Measuring and Assessing Kidney Function

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Summary: Assessment of kidney function is important for the detection and management of chronic kidney disease. The glomerular filtration rate (GFR) and level of albuminuria are two frequently used indices of kidney function assessment. Administration of an exogenous filtration marker to measure GFR and collection of urine for 24 hours to measure albumin excretion generally are considered the gold standard for GFR and albuminuria, respectively, but they are time consuming and onerous for the patient. Thus, in routine clinical practice, other methods are used more frequently to assess GFR and albuminuria. In this review, we discuss the role of GFR and albuminuria in staging of chronic kidney disease as well as the pros and cons and prognostic implications of various methods of assessment of GFR and albuminuria.
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Kidneys are essential to life. Through the regulation of osmolarity, acidity, and electrolytes, and the excretion of toxins and fluid, kidneys maintain the composition and volume of body fluids. Impairment in these functions can result in an excess of fluid and metabolites as well as disturbance of important regulatory processes. A persistent impairment in kidney function, called *chronic kidney disease* (CKD), is common, affecting up to 13% of the US population,[1] with one in two Americans expected to develop CKD during their lifetime.[2] The consequences of CKD are wide-ranging: persons with CKD may experience disease progression to kidney failure, and they disproportionately develop cardiovascular disease, infection, acute kidney injury, and all-cause mortality.[3–8] Thus, determining the level of kidney function is vital for the detection and management of CKD. Kidney function is assessed most commonly by the levels of glomerular filtration rate (GFR) and/or albuminuria.

GLOMERULAR FILTRATION RATE

The GFR is a physiological property determined by the permeability and surface area of the filtration site of the glomerular capillary wall, as well as the differences in hydraulic and oncotic pressures between the glomerular capillary and Bowman's space. In human beings, GFR usually signifies overall GFR, or the function of all single nephrons taken together. It is the key parameter in the clinical assessment of kidney function, and decrements in GFR largely correlate with deterioration in other kidney functions, including hormone production (eg, erythropoietin) and metabolic function (eg, participation in gluconeogenesis).

The normal value for GFR has been reported as 120 and 96 mL/min for men and women, respectively.[9] However, there can be considerable variation in GFR levels among individuals depending on their age, sex, and body size.[10] Within individuals, diet and time of day of the measurement can also affect GFR, thus an average GFR over a period of time may be the most accurate assessment of GFR.[11]

Glomerular Filtration Rate: Measurement

In the absence of methods to directly measure the number of nephrons and single-nephron GFR, overall GFR is measured indirectly from clearance of exogenous or endogenous markers. Measured GFR generally refers to the administration of an exogenous filtration marker such as inulin, iothalmate, iohexol, ethylenediamine tetraacetic acid (EDTA), or diethylene triamine pentaacetic acid (DTPA) either subcutaneously or intravenously. Clearance is assessed with serial measurements of serum and/or urine concentrations.

Filtration markers: renal handling and measurement issues

Inulin. Inulin is a small molecular compound that has ideal filtration marker properties: it is freely filtered at the glomerulus, and does not undergo synthesis, secretion, reabsorption, or metabolism by the kidney. Thus, urinary clearance of inulin is considered the gold standard measurement of GFR.[12] However, inulin is expensive, with complicated procedures for measuring clearance.[13] Classic measurement of inulin requires

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continuous intravenous infusion, multiple blood samples, and bladder catheterization, and consequently has considerable patient burden.

Iothalamate. An alternative exogenous filtration marker is iothalamate. Iothalamate is administered with a radioactive iodine label and measured using high-performance liquid chromatography. Unlike inulin, iothalamate is thought to undergo tubular secretion. Indeed, most studies comparing urinary clearance of iothalamate to inulin showed iothalamate clearance to be slightly higher than inulin clearance.[14,15] Measuring iothalamate clearance, however, is somewhat easier than measuring inulin clearance. Iothalamate can be given as a single bolus injection and does not require bladder catheterization.

Iohexol. Iohexol, a nonradioactive radiographic contrast agent, is an alternative exogenous agent.[16] Compared with inulin clearance, iohexol slightly underestimates measured GFR, which may suggest that it undergoes some tubular reabsorption or has protein binding properties.[17] Similar to iothalamate, measuring iohexol clearance is less cumbersome compared with inulin clearance, and iohexol is less expensive, widely available, and stable in biologic fluids. In addition, clearance typically is measured in plasma rather than in urine, obviating concerns about overcollection or undercollection.

EDTA and DTPA. Other less commonly used exogenous filtration markers for GFR measurement include EDTA and DTPA. Similar to iohexol, EDTA underestimates inulin clearance by 5% to 15%, suggesting tubular reabsorption.[18] However, only DTPA is commercially available in the United States. DPTA has a short half-life, thus posing a lower risk of exposure to radiation than iothalamate. However, DTPA has known protein-binding properties, which might lead to inaccuracy in GFR measurement. In addition, assays of DTPA are not standardized, making it difficult to compare measurements across different laboratories.

Creatinine. Urinary clearance of creatinine, an endogenous filtration marker, is a method to assess GFR. Creatinine, a small molecule (molecular weight, 113 Daltons), is endogenously produced by skeletal muscle and also derived from metabolism of dietary protein, and it is freely filtered by the glomerulus. The advantages of measuring urinary creatinine clearance are that it does not require external administration, and creatinine assays are standardized and widely available. However, creatinine is known to have tubular secretion, which is particularly pronounced in individuals with low kidney function.[19] Therefore, creatinine clearance tends to overestimate kidney function, likely with more inaccuracy among individuals with lower GFR. In addition, similar to the measurement of exogenous filtration markers, measuring urinary clearance is prone to error owing to overcollection or undercollection of urine.

Assessing clearance of filtration markers: urinary versus plasma clearance

Protocols for measuring clearance of filtration markers are complex, and both urinary and plasma clearance are subject to measurement errors.

Urinary clearance. Urinary clearance of a filtration marker directly estimates GFR using multiple urine collections after administration of the filtration marker (in the case of exogenous markers).[20] Unfortunately, timed urine collection can be difficult and error-prone, particularly in populations with urinary retention or incontinence.[21]

Plasma clearance. The rate of decrease in the plasma concentration of an exogenous filtration marker shows strong correlation with urinary clearance ($r > 0.90$).[17,22] However, the technique requires multiple blood samples over a relatively long amount of time and requires that there is little nonrenal excretion of a filtration marker.[23]

Others. Noninvasive procedures of counting radioactive exogenous filtration markers (eg, DTPA) in the kidneys and bladder have been investigated but showed poor correlation with urinary or plasma clearance.[24–26]

Glomerular Filtration Rate: Estimation

In clinical practice, GFR is most often estimated from serum levels of endogenous filtration markers rather than measured directly. There are estimating equations for creatinine, cystatin C, β_2-microglobulin (B2M), and β-trace protein (BTP).

Filtration markers: issues related to GFR estimation

Serum creatinine. Serum creatinine is the most widely available marker for GFR estimation in clinical practice, with broadly standardized assays to minimize intralaboratory variation.

Serum creatinine, however, is not a perfect filtration marker. Although it is neither metabolized nor reabsorbed by kidneys, creatinine is actively secreted by renal tubules. Moreover, serum creatinine can vary owing to non-GFR determinants, such as age, sex, race, diet, supplements, extremes of muscle mass, or medications such as cimetidine.[27]

Cystatin C. Cystatin C is the second most common endogenous marker used to estimate GFR. It is