurement errors



Creatinine measurements

- Assay calibration bias, lack of standardization
- Bias of 0.23 mg/dL:
  - 70 yo WF, sCr = 0.77 mg/dL (MDRD central lab)
    eGFR = 79 ml/min/1.73m^2
  - Another lab sCr = 1.0 mg/dL
    eGFR = 58 ml/min/1.73m^2

CAP survey of >500 clin lab, mean error of +0.14 mg/dL (-0.09 - +0.37, 95%CI)

- Such error is especially important in patients with low sCr, if sCr is 3 mg/dL vs 2.77 mg/dL
  eGFR: 16 vs 18 ml/min/1.73m^2

Which one is better? CG or MDRD

- Issues to considered for performance evaluation
- Depends on the intended use and patient populations

Practical use

- Healthy, kidney donors
  - Both MDRD and CG underestimate GFR
  - Filtration markers or multiple 24 hr urine collection, not MDRD
  - Assay calibration may reduce bias
- Subjects at risk for CKD, in need of diagnostic evaluation
  - eGFR + BP, BUN changes, proteinuria, calibrated sCr?
- ?? Wisdom of routine reporting of eGFR, from uncalibrated sCr and using MDRD in subjects with no CKD

Practical use: CKD patients

- Both CG and MDRD performs better in GFR 15-60 ml/min/1.73m^2
- MDRD with lower bias and better accuracy
- Calibrated sCr assays improved performance for GFR > 60 (both MDRD and CG)
- Both DM and non-DM with GFR <60:
  MDRD is reliable and satisfactory

Practical use: Disease conditions

Sick hospitalized patients:

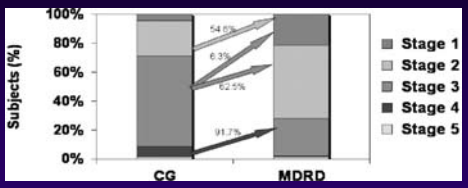
- Both MDRD and CG significantly overestimates GFR
- 6-variable MDRD (with albumin and BUN) improves estimation

Practical use: Race and ethnic groups

- African-Americans
  - MDRD
- Chinese, ? Other Asians
  - Modified MDRD equations
- Hispanics
  - ? Altered Cr metabolism
  - ? Cultural and social habits (diets)

Practical use: CKD staging

•180 patients, age (mean) =85, 30% Asians
•63% discordant GFR estimation and were categorized in different stages by CG and MDRD equations



•MDRD results in 20% fewer dose reduction of amantadine

Gill, J. et al. Nephrol. Dial. Transplant. 2007 22:2894-2899

Practical use: drug dosing

- Most dosing guidelines developed according to Cl_{Cr} and stratified accordingly.

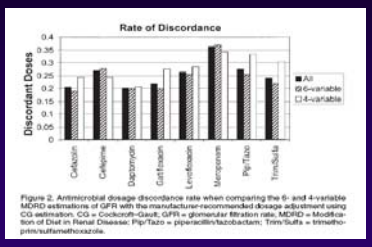


Figure 2. Antimicrobial dosage discordance rate when comparing the 6- and 4-variable MDRD estimations of GFR with the manufacturer-recommended dosage adjustment using CG estimation. CG = Cockcroft–Gault; GFR = glomerular filtration rate; MDRD = Modification of Diet in Renal Disease; Pip/Tazo = piperacillin/tazobactam; Trim/Sulfa = trimethoprim/sulfamethoxazole.

Wargo et al, Ann Pharmcother. 2006; 40:1248.

Practical use: drug dosing

Carboplatin for gynecologic malignancies

- 96 patients, mean sCr=71 µmol/L, GFR=91ml/min

GFR group (ml/min)	Measured GFR (mg)	CG (mg)	MDRD (mg)
Overall (n=94)	622	557	575
<30 (n=3)	250	219	210
30-59 (n=13)	405	361	405
≥60 (n=78)	657	573	587

- 85% have significant (>5%) dosing variance
- MDRD more accurate than CG

[de Lemos ML, et al. Gynecologic Oncol. 2006; 103:1063]

Which one is better? CG or MDRD

- Issues to considered for performance evaluation
- Depends on the intended use and patient populations
- There are times that neither works well:
  - Low muscle mass (creatinine production)
  - Rapidly changing renal function

Case scenarios

- 50 yo M, 60 Kg, sCr = 1.7 mg/dL,
  developed acute renal failure after major surgery,
  urine output =100 ml over past 24 hours,
  needs renal function assessment for drug dosing
  CG: 32 ml/min
  MDRD: 46 m;/min/1.73m^2