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The estimated glomerular filtration rate: Linchpin of the chronic kidney disease guidelines

The standardized reporting of serum creatinine values by BC laboratories will aid both patient care and outcomes analysis.

ABSTRACT: Modern management of chronic kidney disease depends upon the measurement of serum creatinine for case finding and categorizing severity. A mathematical formula can be used to convert serum creatinine values into an estimate of the glomerular filtration rate, which is easier to relate to kidney function and to build into practice guidelines than serum creatinine results. As with all tests, there are caveats, the understanding of which can lead to greater interpretive power. A unique step being taken in BC is to standardize the reporting of kidney function testing through a sophisticated external control program.

British Columbia is the first multilab jurisdiction in the world to routinely analyze serum creatinine values using an equation that provides an estimate of the glomerular filtration rate (eGFR), and the first to initiate a broad-based creatinine testing standardization program. Because kidney disease evolves without notable signs or symptoms, a simple, reliable, objective test is required for case finding and categorizing severity. The eGFR has been selected as the essential marker for the new BC chronic kidney disease (CKD) clinical practice guidelines.

The test

An ideal routine test of glomerular function would inexpensively measure an endogenous substance that is continually and consistently released into the circulation and is removed exclusively by glomerular filtration. Serum urea is easy to analyze, but results are influenced greatly by hydration and protein intake. Serum cystatin C provides a better estimate of glomerular function, but is currently at least 10 times more costly to analyze.[1] Actual measurement of the glomerular filtration rate (GFR) using administered inulin, radioactive ^{125}I-iothalamate, or ^{99m}Tc-DPTA is very accurate and suitable for research and special studies, but all of the methods involved are invasive, highly expensive, and time-consuming. The time-honored analysis of serum creatinine is efficient to perform and fulfills most of the desired physiological criteria.

The relationship between serum creatinine and glomerular function (expressed as the glomerular filtration rate) is logarithmic. In the critical region where normal kidney function passes into CKD a large change in the GFR is represented by a relatively small change in the serum creatinine. In order to define all these variables, the adult ranges for serum creatinine tend to be overly liberal. As well, 40% of people with reduced GFR have been found to have normal serum creatinine concentrations.

The traditional way to account for differences in creatinine production is

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to measure the amount of creatinine in the urine by collecting 24-hour urine samples. This allows the calculation of a creatinine clearance (u−Cr × V/s − Cr). In practice, there are limitations to this formal measurement of creatinine clearance using the 24-hour urine test, as follows:

- Timed urine collections are notoriously unreliable, inconvenient, and add to the expense of the investigation.
- Urine creatinine assays are not as accurate as those in serum.
- It is difficult to estimate the lean body mass in order to standardize the measurement.

This last difficulty is shown dramatically in **Figure 1**, where the body weight and 24-hour creatinine excretion of 453 patients are compared. Theory would predict a good correlation. However, because body weight alone does not permit an estimation of the lean body mass, and because urine collection is so unreliable, measuring the urine creatinine ends up being no more accurate than taking a guess.

To eliminate the problem of urine collections and urine assays, more than 30 equations have been published to calculate eGFR directly from serum creatinine. One of the most popular has been the simple arithmetical equation of Cockcroft and Gault (see **Figure 2**), which uses serum creatinine, age, and weight.[2] The new BC CKD guidelines[3] recommend the Modification of Diet in Renal Disease (MDRD) equation for calculating GFR (see **Figure 2**). This equation was originally developed by Levey and colleagues for the baseline period of the MDRD study.[4] The full equation uses creatinine, albumin, urea, age, gender, and race. It correlates well with an iothalamate method (R^2 = 0.90). The Kidney Disease Outcomes Quality Initiative (K/DOQI) concluded that: "…estimates of GFR are the best overall indices of the level of kidney function…the serum creatinine concentration should not be used alone to assess the level of kidney function."[5] A major advantage to the use of the eGFR is that the "normal" range (and other critical values) is the same for all patients of any age or gender. In order to enjoy the same advantage, an alternative method would need to adopt a minimum of 14 different adult ranges. This would render the clinical practice guidelines unnecessarily complex.

A simplified version of the MDRD calculation (sometimes referred to as the abbreviated MDRD) using serum creatinine, age, gender, and race (black

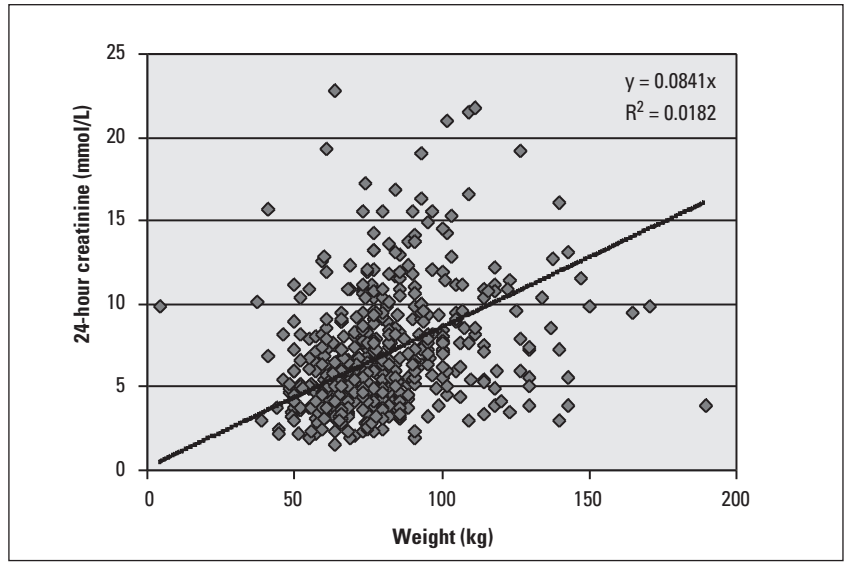

Figure 1. The lack of relationship can be seen between the weight of 453 patients and their 24-hour urine creatinine results. A close relationship is the basis for the formal creatinine clearance determination.

Cockroft-Gault equation[2]

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight}}{s_{Cr} \times 0.81} \times (0.85 \text{ if female})$$

MDRD equation[4]

$$\text{GFR (mL/min/1.73 m}^2) = 186 \times (s_{Cr} \times 0.0113)^{-1.154} \times (\text{age})^{-0.203} \times (0.742 \text{ if female})$$

Figure 2. Common equations for calculating GFR.

These equations are available online and with PDA and PC downloads from www.kidney.org/professionals/kdoqi/cap.cfm

A manual conversion table is available on the BC Protocols and Guidelines web site.[3]

Note: Now that the method-based factor has been introduced into BC (as of November 2004), the web-based calculations of eGFR do not equate precisely to the lab-reported eGFR.

vs white) was shown to closely approximate the full formula ($R^2 = 0.89$).[6] The Cockcroft-Gault equation, after readjustment, is very close to the MDRD and, in addition, is a Canadian invention. However, the MDRD does not require the patient's weight, and therefore can be programmed into computers with minimal information, and thus will probably gain greater acceptance worldwide. For this reason, it was selected as the BC standard. For practical reasons, it was decided not to adjust for the factor of race in BC, as there is insufficient information about creatinine in relation to our province's racial demographics. It is important to recognize that the race adjustments may be important modifiers. Further research regarding the equation's use in Indo-Canadian, Asian, and other ethnic groups is required.

Unfortunately, calculating with the MDRD equation is more complicated than with the Cockcroft-Gault equation and even a nephrologist would be hard-pressed to make the computations without a PDA. The calculations are only valid in adults, so the laboratories will not calculate the eGFR for those under 18 years of age. For children, the K/DOQI guidelines recommend the equations of Schwartz and Counahan-Barratt, and the BC Children's Hospital has developed an excellent equation of its own.[7]

Interpreting the test

The BC guidelines define the reference interval as a GFR ≥60 mL/min/1.73 m^2. "Persistent eGFR values <60 mL/min indicate abnormal kidney function, either as an isolated condition or as a symptom of a systemic disease."[3] (The clinical application of eGFR values is covered in the other articles in this issue.)

Because the MDRD equation for calculating eGFR was developed from 1628 patients it cannot be expected to be exact for all persons. Any cause of an increased or decreased serum creatinine will cause the eGFR to fall or rise respectively. There are several causes of factitious change of serum creatinine that must be kept in mind. Perhaps most important is rapidly changing renal function and rapid body water shifts, for which the calculation is meaningless. The calculation is also not valid for a GFR <30 mL/min (Stage 4). The formula has not been assessed for use in pregnancy. Abnormal production of creatinine related to unusual size or abnormal muscle metabolism will also alter the results. Certain drugs will alter the metabolism or renal handling of creatinine; other drugs may interfere with the chemical reaction used in the assay. Such drugs will cause factitious results and should be distinguished from those that are nephrotoxic. A list of caveats should be considered (see **Table**).

If there is doubt about the validity of an eGFR because of an individual's musculature, you can modify the GFR by estimation. Muscular differences can be accounted for using a simple multiplier (in the same way a modifier is used for women.) So, if your patient is a 170-cm tall male who weighs 82 kg and is not particularly muscular, the equation will be valid. But if your patient is a lean, athletic, 110-kg male, he will produce large amounts of creatinine that may be reflected by a raised serum creatinine and thus a lowered eGFR. Since your athletic patient probably has at least 20% more muscle mass than your less athletic patient, you may wish to multiply his eGFR by 1.20 to see if this product is more clinically appropriate. This is the factor that is used in the US to adjust for more highly muscled black patients. However, when in doubt, it may be reasonable to carry out a more detailed evaluation that includes a nuclear GFR, which is readily available in most parts of BC and does not suffer from the pitfalls of 24-hour urine collections that may overestimate the GFR by 10% to 25%. The same advice applies before administering toxic drugs that depend upon renal removal as well as in cases involving severe malnutrition, obesity, disease of skeletal muscle, paraplegia, quadriplegia, and vegan diets.

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Table. Caveats to the interpretation of serum creatinine and eGFR.

General limitations (calculation not necessarily valid)
- Children under 18 years (alternative calculation required)
- Racial groups (not yet defined)
- Rapidly changing kidney function
- Rapidly changing body fluid distribution
- Pregnancy
- GFR < 30 mL/min

Increase in serum creatinine (decrease eGFR)

- **Physiological**
  - Kidney disease (reduced glomerular function)
  - Reduced renal perfusion
  - Large muscle mass (Do not confuse with fat. Adipose tissue does not contribute creatinine.)
  - Abnormally rapid muscle breakdown
  - High protein intake (cooked meat may transiently increase creatinine production; there may be a transient increase in actual GFR)
  - Marked extracellular fluid decrease
  - Very poor glucose control
  - Drugs causing increased creatinine release from muscle: active vitamin D metabolites,[1] corticosteroids,[8] fenofibrate[9,10]
  - Drugs causing decreased proximal tubular secretion of creatinine: cimetidine,[8] phenyl acetamide,[8] pyrimethamine,[8] salicylates,[8], trimethoprim[8,11]
  - Drugs having effect not understood: nonsteroidal anti-inflammatories, pyrimethamine[8]
- **Analytical**
  - Chromogens causing a positive analytical interference: ascorbic acid, bilirubin,[12] ketoacids (picric acid method), nonspecific chromogens (some methods),[11] sarcosine[11]
  - Drug causing a positive analytical interference: dopamine[11,12]
  - Drugs causing a positive analytical interference that varies with different assay conditions: cephalosporins,[13] flucytosine[11]

Decrease in serum creatinine (increase eGFR)

- **Physiological**
  - Kidney disease (tubular secretion may increase in some disorders, muscle mass may decline in CKD, a significant amount of creatinine can be degraded by bacterial overgrowth in the small bowel in severe CKD)[12]
  - Reduced muscle mass (small persons, amputation, malnourishment, paraplegia, quadriplegia)
  - Low protein intake
  - Massive extracellular fluid increase

No effect (though effect previously reported)
- fluoroquinolones[14]

The BC program

In concert with the development of the CKD guidelines, the BCMA Section of Laboratory Medicine developed a common approach, and in October 2003 almost all laboratories in the province began to use the modified MDRD equation to calculate eGFR for every outpatient adult serum creatinine ordered.

One serious limitation to the use of "absolute" eGFR values in the guidelines is the fact that not all serum creatinine assays are the same. Each analyzer has a different calibration system assigned by its manufacturer and different labs measuring the same sample are known to produce different values. In order to minimize this variation, a program was developed by the Canadian External Quality Assessment Laboratory (CEQAL, 307–2083 Alma Street, Vancouver, BC V6R 4N6) and supported by a grant from the BC Ministry of Health.

In this endeavor, each lab was sent three samples with absolutely known values determined by isotope dilution mass spectrometry. All labs measured these samples in triplicate over a period of 3 days and the data were analyzed by CEQAL. The study showed that there is an approximate 30% spread in the results over the clinically important range of 50 to 150 µmol/L. Precision (ability for each lab to replicate the same result on the same sample) was excellent and most labs demonstrated an ability to reproduce multiple results on the same sample within 5%. The study allowed the computation of a factor for each laboratory that can be applied to the eGFR to minimize lab-to-lab differences to under 6% for two-thirds of labs and under 10% for all. The use of this modified calculation with standardized report comments went into effect in late 2004. Since most labs overestimate true creatinine by some amount, the application of the factor will raise the eGFR on all samples to some degree after the change date. For example, in August 2004 a 60-year-old man has a serum creatinine of 110 µmol/L and a GFR of 63 mL/min. In December 2004, when he has a second serum creatinine performed in the same lab, his serum creatinine is exactly the same at 110 µmol/L, but his eGFR (now adjusted) is 74 mL/min. This apparent "improvement" in renal function should be considered when evaluating patients over time.

Summary

As we gain more experience with the treatment and outcomes of CKD patients, a solid set of objective laboratory results will be an extraordinary resource for program management and outcomes analysis, and a significant support to direct patient care.

In concert with the development of the CKD guidelines, the BCMA Section of Laboratory Medicine developed a common approach, and in October 2003 almost all laboratories in the province began to use the modified MDRD equation to calculate eGFR for every outpatient adult serum creatinine ordered.

Competing interests

Dr McNeely is employed as director of chemistry at MDS Metro Laboratory Services, which carries out some of the testing described in this article.

Acknowledgments

The author would like to acknowledge the work of Drs J. Heathcote, D. Seccombe, F. Rosenberg, and the chemistry science section of the BC Association of Laboratory Physicians for making this project possible.

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