2004-03-08
Clem,

Yes, there are lots of variables in the "creatinine clearance" business.

I have tried in the following paragraphs to organize my own thoughts on this topic, and hope that the text will be of some interest to you. At the end of the document are various references and formulae - probably more than you could possibly be interested in!

Before starting I though it important to make an important distinction:

(a) in developing the Cockroft-Gault formula, C and G used data from patients with creatinine clearance (CrCl) measured in a standard way - so their formula predicts CrCl, from which one could infer the GFR, which is the real target.

(b) in developing the MDRD formula **(M**odification of **D**iet in **R**enal **D**isease project), Levey et al used data from patients with glomerular filtration rate (GFR) measured in a standard way - so their formula predicts GFR directly, normalized for a BSA of 1.73 sq m. This makes for more entries in the LOINC database, but I think the distinction is important.

As well, please tolerate my indiscriminate use of P-creatinine and S-creatinine as a short form for plasma and serum creatinine. They should be considered equivalent.

So, herewith some thoughts on the topic.

1.0 Assessment of renal function is important in

1.1 monitoring renal disease

1.2 selecting drug doses

2.0 Glomerular filtration rate (GFR) is the best measure of renal function

2.1 best measures of GFR are inulin clearance or methods based on isotope excretion (e.g. iodothalamate) but both are technically complex, so seek proxy

3.0 Proxies for GFR

3.1 simplest is P-creatinine or P-cystatin C

3.2 next may be endogenous creatinine clearance CrCl *(for interim convenience, let's call this actual creatinine clearance, aCrCl)*

3.2.1 clearance is known to be related to body surface area (BSA)

3.2.2 can improve usefulness of CrCl by normalizing to a specified body surface area – which is usually 1.73 sq m, but may be 1.0 sq m. There are numerous formulae/nomograms for estimating BSA from height and weight (see references below)

3.2.3 aCrCl requires measurement of P-creatinine, U-creatinine and U-volume in specified time, and may be reported as ml/min, ml/min/sq m, or ml/min/1.73 sq m, or less frequently with a time base of per second, rather than per minute: ml/sec, ml/sec/sq m, or ml/sec/1.73 sq m. The duration of urine collection may be 4, 8, 12 or 24 hours, or some other specified time

3.2.4 Alternatives for actual CrCl

3.2.4.1 Need for timed urine collection for aCrCl makes the test inconvenient, so alternatives sought through prediction formulae – formulae that would permit prediction of CrCl from a measured P-Cr. *(For convenience, let's call this predicted creatinine clearance, or pCrCl.)*. Most widely used formula for pCrCl has been Cockroft-Gault.

3.2.4.1.1 Cockroft-Gault: uses P-creatinine, age, weight, gender to predict CrCl

3.2.4.1.2 Jelliffe: uses P-creatinine, age and gender

3.3 Using the MDRD formula, it is possible to predict the GFR directly from S-creatinine, plus other factors

3.3.1 MDRD: uses S-creatinine, age, gender, race, and optionally, S-urea nitrogen and S-albumin to predict GFR

4.0 LOINC requirements: we have potential need for entries:

[Bracketed entries (4.1), (4.3.3) may not be required]

(4.1) actual GFR - from inulin clearance or equivalent

4.2 predicted GFR (results in ml/min/1.73 sq m - from either MDRD formula; system will be SER/PLAS, time aspect=PT, possibly method=MDRD formula)

4.3 actual CrCl (creatinine in P and U, timed U collection, results in ml/min; system will be SER/PLAS and U, time aspect as required for urine collection)

4.3.1 without BSA correction
4.3.2 with BSA normalized to 1.73 sq m
(4.3.3) with BSA normalized to 1 sq m

4.4 predicted CrCl (from P-creatinine only, results in ml/min, system will be SER/PLAS, time aspect PT, possibly method=Cockroft-Gault formula)

4.4.1 without BSA correction
4.4.2 with BSA normalized to 1.73 sq m

5.0 LOINC Status, version 2.12

See separate Excel attachment, file name <Clearance in LOINC v 212.xls> for current status and item numbers linked to following comments. Items in LOINC v 2.12 are numbered 1 through 18. Where I have proposed a modification I have inserted a new line, and the item number has an "m" attached. For example, I have proposed a modification to item 1, and the modification is shown with the item number 1m. General question: do we need "renal" in the various creatinine renal clearance items? As well, what about using the PanelElements field - see my item 3-9m as an example.

Item 1 From LOINC Comment this appears to be a predicted GFR, rather than a true GFR, and component name should reflect this. Suggest "Predicted Glomerular Filtration Rate". Perhaps Method field should contain "MDRD formula". This would satisfy need for 4.2 above.

Item 2 OK - no comment

Items 3 to 9 OK – these would satisfy need 4.3.1 above; System=Ser/Plas+U

Items 10 to 14 Suggest changing component name to CREATININE CLEARANCE/1.73 SQ M thus satisfying 4.3.2 above. System=Ser/Plas+U. In my note of 2004-03-01 I proposed /SQ M, but I have not seen any examples of this use recently – so suggest not offering this option – i.e., 4.3.3 above - until specifically requested.

Item 15 This will become a duplicate of 14, so delete and map to 13445-2

Item 16 Doubtful if ever used, but Property should be VRAT
Item 17 Doubtful if ever used
Item 18 Almost certainly should be INULIN, not INSULIN and so is duplicate of item 2

New item to satisfy 4.4.1: Component name Predicted Creatinine Renal clearance, System=Ser/Plas, Time=PT, and in Method field show "Cockroft-Gault formula"

New item to satisfy 4.4.2: Component name Predicted Creatinine Renal Clearance/1.73 sq m, System=SER/PLAS, Time=PT, and in Method field show "Cockroft-Gault formula and BSA formula"

References for Surface Area

JGH note: unable to find source for use of "1.73 sq m", but table from BC Cancer Institute web site interesting:

Average values of BSA:

Man	1.9 m²
Woman	1.6 m²

9 year old child	1.07 m²
10 year old child	1.14 m²
12-13 year old child	1.33 m²

1. DuBois D, DuBois DF. A formula to estimate the approximate surface area if height and weight be known. Arch Int Med **<u>1916</u>**;17:863-71.

$BSA\ (m^2) = Wt\ (kg)^{0.425} \times Ht\ (cm)^{0.425}$

This is the classic formula, published in 1916, on which many nomograms are based. It was based on measurements of 9 individuals, one of whom was a child.

2. Boyd **<u>1935</u>**

$BSA = 0.0003207 \times Ht\ (cm)^{0.3} \times Wt\ (g)^{[0.7285-(0.0188 \times \log(g))]}$

3. Gehan EA, George SL. Estimation of human body surface area from height and weight. Cancer Chemother Rep **<u>1970</u>**;54:225-35.

$BSA\ (m^2) = Wt\ (kg)^{0.51456} \times 0.02350 \times Ht\ (cm)^{0.42246}$

This formula is based on direct measurements of 401 individuals.

4. Haycock GB, Schwartz GJ, Wisotsky DH. Geometric method for measuring body surface area: A height-weight formula validated in infants, children and adults. J Pediatr **<u>1978</u>**;93:62-6.

$BSA\ (m^2) = Wt\ (kg)^{0.5378} \times Ht\ (cm)^{0.3964} \times 0.024265$

Haycock et al reported that the formula of DuBois and DuBois increasingly underestimated BSA as values fell below 0.7 m². Their formula was based on measurements of 81 individuals ranging from premature infants to adults.

5. Mosteller RD. Simplified calculation of body-surface area. N Engl J Med **<u>1987</u>**;317:1098.

BSA in m² = SQR RT (Ht in cm x Wt in kg)/3600
Or
BSA in m² = SQR RT (Ht in inches x Wt in lbs)/3131

This formula is a simple modification of an equation by Gehan and George. The formula has been confirmed as being applicable to children by Lam and Leung. (SQR RT = Square Root of...)

6. Lam TK, Leung DT. More on simplified calculation of body-surface area. N Engl J Med **<u>1988</u>**;318:1130.

<u>References for Estimation of pCrCl and pGFR (Prediction Equations)</u>

1. **Jelliffe, Ann Int Med 1973;79:604-605**

   CrCl (ml/min) = [98-(0.8 x (age – 20))] / P-Cr,
   where age is in years to the nearest decade, and in females, the result is multiplied by 0.9.

2. **Cockroft and Gault, Nephron 1976;16:31-41**

   CrCl (ml/min) = [(140 – age) x weight] / 72 x P-Cr,
   where age is in years, weight is in kg, and P-Cr is in mg/dL; in females, the result is multiplied by 0.85

   If P-Cr is in micromoles/L, use
   CrCl (ml/min) = [(140-age) x weight] x 1.23 / P-Cr

3. **MDRD formula (M**odification of **D**iet in **R**enal **D**isease project**) (**result is **GFR)**
   [Sources:

   a) http://www.postgradmed.com/issues/2001/12_01/manjunatht3.htm

   b) Levey AS, et al A more accurate method to estimate GFR from S-creatinine: a new prediction equation. Ann Intern Med 1999;130(6):461-70

   c) Levey As, et al A simplified equation to predict GFR from S-creatinine. (Abstr) J Am Soc Nephrol 2000; 155A

   3.1 4-variable formula:

   GFR (ml/min/1.73 sq m) = 186.3 $(\text{S-Cr})^{-1.154}$ x $(\text{age, yr})^{-0.203}$ x 0.742 (if female) x 1.210 (if African American).

   3.2 6-variable formula:

   GFR (ml/min/1.73 sq m) = 170 x $(\text{S-Cr})^{-0.999}$ x $(\text{age, yr})^{-0.176}$ x 0.762 (if patient is female) x 1.18 (if patient is black) x $(\text{S-urea nitrogen})^{-0.17}$ x $(\text{S-albumin})^{0.318}$

JGH Notes on Prediction Equations

Note 1: The formulae of Jelliffe and of Cockroft and Gault produce an estimate of the CrCl, not related to BSA. In order to express results in "conventional units" of ml/min/1.73 sq m, height must also be measured, and the BSA calculated.

Note 2: The MDRD formula produces an estimate of the GFR, normalized to BSA of 1.73 sq m. See abstract below that indicate MDRD is no better than Cockroft-Gault at estimating “GFR”.

Note3: some MDRD calculators available on the web (e.g., see www.hdcn.com/calc.hhtm) offer the option of including S-urea nitrogen and S-albumin as input into the MDRD formula - i.e., can use the 4-variable or the 6-variable equation.

References to Validity of Prediction Equations

1. Vervoort G, Willems HL, Wetzels JF. Nephrol Dial Transplant. 2002 Nov;17(11):1909-13.
Assessment of glomerular filtration rate in healthy subjects and normoalbuminuric diabetic patients: validity of a new (MDRD) prediction equation.

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BACKGROUND: Based on the data derived from the Modification of Diet in Renal Disease (MDRD) study, a new equation was developed for the estimation of glomerular filtration rate (GFR). This equation, which takes into account body weight, age, sex, serum creatinine, race, serum urea, and serum albumin, provided a more accurate estimation of GFR in patients with renal insufficiency. However, this prediction equation has not been validated in subjects with normal or supra-normal GFR. METHODS: In a cross-sectional study, we measured GFR by inulin clearance in 46 healthy controls and 46 non-complicated type 1 diabetic patients. In this study population, GFR was predicted by measured creatinine clearance, the Cockcroft-Gault formula, and the MDRD equation. RESULTS: In the healthy subjects, mean GFR (+/-SD) was 107+/-11 as compared to 122+/-18 ml/min per 1.73 m(2) in the diabetic patients. This difference in GFR was reflected by a lower serum creatinine (76+/-8 vs 71+/-8 micro mol/l) in the diabetic patients. In the healthy controls, median absolute differences (and the 50th-75th-90th percentile of percentage absolute differences) between predicted and measured GFR were 5.2 ml/min per 1.73 m^2 (4.9-9.8-18.5%) for creatinine clearance, 9.0 ml/min per 1.73 m^2 (8.6-14.3-24.6%) for the Cockcroft-Gault formula, and 10.7 ml/min per 1.73 m^2 (10.9-16.3-25.5%) for the MDRD equation. In the diabetic patients, these differences were 8.3 ml/min per 1.73 m^2 (7.6-9.3-13.0%) for creatinine clearance; 11.8 ml/min per 1.73 m^2 (10.1-16.0-22.5%) for the Cockcroft-Gault formula, and 18.8 ml/min per 1.73 m^2 (16.0-24.2-31.9%) for the MDRD equation. **CONCLUSIONS**: In subjects with a normal or increased GFR, the new MDRD-prediction equation of GFR is less accurate than creatinine clearance or the Cockcroft-Gault formula, and offers no advantage.

2. Burkhardt H, Bojarsky G, Gretz N, Gladisch R. Gerontology. 2002 May-Jun;48(3):140-6.

Creatinine clearance, Cockcroft-Gault formula and cystatin C: estimators of true glomerular filtration rate in the elderly?

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BACKGROUND: The aim of this study was to assess the accuracy and precision of estimators of true glomerular filtration rate (GFR) (Cockroft formula, measured creatinine clearance (CCR) and a cystatin-C-based estimation) in elderly patients attending a geriatric department. Additionally, parameters influencing GFR in the elderly were evaluated. METHODS: 30 patients aged 57-90 years treated in the Geriatric Department for pulmonary or cerebral diseases were included in the study. Nine patients were diabetic and 16 hypertensive. Exclusion criteria were advanced dementia, acute heart failure and primary renal disease. Inulin clearance (CINU), CCR and estimation by Cockroft-Gault equation (CG) were performed on the same day. For comparison of the methods an analysis according to Bland and Altman was used, depicting the mean difference between the methods and the limits of agreement of the differences, representing their 95% interval of confidence. Furthermore, the influence of confounding variables on GFR estimation was analyzed by multiple regression. RESULTS: Baseline characteristics showed a median age of 74.5 years and a median body weight of 66.7 kg. Median values for serum creatinine 88.4 micromol/l, 5.74 mmol/l for urea and 1.57 mg/l for cystatin C. CCR (median: 51.6 ml/min) and CG (median: 63.0 ml/min) underestimated CINU (median: 83.3 ml/min). Both methods showed poor precision compared with CINU. The upper limit of agreement of the difference was 101.3 ml/min for CCR and 81.4 ml/min for CG, the lower limit was -33.8 ml/min for CCR and -24.6 ml/min for CG. Among frequently used variables to predict GFR, the reciprocal of serum creatinine and body weight revealed a significant influence but not age or gender. A cystatin-C-based estimation of GFR, derived from regression analysis, did not improve the precision of the estimation of GFR compared to CG. Additionally, the occurrence of diabetes mellitus disclosed a borderline influence on the estimation of GFR. **CONCLUSION:** CCR is not only inconvenient and time consuming, but also imprecise and inaccurate in the elderly, mainly due to reduced muscle mass and erroneous urine sampling. CG and a cystatin-C-based estimation are slightly more adequate, but overall there is no sufficiently precise formula for GFR estimation in the elderly.