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Self-test questions

The following statements are either true or false (answers on page 23)

5. When changing from one antidepressant to another it can be difficult to differentiate discontinuation symptoms from adverse effects of the new medication.
6. After a patient has recovered from depression, the antidepressant dose is usually tapered off.

ABNORMAL LABORATORY RESULTS

Creatinine clearance and the assessment of renal function

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SYNOPSIS

The selection of the most appropriate measurement of renal function depends on the clinical question being asked, the accuracy required and the inconvenience to the patient. Serum creatinine and calculated creatinine clearance yield a reasonable estimation of renal function with minimal cost and inconvenience. A urinary creatinine clearance is more accurate if the urine collection is complete. Isotopic measurement of glomerular filtration rate can be used when greater accuracy is required, when renal function is poor or muscle mass is significantly outside the normal range. Glomerular filtration rate should be corrected for body surface area and interpreted in the context of physiological effects such as pregnancy and blood pressure.

Index words: glomerular filtration, kidney.

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Introduction

Estimation of renal function is important in a number of clinical situations (Table 1), including assessing renal damage and monitoring the progression of renal disease. Renal function should also be calculated if a potentially toxic drug is mainly cleared by renal excretion. The dose of the drug may need to be adjusted if renal function is abnormal.

Renal function and glomerular filtration rate

The glomerulus is a high-pressure filtration system, composed of a specialised capillary network. It generates an ultrafiltrate that is free of blood and significant amounts of blood proteins. Renal damage or alterations in glomerular function affect the kidneys' ability to remove metabolic substances from the blood into the urine.

Glomerular filtration rate (GFR) is the rate (volume per unit of time) at which ultrafiltrate is formed by the glomerulus. Approximately 120 mL are formed per minute. The GFR is a direct measure of renal function. It is reduced before the onset of symptoms of renal failure and is related to the severity of the structural abnormalities in chronic renal disease. The GFR can

Table 1

Indications for renal function testing

Test	*Setting*	*Clinical indication*
Serum creatinine	Screening for renal disease	Hypertension Urine abnormalities Potential renal diseases (e.g. diabetes) Non-specific symptoms (e.g. tiredness)
	Monitoring renal function	Chronic renal disease Transplantation Drug toxicity
Calculated GFR/ creatinine clearance	Initial evaluation of renal disease	Glomerulonephritis Proteinuria Chronic renal failure Chemotherapy dosing
	Monitoring of renal disease	Glomerulonephritis Chronic renal failure
Isotopic GFR	Accurate GFR	Monitoring therapy in glomerulonephritis
	Low levels of GFR	Deciding when to start dialysis Chronic renal failure
	Altered muscle mass	Body builder Chemotherapy dose in wasted patient

GFR = Glomerular filtration rate

predict the signs and symptoms of uraemia, especially when it falls to below 10–15 mL/min. Unfortunately it is not an ideal index, being difficult to measure directly, and is sometimes insensitive for detecting renal disease.

Tubular function

Although glomeruli control the GFR, damage to the tubulointerstitium is also an important predictor of GFR and progression towards renal failure. Renal tubules make up 95% of the renal mass, do the bulk of the metabolic work and modify the ultrafiltrate into urine. They control a number of kidney functions including acid-base balance, sodium excretion, urine concentration or dilution, water balance, potassium excretion and small molecule metabolism (such as insulin clearance). Measurement of tubular function is impractical for daily clinical use, so we usually use the GFR to assess renal function.

Normal range for GFR

The GFR varies according to renal mass and correspondingly to body mass. GFR is conventionally corrected for body surface area (which equates with renal mass), which in normal humans is approximately 1.73m^2 and represents an average value for normal young men and women. When the GFR is corrected for body surface area, a normal range can be derived to assess renal impairment.

The normal corrected GFR is 80–120 mL/min/1.73m^2, impaired renal function is 30–80 mL/min/1.73m^2 and renal failure is less than 30 mL/min/1.73m^2. The corrected GFR is approximately 8% lower in women than in men, and declines with age at an annual rate of 1 mL/min/1.73m^2 from the age of 40.

In addition to ageing there are a number of physiological and pathological conditions that can affect GFR, including pregnancy, hypertension, medications and renal disease. These conditions should be considered when interpreting a patient's GFR.

Measurement of GFR by renal clearance

The GFR cannot be directly measured in humans, but can be estimated from urinary clearance of a substance (x), given by the equation:

$$\text{Urinary clearance (x)} = \frac{U_x V}{P_x}$$

where U is the urinary concentration of an ideal filtration marker of x, V is the urine flow rate and P_x is the average plasma concentration of x.

An 'ideal filtration marker' is a substance that is freely excreted by glomerular filtration, without tubular reabsorption or secretion. The clearance of ideal filtration markers can be shown mathematically to be an accurate estimate of GFR.

The balance concept

The plasma concentration of a substance in a steady state depends on the balance of the input (from either endogenous production or exogenous intake) and the clearance from the blood (by either excretion or metabolism). When an ideal filtration marker is used (and there is no hepatic metabolism or non-renal clearance) and the input is constant (for example, by endogenous creatinine generation), then the plasma concentration is inversely proportional to the GFR.

Methods to estimate GFR

The GFR can be estimated from the serum concentration of filtration markers (such as creatinine or urea) or the renal clearance of these markers. Each method has its advantages and disadvantages in terms of accuracy, cost and convenience (Table 2).

Serum creatinine or calculated creatinine clearance are the most convenient estimates of GFR, requiring only a single blood sample. Measured creatinine clearance requires a 24-hour urinary collection while isotopic methods involve intravenous injection of a nuclear tracer, and two subsequent blood samples to estimate clearance. Both these methods are more expensive and less convenient to the patient. Selection of the most appropriate test depends on the clinical question, the required accuracy and cost (Table 2).

Serum creatinine

Serum creatinine is commonly used to screen for renal disease or to investigate urinary sediment abnormalities, hypertension or non-specific symptoms such as tiredness. It is also used to monitor renal function after transplantation, in chronic renal disease, and in patients with glomerulonephritis taking disease-modifying therapy. Serum creatinine can also be used to monitor the effects of nephrotoxic drugs such as gentamicin or anticancer drugs. Serum urea can be used to estimate renal function but is highly variable, less accurate and prone to errors.

Serum creatinine is mainly produced by the metabolism of creatine in muscle, but also originates from dietary sources of creatinine such as cooked meat. Creatinine generation from the muscles is proportional to the total muscle mass and muscle catabolism. In people with a relatively low muscle mass, including children, women, the elderly, malnourished patients and cancer patients, the serum creatinine is lower for a given GFR. There is a danger of underestimating the amount of renal impairment in these patients, as their serum creatinine is also relatively lower. For example, the GFR may be reduced as low as 20–30 mL/min in a small elderly woman, while her serum creatinine remains in the upper range of normal.

Table 2

Assessment of renal function

Method	*Accuracy*	*Cost*	*Convenience*
Serum creatinine	**	$	***
Serum urea	*	$	***
Calculated creatinine clearance	***	$	***
Measured creatinine clearance	** to ***	$$	*
Isotopic glomerular filtration rate	****	$$$	*

Creatinine is an imperfect filtration marker, because it is secreted by the tubular cells into the tubular lumen, especially if renal function is impaired. When the GFR is low, the serum creatinine and creatinine clearance overestimate the true GFR. Some drugs (such as cimetidine or trimethoprim) have the effect of reducing tubular secretion of creatinine. This increases the serum creatinine and decreases the measured creatinine clearance (Table 3). Paradoxically, when these drugs are used, a more accurate measurement of GFR is obtained as it is largely free from the error contributed by the physiological tubular secretion of creatinine.

Calculated creatinine clearance

As serum creatinine is so highly dependent on age, sex and body size, a number of corrections and formulae have been developed to estimate the muscle mass and assumed creatinine production. The most well-known formula is the Cockcroft-Gault formula, which is relatively simple to use and reasonably accurate. It is given as:

$$\text{Creatinine clearance (mL/min)} = \frac{(140 - \text{age [yrs]}) \times \text{weight [kg]}}{\text{serum creatinine (micromol/L)}}$$

Multiply result x 1.22 for male patients

This is a good estimate of GFR, but it becomes inaccurate when a patient's body mass is significantly outside the normal range (for example, morbid obesity or severe malnutrition) or when renal function is very impaired (i.e. GFR <20 mL/min). In these circumstances an isotopic method can be used if the GFR needs to be accurately measured.

Creatinine clearance

Creatinine clearance has been used for many decades to estimate GFR. It involves a 24-hour urine collection to measure creatinine excretion. As the same sample can be used to measure the protein excretion rate, creatinine clearance is often used for the initial evaluation of renal diseases, such as glomerulonephritis. It can also be used to monitor the progression of chronic renal failure, the response to therapy or to help decide when to start dialysis in patients with declining renal function.

The major problem with measuring creatinine clearance is that the collection may be incomplete; often urine is passed into the toilet rather than into the collection bottles. This results in an underestimation of renal function, and has led some commentators to recommend alternative measures such as calculated creatinine clearance or an isotopic GFR. In hospital, especially when the patient is catheterised, creatinine clearance provides an accurate estimate of GFR. Overestimation of the GFR occurs at low levels of renal function, due to tubular secretion of creatinine. This can be corrected by collecting the urine while the patient is taking cimetidine or by averaging a urea and creatinine clearance in a single 24-hour collection. To accurately define the GFR at low levels of renal function, an isotopic GFR is recommended.

Table 3

Errors in measurement of renal function using creatinine

	Effects on creatinine clearance	*Effects on serum creatinine*
Assay interference		
ketosis	Nil	↑
hyperbilirubinaemia	Nil	↑
cephalosporin	Nil	↑
Inhibition of tubular secretion of creatinine		
cimetidine or trimethoprim	↓*	↑
Alteration of creatine/creatinine load		
eating cooked meat	↑	↑
low protein diet	↓	↓
body building	Nil	↑
muscle wasting	Nil	↓
Renal disease	↓	↑

* becomes **more** accurate at low levels of GFR when increased tubular secretion of creatinine is blocked

Isotopic GFR

Isotopic GFR is the most accurate measurement of GFR, especially at low levels of renal function or with alterations of muscle mass. The most common isotopic marker is technetium 99m DTPA, given as a single injection. Two plasma samples are taken at 1–3 hours after injection. The GFR is calculated from the plasma clearance of the isotope. Isotopic GFR can be used for monitoring renal function over time, or in chronic renal failure patients approaching dialysis. Patients are usually tested every two to five years, because of the cost and inconvenience of the procedure.

Summary

Renal function can be evaluated by measuring the GFR. As it is not easy to measure the GFR directly, the serum creatinine concentration is often used to assess renal function. Creatinine clearance provides a more accurate assessment and can be calculated from the serum creatinine or more exactly from the results of a 24-hour urine collection. Isotopic methods can be used if a very accurate measurement of the GFR is required.

Self-test questions

The following statements are either true or false (answers on page 23)

7. In renal disease the creatinine clearance is increased.
8. Cimetidine can increase the serum concentration of creatinine.