EDUCATIONAL COMMENTARY – RENAL FUNCTION TESTING

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LEARNING OUTCOMES

On completion of this exercise, the participant should be able to

- describe the role of the glomerulus in renal function.
- compare the usefulness of the different equations for calculating clearance or the estimated glomerular filtration rate (eGFR).
- discuss the analytic and physiologic concerns with the measurement of creatinine and its use in estimating the GFR.
- describe the use of cystatin C as a renal function biomarker.
- apply the criteria for categorizing GFR and urinary albumin values in the setting of chronic kidney disease (CKD).

Introduction

Although the kidneys are involved in several homeostatic functions (e.g., acid-base balance and electrolyte and blood pressure regulation), their best known function is to filter the blood, retaining needed constituents and removing metabolic waste products for excretion in urine. The basic functional unit of the kidneys is the nephron. Within each nephron, the first step in the filtration of blood occurs at the glomerulus, a network of capillaries. After filtration, secretion and reabsorption occur in the tubules of the nephrons. The normal kidney contains approximately one million nephrons, which provide reserves of function. Researchers have developed multiple methods for estimating actual kidney function to diagnose, monitor, and treat chronic kidney disease (CKD).

Clearance and Glomerular Filtration Rate

The initial blood tests for assessing kidney function are creatinine and urea nitrogen measurements, which are frequently included in a basic or comprehensive metabolic panel. Although elevated levels suggest conditions affecting kidney function, the tests cannot detect early renal disease; because of the kidneys' reserves of nephrons, significant loss of nephrons occurs before urea nitrogen and creatinine concentrations become elevated. A better indicator of renal function is the glomerular filtration rate (GFR), which correlates with the amount of functioning nephrons. The GFR is the average volume of blood filtered per unit of time by each glomerulus, multiplied by the total number of glomeruli. The average GFR for healthy white adults, based on an average body surface area (BSA) of 1.73 m^2, is approximately 120-130 mL/min/1.73 m^2. The GFR can be directly measured using exogenous

compounds such as inulin, iohexol, or iothalamate, which are completely filtered by the glomeruli without subsequent secretion or absorption. Because direct measurement of GFR using these compounds has several disadvantages, including time, expense, inconvenience, and the rare risk for allergic reactions, it is usually performed in a research setting.

While measuring GFR using exogenous compounds is difficult, the GFR can be indirectly measured by calculating clearance, using measured serum and urine concentrations of compounds filtered through the kidneys. The endogenous compound creatinine can be used as an indirect measurement of glomerular function. Nearly all endogenous creatinine is filtered through the glomeruli and excreted in the urine. In fact, for compounds that are 100% filtered and neither secreted nor reabsorbed in the tubules, the clearance equals the GFR.

Creatinine Clearance and the Cockroft Gault Equation

The creatinine clearance (C_{CR}) in mL/min can be calculated using creatinine concentrations in plasma and in a timed (usually 24-hour) urine sample using this equation:

$$\mathbf{C_{CR} = UV / P \times 1.73 / A}$$

where P is the plasma creatinine in mg/dL, U is the urine creatinine in mg/dL, and V is the total volume of urine in mL divided by the minutes of the timed collection [1440 for a 24-hour collection].

Creatinine clearance is influenced by BSA, and the clearance can be adjusted for an individual's BSA by dividing the average BSA (1.73 m^2) by the individual's BSA (represented by A in the equation) determined using height and weight tables and calculations.

The creatinine clearance is a surrogate for the GFR, and values are often similar to the values of a measured GFR. Shortcomings of using creatinine clearance include the active secretion of creatinine in the tubules, difficulty obtaining an accurately timed, complete urine sample, and the influence of factors such as muscle mass and diet on serum creatinine levels.

In a 1976 study involving 249 subjects, Cockroft and Gault[1] developed the following modification of the creatinine clearance equation.

$$\mathbf{C_{CR} = \frac{(140 - age) \times (wt\ in\ kg) \times 0.85\ (if\ female)}{72 \times (serum\ creatinine\ in\ mg/dL)}}$$

When many prescription medications requiring dosage adjustment for patients with kidney disease were initially approved by the U.S. Food and Drug Administration, the Cockroft-Gault equation was used for

dosage adjustment calculations. For this reason many physicians continue to prefer this equation to measure renal function when adjusting dosage.

Estimated GFR: MDRD and CKD-EPI

Several large population studies have contributed to the further development of estimated GFR (eGFR) calculations utilizing serum creatinine levels and demographic information (age, sex, race). The National Kidney Disease Education Program (NKDEP) recommends that eGFR be reported with a serum creatinine (S_{cr}) concentration, using the equation developed in the Modification of Diet in Renal Disease (MDRD) study.[2]

$$\textbf{GFR (mL/min/1.73 m}^2\textbf{)} = 175 \times (S_{cr})^{-1.154} \times (\text{Age})^{-0.203} \times 0.742 \text{ (if female)} \times 1.212 \text{ (if black)}$$

This MDRD equation has been shown to underestimate the GFR at higher values, and it is recommended that values above 60 mL/min/1.73 m^2 be reported as "greater than 60 mL/min/1.73 m^2." The MDRD equation can be used for drug dosage adjustments, but the Cockroft Gault equation is often requested by physicians.[3]

In 2009, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) developed another eGFR equation using the same variables (serum creatinine [S_{cr}], age, sex, race):[4]

$$\text{GFR} = 141 \times \min(S_{cr}/\kappa, 1)^{\alpha} \times \max(S_{cr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (if female)} \times 1.159 \text{ (if black)}$$

where κ is 0.7 for females and 0.9 for males, α is –0.329 for females and –0.411 for males, min indicates the minimum of S_{cr}/κ or 1, and max indicates the maximum of S_{cr}/κ or 1.

This CKD-EPI equation is more accurate than the MDRD equation for GFR values above 60 mL/min/1.73 m^2 and is the recommended equation if a laboratory chooses to report a numerical value for values greater than 60.

Creatinine Measurement

The analytic quality of creatinine measurement affects all creatinine-based eGFR or clearance equations. Many of these equations were developed using older creatinine assays. In 2007, the National Institute of Standards and Technology (NIST) made available a creatinine standard traceable to the values obtained using the isotope dilution mass spectrometry (IDMS) creatinine reference procedure. Laboratories should verify that the creatinine assay and the eGFR equation they select use IDMS-traceable calibration. Another potential weakness of creatinine measurement is both the imprecision and inaccuracy at concentrations below 0.6 mg/dL.

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Interpreting eGFR Results

Several variables should be considered when interpreting eGFR results. Creatinine-based equations should not be used if the patient has any condition, such as acute kidney injury, that causes concentrations of serum creatinine to change rapidly. Also, creatinine concentrations depend on body mass and diet, and some medications may interfere with the measurement of creatinine. It must be remembered that the eGFR is not the measured GFR; the equations for estimating GFR were developed from population-based data. For any particular individual, the eGFR may not correlate closely with the measured GFR. The performance measure used for these estimating equations is the P30, which refers to the percentage of eGFR values that are within 30% of the measured GFR. The P30 for the MDRD and CKD-EPI are 77.2% and 79.9%, respectively. With these performance indicators, it is evident that equations that produce more consistent and accurate estimates of the GFR are needed. Finally, in most studies, the population was not diverse, which may limit the usefulness of the equations developed using these data. In particular, there are few, if any, studies in the pediatric population, and neither the MDRD nor CKD-EPI equations are appropriate for use in pediatric patients.

Cystatin C

Serum levels of the low molecular weight protein cystatin C also reflect renal function. Cystatin C is filtered by the glomeruli, reabsorbed, and catabolized by the tubules. Increases in blood levels of cystatin C correlate with a decline in renal function, and cystatin C levels appear to vary less with age, sex, race, and muscle mass than creatinine levels. Cystatin C increases are an earlier indicator of acute kidney injury in patients in intensive care and a better predictor of mortality in patients with CKD, heart failure, or cardiovascular disease. Several eGFR equations using cystatin C have been developed, including the following equation by the CKD-EPI group.[5]

$$\mathbf{GFR_{cysC} = 127.7 \times CysC^{-1.17} \times age^{-0.13} \times 0.91\ (if\ female) \times 1.06\ (if\ black)}$$

Variations of this equation have been developed for males and females specific for cystatin C values equal to, below, or above 0.8 mg/dL.[6] The CKD-EPI group also developed the following equation that utilizes cystatin C in combination with creatinine.[5]

$$\mathbf{GFR_{cysC\ Cr} = 177.6 \times S_{cr}^{-0.65} \times CysC^{-0.57} \times age^{-0.20} \times 0.82\ (if\ female) \times 1.11\ (if\ black)}$$

Equations for eGFR based on cystatin C may be useful when race is not specified and to confirm CKD when the eGFR is 45-59 mL/min/1.73 m^2.

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Chronic Kidney Disease: Diagnosis and Monitoring

Chronic kidney disease is defined in the 2012 guidelines of the Kidney Disease: Improving Global Outcomes (KDIGO) Chronic Kidney Disease Work Group as abnormalities of kidney structure or function that persist for more than three months and have implications for health. The guidelines list the criteria for CKD as a GFR of less than 60 mL/min/1.73 m^2 or the presence of one or more markers of kidney damage.[6] The eGFR is accepted as a measure of the GFR, and values are used to define the six categories of CKD shown below.

Category	GFR, mL/min/1.73 m^2	Description
G1	≥90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-29	Severely decreased
G5	<15	Kidney failure

The measurement of urine albumin (formerly called *microalbumin*) has been used to monitor patients at risk, particularly patients with diabetes mellitus, for early indications of renal dysfunction. The 2012 KDIGO guidelines added albuminuria and cause to the use of the GFR for risk prognosis, monitoring frequency, and referral decisions. When albuminuria is used as a criterion for the definition, staging, or prognosis of CKD, it should be expressed as the albumin excretion rate (AER) for a 24-hour sample or as the albumin to creatinine ratio (ACR) for a random sample.

The 2012 guidelines define three categories of albuminuria, A1 to A3, as shown below.

Category	AER, mg/24 h	ACR, mg/g	Description
A1	<30	<30	Normal to mildly increased
A2	30-300	30-300	Moderately increased
A3	>300	>300	Severely increased

Category A3 includes the nephrotic syndrome, in which albumin excretion is greater than 2200 mg/24 h or an ACR of greater than 2200 mg/g (>220 mg/mmol). The KDIGO guidelines include colored heat grid tables (green, yellow, orange, red) of GFR categories versus albuminuria categories to guide risk prognosis, frequency of testing, and referral decisions.[6]

Summary

Current renal function testing relies heavily on estimating the GFR, frequently using calculations that include serum creatinine concentration and demographic information (i.e., age, sex, or race). Creatinine concentrations should be obtained using methods and equations developed in studies using calibrations

traceable to the National Institute of Standards and Technology (NIST) IDMS creatinine reference material. The eGFR equation developed by the MDRD study is recommended by the NKDEP. When the MDRD equation is used, values greater than 60 mL/min/1.73 m^2 should be reported as "greater than 60 mL/min/1.73 m^2." When values greater than 60 mL/min/1.73 m^2 are to be reported, the recommended equation is the one developed from the CKD-EPI study. Cystatin C is a renal function biomarker that can be used alone or as a component of eGFR equations such as one developed by the CKD-EPI group. The 2012 guidelines of the KDIGO Chronic Kidney Disease Work Group include using the GFR value to categorize six stages of CKD and using urinary albumin levels for three categories of albuminuria. These guidelines combine the GFR and albuminuria categories to determine prognosis, monitoring frequency, and referral recommendations. A summary of the KDIGO recommendations can be accessed at http://www.nature.com/kisup/journal/v3/n1/pdf/kisup201277a.pdf.

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