Laboratory tests of renal function

Laura Chadwick

Ross Macnab

Abstract

The human kidney provides essential regulatory and excretory functions. Body water content, plasma electrolyte composition and plasma pH are all under the regulatory control of the kidney. In addition, the kidney provides a path of excretion for blood-borne, water-soluble, low-molecular-weight compounds. These include the end-products of protein metabolism, such as urea and creatinine, as well as foreign compounds with similar physicochemical characteristics and their metabolites. Endocrine activity of the human kidney includes the secretion of the hormones erythropoietin and renin and the activation of vitamin D by hydroxylation to its 1,25-dihydroxycholecalciferol form. The renal blood flow is immense, constituting 20–25% of resting cardiac output. The glomeruli form 170–200 litres of ultrafiltrate per day and the selective reabsorption of water and solutes results in the final formation of approximately 1.5 litres of urine. Here, commonly used laboratory tests of renal function are discussed, including glomerular filtration rate (GFR), creatinine clearance, serum creatinine concentration estimation of GFR, serum urea concentration, novel measures of renal function, emerging biomarkers for acute kidney injury, urinalysis, free water clearance and endocrine changes in renal disease. It must be noted, however, that these tests require a clinical assessment of the patient to allow meaningful interpretation.

Keywords Acute kidney injury; biomarkers; creatinine; creatinine clearance; glomerular filtration rate; renal function; urea; urinalysis

Royal College of Anaesthetists CPD matrix: 1A01, 1A03, 2A03

Learning objectives

After reading this article, you should:

- be able to list six laboratory tests that assess renal function
- know how to calculate glomerular filtration rate
- be able to state normal blood and urine biochemistry values

Assessment of renal function

The assessment of renal compromise requires a number of laboratory investigations in conjunction with a thorough clinical evaluation. Deviation from 'normal' levels of many blood and urinary constituents can reflect renal insult or systemic disorder.

Glomerular filtration rate (GFR)

This is the rate at which substances are filtered from the blood of the glomeruli into the Bowman's capsules of the nephrons. It is an overall index of renal function calculated by the clearance of specific substances. Endogenous substances should have a constant plasma concentration. Any substance freely filtered by the glomerulus and not subsequently secreted, reabsorbed or metabolized by the distal parts of the renal system has a clearance equivalent to the GFR. Renal clearance is the volume of plasma cleared of a specific substance per unit time. It is measured in ml/minute and can be derived using the following formula:

$$C_s = (U_s \times V)/P_s$$

Where C_s is the volume of plasma cleared of the substance per minute, U_s is the urinary concentration of the substance, V is the volume of urine produced per minute and P_s is the plasma concentration of the substance.

The clearances of many substances have been measured and used as an index for GFR. Exogenous markers include the carbohydrate compound inulin, ^{124}I-iothalamate and ^{48}Cr-EDTA. Practical difficulties in the administration and measurement of these substances preclude their usefulness in clinical settings, so they remain predominantly utilized in research. Therefore, the common practice is to use endogenous compounds as markers for GFR (Table 1).

Creatinine clearance

Creatinine is the most commonly used endogenous marker for renal function. It is a product of muscle metabolism that is freely filtered at the glomerulus. Yet creatinine is also secreted in small amounts in the proximal tubule resulting in a small overestimation of GFR, the impact of which is attenuated by the plasma creatinine assay, which generally also leads to an overestimation of the actual concentration of creatinine. The measurement of the clearance of creatinine normally involves a 24-hour collection of urine and a measurement of serum creatinine concentration, assumed to represent the steady-state concentration for the measurement period. A clearance value is then given and expressed in terms of millilitres per minute, thus giving an interpretable value for estimation of the GFR. Shorter time periods for collection, for example 2 hours, have been used in catheterized patients on an intensive care unit. The limitations of this method include collection errors and inconvenience for the patient.

Creatinine-based equations for glomerular filtration rate

The predictions of GFR made from serum creatinine levels are more convenient and are a mainstay of modern GFR assessment. However, it is less than ideal as serum creatinine levels are affected by sex, age, muscle mass, abnormal volumes of distribution, exercise and ethnicity.

Several mathematical models have been generated aiming to increase the extent to which serum creatinine concentration reflects actual GFR. The most commonly used are the Cockroft–Gault (CG) and modification of diet in renal disease (MDRD) formulae. The CG model estimates creatinine clearance (eC_{cr}), and hence GFR, based on serum creatinine, age, sex and body

Laura Chadwick *MBBS BMedSci (Hons) is a Foundation Year 2 Doctor in the North Western Deanery, UK. Conflicts of interest: none declared.*

Ross Macnab *BSc MB ChB FRCA is a Consultant in Anaesthesia at the Manchester Royal Infirmary, UK. Conflicts of interest: none declared.*

Equations for assessment of renal function

1 The Cockroft-Gault equation (UK)

$eC_{cr} = \frac{(140-Age)\times Weight\ (Kg)\times(constant)}{Serum\ creatinine\ (\mu mol/litre)}$

eC_{cr} = estimated creatine clearance

The constant is 1.23 for men and 1.04 for women.

This formula provides a simple way to estimate GFR.

2 The Modification of Diet in Renal Disease Study Group equation

eGFR (ml/minute/1.73 m^2) = 186 × Serum Creatinine (μmol/litre)$^{-1.154}$ × Age$^{-0.203}$ × 1.21(if black) × 0.742 (if female)

3 CKD EPI equation (for estimating GFR expressed for specified race, sex and serum creatinine in mg/dl)

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

where:

S_{cr} is serum creatinine in mg/dl,

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.

4 The Schwartz equation

$eC_{cr}(ml/minute/1.73\ m^2) = \frac{length\ in\ cm\times k}{serum\ creatinine\ (mg/dl)}$

k = 0.33 for prem infants

k = 0.45 for infants term to 1 year

k = 0.55 for children 1 year to 13 years

k = 0.70 in adolescent males (females constant remains at 0.55)

5 Free Water Clearance (FWC)

$FWC = V(1-U_{osm}/P_{osm})$

V = urine volume

U_{osm}= urine osmolality

P_{osm} = plasma osmolality

Table 1

mass. The original formula used weight in kilogrammes and creatinine in milligrammes per decilitre, as is standard in the USA:

$$eC_{cr} = ((140 - age) \times weight\ (kg) \times (0.85\ \textit{if female}))/72 \times serum\ creatinine\ (mg/dl)$$

Because serum creatinine in the UK is measured in micromoles per litre, the formula is modified and a constant is used for both men and women to complete the estimation:

$$eC_{cr} = ((140 - age) \times weight(kg) \times (constant))/serum\ creatinine(\mu mol/litre)$$

The constant is 1.23 for men and 1.04 for women. This formula is well supported as it provides a simple way to estimate GFR but overestimates GFR in individuals who are obese or oedematous and does not account for ethnicity.

The MDRD Study Group developed an alternative to this formula that was indexed to body surface area. In its original form, it used six measurements to estimate GFR (eGFR), including blood urea nitrogen (BUN) and albumin levels. A basic four-variable form of the calculation containing serum creatinine, age, race and gender is:

$$eGFR(ml/minute/1.73m^2) = 186 \times (serum\ creatinine(\mu mol/litre)/88.4)^{-1.154} \times age^{-0.203} \times 1.21(if\ black) \times 0.742(if\ female)$$

However, the MDRD estimate is a poor measure of GFR in healthy individuals without renal pathology.[1] For initial diagnosis of chronic kidney disease the CKD-EPI formula is recommended by NICE as the most appropriate method to estimate GFR; it is based on the four-variable form of the MDRD equation but is more accurate, especially at higher GFR.[2]

These equations are not validated in children, in whom an alternative, the Schwartz equation, should be used. Height in centimetres is multiplied by an age-dependent constant; this total is then divided by the serum creatinine concentration to give an estimation of GFR indexed to body surface area.

Creatinine-based equations have many limitations, reflecting the variability of creatinine production with many factors. The diuretics spironolactone and triamterene, as well as other drugs such as trimethoprim, cimetidine and probenecid, interfere with tubular secretion of creatinine, and thus can increase serum creatinine concentrations while not reflecting alterations in GFR. Extremes of muscle mass or breakdown, pregnancy, very low body mass index, creatinine supplements or rapidly changing renal function impair accuracy and extrapolation of GFR.

Note that the above equations are based on an assumption of stable creatinine production and excretion and were designed to reflect chronic kidney disease. These equations are therefore inappropriate in the assessment of acute kidney injury (AKI).[1]

Creatinine and acute kidney injury

Serum creatinine levels are a longstanding and convenient method of assessing AKI. Yet in addition to the numerous factors influencing serum creatinine levels outlined above a decline in GFR is also associated with increased extrarenal creatinine degradation. Subsequently serum creatinine levels underestimate the extent of renal function deterioration. Furthermore, a small increase in serum creatinine within its normal range reflects a large decrease in GFR hence early rises in creatinine over short periods of time require close scrutiny (Figure 1).[3] Moreover, serum creatinine levels lag behind the acute injury process, with levels only rising a day or so after the initial renal insult. In summary serum creatinine concentration is limited in reflecting the extent of renal damage in AKI and is a late diagnostic aid.

Serum urea

Serum urea has long been used as a marker of renal dysfunction. However, it is neither a sensitive nor specific test and is a poor indicator of GFR. Serum urea levels can be raised by increased production, as seen after a nitrogenous dietary load, or decreased excretion, as seen in renal dysfunction. Levels may also be falsely low in decreased production as seen in liver failure.

Novel measures of renal function

Serum cystatin C

This alkaline non-glycosylated protein is produced at a constant rate by almost all nucleated cells and is freely filtered at the