Laboratory tests of renal function

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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.

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 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 for excretion. Here, commonly used laboratory tests of renal function are discussed, including glomerular filtration rate (GFR), creatinine clearance, serum creatinine concentration estimation of GFR, cystatin C assay, serum urea concentration, 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 creatinine; creatinine clearance; glomerular filtration rate; renal function; urea; urinalysis

Assessment of renal function

The assessment of renal compromise requires a number of laboratory investigations in conjunction with a thorough clinical evaluation (Box 1). Deviation from 'normal' levels of many blood and urinary constituents can reflect renal insult or systemic disorder (Table 1).

Glomerular filtration rate

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 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 glomerular filtration rate (GFR).[1–3] Renal clearance is calculated using a formula that equates the total mass of substance cleared from plasma to that found in urine:

$$C_s \times P_s = U_s \times V$$

where C_s is the volume of plasma containing the substance, P_s is the plasma concentration, U_s is the urinary concentration of the substance and V is the urinary volume containing the filtered substance. Rearranging the equation and expressing the volumes as millilitres per minute gives us the equation for clearance:

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

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 ^{51}Cr-EDTA.

Equations for assessment of renal function

1 The Cockroft–Gault equation (UK)
eC_{cr} = (140 – age) × weight (kg) × (constant)/serum creatinine (μmol/l)
where eC_{cr} is the estimated creatine clearance; the constant is 1.23 for men and 1.04 for women. This formula provides a simple way to estimate glomerular filtration rate (GFR).
2 The Modification of Diet in Renal Disease Study Group equation
eGFR (ml/min/1.73 m^2) = 186 × serum creatinine (μmol/l) – 1.154 × age – 0.203 × 1.21 (if black) × 0.742 (if female)
3 The Schwartz equation
eC_{cr} (ml/min/1.73 m^2) = (length in cm × k)/serum creatinine(mg/dl)
where k is 0.33 for premature infants, 0.45 for infants term to 1 year, 0.55 for children 1–13 years and 0.70 in adolescent males (constant for females remains at 0.55).
4 Free water clearance (FWC)
$FWC = V(1 - U_{osm}/P_{osm})$
where V is the urine volume, U_{osm} is the urine osmolality and P_{osm} is the plasma osmolality.

Box 1

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Normal values[a]

Blood biochemistry	Urine biochemistry
Sodium 132–144 mmol/l	Sodium 100–200 mmol/24 h
Potassium 3.5–5.5 mmol/l	Potassium 30–90 mmol/24 h
Urea 3.5–7.4 mmol/l	Urate 3–12 mmol/24 h
Creatinine 44–80 μmol/l	Protein < 0.15 g/24 h
Chloride 95–110 mmol/l	Creatinine 9–17 mmol/24 h
Venous bicarbonate 24–30 mmol/l	Creatinine clearance 120 ml/min
Urate (male) 0.17–0.48 mmol/l	
Urate (female) 0.14–0.39 mmol/l	
Plasma osmolality 275–295 mosmol/kg	
Anion gap ($Na^+ + K^+$) – ($HCO^-_3 + Cl^-$) 12–16 mmol/l	

Reference ranges quoted from the Biochemistry Laboratories at the Manchester Royal Infirmary, 2009.
[a] Always consult local laboratory for values.

Table 1

Practical difficulties in the administration and measurement of these substances preclude their usefulness in clinical settings, so they remain predominantly research tools. Therefore, the common practice is to use endogenous compounds as markers for GFR.

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 and secreted in small amounts in the proximal tubule. This results 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 by also measuring non-creatinine chromogens(such as acetone and ascorbic acid). 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.[4] The limitations of this method include collection errors and inconvenience for the patient. The predictions of GFR made from serum creatinine levels are more convenient and are a mainstay of modern GFR assessment.

Creatinine-based equations for glomerular filtration rate

Creatinine concentration alone can be used to estimate GFR by a number of mathematical models. 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 mass. The original formula used weight in kilograms and creatinine in milligrams per decilitre, as is standard in the USA:

eC_{cr} = ((140 − age) × weight (kg) × (0.85 *if female*))/72 × serum creatinine (mg/dl)

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

eC_{cr} = ((140 − age) × weight (kg) × (constant))/serum creatinine (μmol/l)

The constant is 1.23 for men and 1.04 for women. This formula provides a simple way to estimate GFR.

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 and albumin levels. A basic four-variable form of the calculation containing serum creatinine, age, race and gender is:

eGFR (ml/min/1.73 m^2) = 186 × (serum creatinine (μmol/l)/88.4)$^{-1.154}$ × age$^{-0.203}$ × 1.21 (if black) × 0.742 (if female)

These equations are not validated in children, in whom an alternative, the Schwartz equation, should be used. (Box 1) 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 or rapidly changing renal function impair accuracy and extrapolation of GFR. It must be noted also that a rise in plasma creatinine concentration is regarded as a late sign of renal dysfunction, with estimates of a reduction in GFR of more than 50% occurring before there is any alteration in serum creatinine.

Serum urea

As a breakdown product of hepatic protein metabolism urea has important physiological functions in the maintenance of the renal concentrating function and provides the route of excretion of nitrogenous waste. Elevated urea levels may indicate renal impairment, but this is a non-specific finding and can be related to other things such as the absorption of blood following gastrointestinal haemorrhage. Urea-based models are to be regarded as less sensitive and specific than creatinine-based models.

Serum cystatin C

This alkaline non-glycosylated protein is produced at a constant rate by almost all nucleated cells. It is freely filtered at the glomerulus and is almost completely reabsorbed and catabolized in the proximal tubule. Estimation of the GFR using cystatin C (e.g. the Filler equation)[1] has been found to compare favourably with creatinine-based methods. Although initially it was thought that serum levels of cystatin C were independent of age, sex,