As the population in the United States continues to age, the number of patients with chronic kidney disease (CKD) has dramatically increased. CKD, a reduction in the glomerular filtration rate (GFR), is increasing, in part because of the aging population as well as the greater prevalence of obesity and hypertension. Because GFR declines 1% per year for every year of life after the third decade, living longer means that it is possible to outlive one’s renal function and to require renal replacement therapy to stay alive. In addition, this longevity increases the risk of developing diseases such as diabetes, hypertension, and coronary artery disease, all of which have direct adverse effects on kidney function. A longer life also increases the risk of exposure to nephrotoxic medications for other health conditions such as arthritis (nonsteroidal anti-inflammatory drugs [NSAIDs]), infections (antibiotics), cancer (chemotherapy), gastroesophageal reflux disease (proton pump inhibitors), and coronary artery disease (radiocontrast agents).

The reported incidence of acute renal failure (ARF) in hospitalized patients is 4-7% and constitutes 1% of all hospitalizations.

Creatinine and Creatinine Clearance as a Marker of Renal Function

Creatinine, a muscle waste product, has an imperfect association with the glomerular filtration rate (GFR) — the volume of fluid filtered from the renal (kidney) glomerular capillaries into the Bowman’s capsule per unit time.

To use the serum creatinine level as a marker of renal function, creatinine production and protein intake must be assumed to be constant (which, obviously, they are not). Glomerular filtration rate can be estimated by measuring creatinine clearance using serum creatinine levels and a timed (complete) urine specimen. However, measuring creatinine clearance in this manner is time-consuming and fraught with errors of timing and urine collection, in addition to the fact that the creatinine level is markedly influenced by factors other than GFR. Thus, other methods of estimating GFR, both those that rely on determining serum creatinine levels and those that do not, have been studied as replacements for creatinine clearance. Some of these include CC, urea, inulin, and radioisotopic methods. The last two are considered “gold standards,” although admittedly “tarnished” gold as they require injections and in the one case, a radioactive tracer.

Serum creatinine and creatinine clearance

Multiple formulas have been proposed and studied to estimate renal function more accurately by correcting for such factors as differences in muscle mass in men vs. women or in “African American” vs. “white” people and changes in muscle mass due to aging. One of the commonly used is the Cockcroft-Gault equation:

$$\text{eGFR} = \frac{140 - \text{Age}}{72} \times \text{Mass} \times \text{Creatinine} \times 0.85$$

This formula expects weight to be measured in kilograms and creatinine to be measured in mg/dL, as is standard in the USA. The resulting value is multiplied by a constant of 0.85 if the patient is female.

Another pair of formulae are the 4-variable and 6-variable Modification of Diet in Renal Disease (MDRD) equations.

It is important to note the following important cautions about estimated GFR:

- **eGFR is only an estimate.** A significant error is possible. eGFR is most likely to be inaccurate in people at extremes of body type, for example malnourished, amputees, etc. See Race, below. It is not valid in pregnant women or in children (see Age, below).
- **Confidence intervals:** 90% confidence intervals are quite wide, e.g., 90% of patients will have a measured GFR within 30% of their estimated GFR; 98% have measured values within 50% of the estimated value. For an individual patient values will be much more consistent than this, just as creatinine values are, e.g., a 20% fall in eGFR is certain to reflect an important change.
- **Race:** Some racial groups may not fit the MDRD equation well. It was originally vali-
dated for US white and black patients. *For Afro Caribbean black patients, eGFR was 21% higher for any given creatinine in the MDRD study.*

- **Not so good near normal levels:** The MDRD equation tends to underestimate normal or near-normal function, so slightly low values should not be over-interpreted. Furthermore, laboratory differences in creatinine estimations may make significant differences. Routine reporting of eGFR values >90 is not recommended and many labs are now reporting all values over 60 as >60. Note, however, that a significant (e.g., 20%) rise in creatinine while eGFR is >60 may still be important as it will usually reflect a real change in GFR.

- **Creatinine level must be stable.**
- **Age:** The MDRD equation is not valid for patients under 18 yrs.

**Cystatin C as marker of renal function**

Cystatin C (CC), a small molecule (MW: 13,000), is filtered by the glomeruli and is followed by tubular reabsorption and degradation resulting in excretion of a minute amount in the urine. It is not secreted in the tubules and also not reabsorbed back into the serum and therefore, *its serum levels reflect the amount of glomerular filtration,* which makes serum CC an alternative marker for glomerular filtration. In contrast to creatinine, age, weight and gender have no influence on the serum CC. In reviewing the recent literature on CC, we found a number of arguments which make compelling arguments for moving from using creatinine and one of the fallible formulae to measuring CC. For example, Williams, *et al.* studied 67 diabetic patients with normal creatinine. They concluded that “CC seems to be a more sensitive parameter than creatinine for the detection of an incipient nephropathy in diabetes.”

The study by Hergert, *et al.* demonstrated a rise in serum CC by 80% a day before the onset of ARF while the serum creatinine level rose only by 21%. Thus, the serum CC was able to detect ARF clearly. This has a significant clinical importance since early detection of ARF, especially in the ICU setting, may alert the physician to avoid or change the dose of potentially nephrotoxic medications. Maillard and coworkers concluded that their data confirm that cystatin C as a GFR marker offers significant advantages over creatinine in renal transplantation. One of the arguments against switching to CC from creatinine is cost. Currently CC is available on several chemistry analyzers and while it is true the CC is a more expensive test to perform, the reimbursement is considerably better. In most cases, the difference between CC net income and that for creatinine is as good as or better than measuring creatinine. CC has been utilized in Europe for more than 15 years and when recently introduced in China was quickly adopted over creatinine.

**References**


(Note: DP has prepared an extensive set of abstracts and references on this topic and would be happy to send them upon request to davidplaut@yahoo.com)
Questions for STEP Participants

Answer questions only on the official STEP answer sheet. If you do not have the official STEP answer sheet, a year’s supply can be obtained (at no cost), simply by writing to: STEP Program Answer Sheets, American Medical Technologists, 10700 W. Higgins Road, Suite 150, Rosemont, IL 60018, or by fax: 847/823-0458, or by e-mail: paula.simoncini@amt1.com.

In addition to marking your answers, be sure to include all the required information on the answer sheet and a processing fee of $3.00 per article.

In the following, choose the one best answer for each question.

1. GFR stands for
   A. Glomerular fixation rate
   B. Glomerular filtration reaction
   C. Glomerular filtrate rate
   D. Glomerular filtration response

2. GFR increases by about 1% per year after age 40.
   A. True
   B. False

3. Kidney disease is associated with which of these diseases?
   A. Coronary artery disease
   B. Diabetes
   C. Hypertension
   D. All of these

4. Acute renal failure is responsible for 4–7% of hospitalizations.
   A. True
   B. False

5. Which one of these has not been used to estimate GFR?
   A. BUN
   B. Albumin
   C. Insulin clearance
   D. Radioisotopic clearance

6. Cystatin C has a molecular weight of about
   A. 130
   B. 1,300
   C. 13,000
   D. 130,000

7. eGFR will be accurate to within about 10% in 95% of the people tested.
   A. True
   B. False

8. Cystatin C may be a more accurate test in kidney transplant patients.
   A. True
   B. False

9. Cystatin C has been found to change before creatinine in acute kidney disease.
   A. True
   B. False

10. Changes in cystatin levels may assist the clinician in adjusting the dosage of certain medications.
    A. True
    B. False