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Clinical review

How to measure renal function in clinical practice

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The reliable measurement of renal excretory function is of great importance in clinical practice and in research. The introduction of routine reporting of estimated glomerular filtration rate and a new definition of chronic kidney disease has renewed interest in methods of measuring renal function. Coupled with this is the fact that several countries are moving towards population screening for renal impairment to try to reduce the associated increased cardiovascular risk. Accurate measurement is methodologically difficult so surrogate measures such as serum creatinine levels and prediction formulas (based on factors such as the patient's age, sex, and serum creatinine level) are more commonly used in routine practice. We describe routine and more specialised methods of assessing renal function and discuss estimated glomerular filtration rate.

The kidney has several interlinked functions (box). These depend on glomerular filtration rate, the unit measure of kidney function. Glomerular filtration rate can be defined as the volume of plasma cleared of an ideal substance per unit of time (usually expressed as ml/min). The ideal substance is one that is freely filtered at the glomerulus and neither secreted nor reabsorbed by the renal tubules.

Summary points

- Estimated glomerular filtration rate forms the basis for the classification of chronic kidney disease
- An estimated glomerular filtration rate of 60-89 ml/min/1.73 m^2 in the absence of other evidence of kidney disease does not signify chronic kidney disease and does not indicate that further testing is required
- Patients with chronic kidney disease are at high risk of cardiovascular disease
- Estimated glomerular filtration rates, calculated using the "4-v MDRD" based formula, are now routinely reported by biochemistry laboratories alongside serum creatinine results (except in non-validated patient groups)
- Serum creatinine levels or estimated glomerular filtration rates may be used to monitor changes in renal function in an individual patient
- Formal measurement of glomerular filtration rate is used for accurate assessment of renal function in potential kidney donors and in research studies
- Radioisotope or iothalamate methods require multiple blood samples and, if renal function is reduced, the duration of sampling may be up to 24 hours

Creatinine

Creatinine is the closest to an ideal endogenous substance for measuring glomerular filtration rate.[w1] Plasma creatinine is almost exclusively a product of the metabolism of creatine and phosphocreatine in skeletal muscle, although ingestion of meat may also contribute slightly.[w2 w3] In patients with stable renal function, serum creatinine levels are usually constant, with variability daily of about only 8%.[w4 w5] Creatinine is freely filtered at the glomerulus and is not reabsorbed, but up to 15% is actively secreted by the tubules.[w6] In advanced renal failure, excretion of creatinine through the gastrointestinal tract increases.[w7]

Creatinine clearance

Measuring the creatinine clearance using serum creatinine level and a timed urine collection gives an estimate of glomerular filtration rate:

creatinine clearance (ClCr) = (urine creatinine×volume)/serum creatinine

As a result of tubular secretion of creatinine, creatinine clearance tends to overestimate true glomerular filtration rate. This is a systematic error of fairly stable magnitude, however, until advanced renal failure is reached, allowing creatinine clearance to be a reasonable method of following changes of renal function in patients. The main problem with creatinine clearance is the requirement for urine collection over 24 hours; patients find this inconvenient and therefore collections are often inaccurate. Also a 25% daily variation in the values obtained using this method has been reported.[w8] Creatinine clearance is therefore no longer much used in clinical practice.

References w1-w21 are on bmj.com

Sources and selection criteria

We searched Medline from 1966 onwards using the search terms: "measurement of renal function", "modification of diet in renal disease", "Cockcroft and Gault", "radio-isotopes", "glomerular filtration rate", "inulin clearance", and "cystatin C"

We also referred to several textbooks, including the *Oxford Textbook of Clinical Nephrology* third edition (Oxford University Press) and *Comprehensive Clinical Nephrology* second edition (Mosby)

Urea

Serum urea is a less reliable marker of glomerular filtration rate than creatinine because levels are more vulnerable to change for reasons unconnected to glomerular filtration rate. A high protein diet, tissue breakdown, major gastrointestinal haemorrhage, and corticosteroid therapy can lead to an increase in plasma urea whereas a low protein diet and liver disease can lead to a reduction. Also, 40-50% of filtered urea may be reabsorbed by the tubules, although the proportion is reduced in advanced renal failure.[w9]

Mean of urea and creatinine clearance

In advanced renal failure the mean of urea and creatinine clearance may give a more accurate estimate of glomerular filtration rate than either clearance alone, as the effects of urea reabsorption and creatinine secretion tend to cancel each other out.[w10] It is the recommended method for estimating residual renal function[w11] in patients receiving dialysis.

Inulin clearance

No endogenous ideal substance exists for measuring glomerular filtration rate, so the standard method requires infusion of an exogenous agent, such as inulin. Inulin, a polymer of fructose (5200 daltons), is found in Jerusalem artichokes, dahlias, and chicory and was first used for measuring glomerular filtration rate in 1951.[w12] Its use is limited because purified inulin is expensive and difficult to measure and measuring glomerular filtration rate in this way is time consuming for both patients and clinicians. A bolus and infusion of inulin are given to achieve a steady plasma level, followed by collection of regular blood and urine samples over several hours for inulin estimation. This method (nowadays often using polyfructosan (Inutest; Fresenius, Austria) is only used in research studies when very accurate estimation of renal function is necessary.

Functions of kidney related to glomerular filtration rate

- Excretion of:
  - Nitrogenous waste
  - Sodium
  - Free water
  - Potassium
  - Phosphate
  - Water soluble medicines (for example, digoxin, gentamicin)
- Control of blood pressure
- Acid-base balance
- Secretion of erythropoietin
- Hydroxylation of vitamin D1 (activation)
- Gluconeogenesis in the fasting state
- Catabolism of peptide hormones (including insulin)

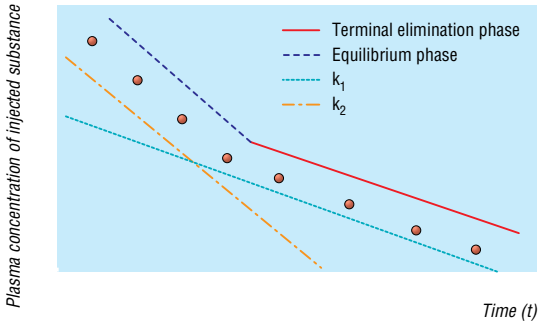

Fig 1 Biphasic disappearance of injected substance from plasma. During the first phase, equilibration of the injected substance takes place between the intravascular and extravascular compartments (k_2). Once equilibration has been reached, the decline in plasma levels (normally measured with a venous sample) should reflect removal of the substance from the arterial system through the kidneys. This is termed the terminal elimination phase (k_1)

Radioisotopic methods

From the late 1960s the use of radionuclides has offered an alternative method of estimating glomerular filtration rate that avoids some of the practical disadvantages of inulin clearance. Estimates using radionuclides correlate closely with inulin clearance.[1–4] Radionuclides are usually given as a single dose and the glomerular filtration rate calculated by their rate of disappearance from the plasma, obviating the need for urine tests. When a substance is given under these conditions, two phases of disappearance occur (fig 1):

Computer software is used to calculate the glomerular filtration rate based on data either from both phases (double pool) or from the terminal elimination phase (single pool). Single pool methods have the advantage that fewer plasma samples are required.

Radioisotopic methods have the disadvantage of precautions being required in handling and disposal of radioactive materials. They are also expensive and not suitable for use during pregnancy. Another important consideration is that the terminal elimination phase is significantly prolonged in advanced renal failure. In patients with moderate renal failure (glomerular filtration rate 30-59 ml/min) samples are taken for up to five hours after injection whereas in patients with advanced renal failure samples are required for up to 24 hours after injection.[5]

Radiocontrast agents

Radiocontrast agents were initially available in the 1960s but difficulties in chemical analysis and

unacceptable amounts of free iodine in the preparations limited their use in favour of radioisotopic agents.[w13] These problems have largely been resolved and radiocontrast agents now offer the advantages of radioisotopes without the concerns of radioactive substances. Agents currently in use are iothalamate (Conray; Mallinckrodt, St Louis, MO), siatrizoate meglumine (Hypaque; Amersham Health, NJ), and iohexol (Omnipaque; Amersham Health, NJ). Iohexol may be the agent of choice as it is relatively quick to use and its results are comparable to inulin clearance.[6 7]

Cystatin C

The past decade has witnessed an upsurge of interest in cystatin C as an endogenous glomerular filtration rate marker. Cystatin C is part of the cystatin "superfamily" of cysteine protease inhibitors. It is freely filtered at the glomerulus. Its use is, however, limited by higher variability of serum levels than creatinine (75% *v* 7%) between patients.[8] Also, serum levels are increased in malignancy,[w14 w15] HIV infection,[w16] and glucocorticoid therapy.[w17] At present cystatin C has no established role, but it may emerge as a useful way of identifying patients with early renal failure as part of screening programmes.[w18]

Prediction formulas

To circumvent the practical difficulties of formal measurement of clearance, several prediction formulas have been published. The most commonly used are the Cockcroft and Gault equation and formulas based on the modification of diet in renal disease study (fig 2). Given the limitations of serum creatinine in identifying renal failure, the increased use of prediction formulas, in particular the modification of diet in renal disease formulas, has been advocated.[9]

Cockcroft and Gault equation

The Cockcroft and Gault equation, which estimates creatinine clearance on the basis of serum creatinine level, age, sex, and weight, was one of the earliest prediction formulas[10] and is still widely used. It was based on creatinine excretion in men with normal renal function with a correction for women, based on three other studies[w19-w21]: it tends to overestimate renal function at lower levels, particularly when obesity or fluid overload is present, as the resultant increase in weight does not reflect an increase in muscle mass. However, as with creatinine clearance, this is largely a systematic error and the equation remains useful for following changes in renal function in a patient.

Modification of diet in renal disease formula

More recently Levey et al introduced a formula derived from data on patients with advanced renal failure in the modification of diet in renal disease study.[11–14] This is referred to as the "6-variable MDRD" or "6-v MDRD" formula.[15] This formula gives an estimate of glomerular filtration rate in millilitres per minute adjusted for body surface area of 1.73 m^2 and is based on a patient's age, sex, race, and levels of serum urea, serum creatinine, and serum albumin. By avoiding inclusion of weight, the formula is less prone to errors from fluid overload and obesity.

In 2000 a simplification of the modification of diet in renal disease formula using only patient's age, sex, race, and serum creatinine level was derived from the original data.[16] This is referred to as the "4-variable MDRD" or "4-v MDRD" formula. With the exception of race, the other variables required are normally provided routinely when a sample is submitted to the laboratory. It is therefore much easier for laboratories to report estimated glomerular filtration rate using this formula.

One important issue concerning the use of prediction formulas is that different laboratories use different methods for creatinine estimation. Some assays are more sensitive than others to non-creatinine chromogens, which falsely increase creatinine values. This error is magnified in prediction formulas, particularly in patients with higher levels of renal function.[17 18] To replicate as closely as possible the results obtained in the modification of diet in renal disease study, all serum creatinine values should ideally be determined using the methods of the Cleveland Clinic laboratory in the original modification of diet in renal disease study.[17 18] This raises problems for different providers of analytical systems and would not be straightforward to achieve. However, some of the difference in assay methods can be corrected for and there are plans to adopt correction factors throughout the United Kingdom. The United Kingdom National External Quality Assessment Service has played a key part in this change. When using a correction factor, the formula used is a slightly modified form of the 4-v MDRD formula.[19]

The modification of diet in renal disease formulas have been validated in an ever increasing number of patient groups, including elderly patients and recipients of renal transplants,[20–22] although concern has been expressed over reliability in different ethnic groups such as Chinese and Indian patients.[23 24] Also, as these formulas were based on data from patients with advanced renal failure, their validity has been questioned in patients with normal or near normal

Cockroft and Gault equation

Estimated creatinine clearance (Cl_{Cr}) = $\frac{(140\text{-age}) \times \text{weight} \times 1.2}{SCr}$ x (0.85 if female)

where age is expressed in years, SCr in μmol/l, and weight in kg[10]

6-variable MDRD[15]

$170 \times (S_{Cr}/88.4)^{-0.999} \times age^{-0.176} \times (SU/0.357)^{-0.170} \times (SAlb \times 10)^{+0.318}$ x (0.762 if female) x (1.180 if black)

where S_{Cr} = serum creatinine in μmol/l, SU = serum urea in mmol/l, SAlb = serum albumin in g/l, and age is expressed in years

4-variable MDRD[16]

$186.3 \times (S_{Cr}/88.4)^{-1.154} \times age^{-0.203}$ x (0.742 if female) x (1.21 if black)

where S_{Cr} = serum creatinine in μmol/l, and age is expressed in years

Modified 4-variable MDRD (traceable by isotope dilution mass spectrometry)[19]

$F \times 175 \times (S_{Cr}/88.4)^{-1.154} \times age^{-0.203}$ x (0.742 if female) x (1.21 if black)

where F = correction factor, S_{Cr} = serum creatinine in μmol/l, and age is expressed in years

Fig 2 Commonly used formulas for estimating renal function. MDRD=modification of diet in renal disease

Clinical relevance of the five stages of chronic kidney disease

Estimated glomerular filtration rate (ml/min)	Clinical significance	Stage of chronic kidney disease
≥90	With another abnormality*, otherwise regard as normal	1
60-89	With another abnormality*, otherwise regard as normal	2
30-59	Moderate impairment	3
15-29	Severe impairment	4
<15	Advanced renal failure	5

*Patients with estimated glomerular filtration rate ≥60 ml/min/1.73 m^2 should be regarded as normal unless they have evidence of kidney disease (persistent proteinuria or haematuria, or both, microalbuminuria in patients with diabetes, structural kidney disease such as polycystic kidney disease in adults or reflux nephropathy).

glomerular filtration rates. It is therefore recommended that they are not used routinely at levels greater than 60 ml/min/1.73 m^2. It should be stressed that these formulas are not valid in certain clinical settings such as acute renal failure, pregnancy, severe malnutrition, diseases of skeletal muscle, paraplegia, and quadriplegia, in children, or when renal function is changing rapidly.

Plans are in progress to report estimated glomerular filtration rates whenever measurement of serum creatinine is requested throughout the United Kingdom. Some centres have already started providing estimated glomerular filtration rates routinely and most centres should be doing so by the end of 2006. This is likely to identify large numbers of patients with reduced glomerular filtration rates who may have been overlooked when their renal function was assessed by serum creatinine levels alone: data from the United States suggest that around 5% of adults have chronic kidney disease stages 3 (glomerular filtration rate 30-59 ml/min), 4 (15-29 ml/min), or 5 (< 15 ml/min). These people have a markedly increased risk of cardiovascular morbidity and mortality and identification of them should enable earlier initiation of measures to reduce cardiovascular risk and also the rate of progression of renal failure. A similar prevalence figure has been reported in the United Kingdom.[25] The table lists the five stages of chronic kidney disease.

The UK Renal Association among associations in other countries, including Canada and Australia, has introduced guidelines for targeted screening to detect reduced renal function in primary care using estimated glomerular filtration rate. These guidelines describe how to manage most patients in primary care and advise which patients should be referred to nephrologists. In the case of Australia and New Zealand, specific attention is recommended to high risk subgroups such as those of aboriginal descent. The potential impact of identifying patients with reduced renal function has been recognised by the United Kingdom's health service and is reflected in the General Medical Services contract for general practitioners, which now provides remuneration for the identification and monitoring of chronic kidney disease.

Additional educational resources

Renal Association (www.renal.org/eGFR/)—this website has clear information on definition of chronic kidney disease and provides guidelines on management. A section is included for patients

NHS Employers (www.nhsemployers.org/primary)—this website provides further details of the general practitioner contract and remuneration of general practitioners within the United Kingdom

National Kidney Foundation (www.kidney.org/kidneyDisease/)—this website provides useful information for patients as well as another good resource for health professionals

Tips for non-specialists

Use estimated glomerular filtration rate as a guide to renal function in conjunction with advice on renal disease from the Renal Association's website (www.renal.org/eGFR/)

If the estimated glomerular filtration rate is < 60 ml/min then:

- Review previous results or repeat the measurement to assess if renal function is stable or declining
- Measure blood pressure and test urine for protein and blood
- Review drugs for potentially nephrotoxic agents, such as angiotensin converting enzyme inhibitors or angiotensin receptor blockers, diuretics, non-steroidal anti-inflammatory drugs, and antibiotics
- Check for urinary symptoms, signs of fluid retention or hypovolaemia, and palpable bladder
- Enter into a chronic disease management programme and decide whether referral to a renal clinic is appropriate, using local guidelines or those from the Renal Association

Conclusion

Prediction formulas using serum creatinine levels are by far the most widely used methods of measuring renal excretory function in routine clinical practice. One of these, the modified 4-v MDRD estimated glomerular filtration rate formula[19] is now being used for direct reporting of estimated glomerular filtration rates by laboratories and has become the standard method used to identify and monitor patients with reduced renal function in the United Kingdom and elsewhere. It is anticipated that recognition and appropriate management of patients with chronic kidney disease will reduce cardiovascular events and slow further deterioration in renal function in these patients.

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When I use a word

Consultation

In his account of the Persian wars, Herodotus tells how the Lydian king Croesus consulted the Delphic oracle, asking whether he should go to war with Persia. If Croesus attacks the Persians, said the oracle, he will destroy a mighty empire. Croesus confidently marched on Cappadocia, but it was his own mighty empire that he destroyed by doing so, not that of the enemy king, Cyrus. Other oracular pronouncements were equally ambiguous. According to Ennius, "Aio te Romanos vincere posse" (quoted by Shakespeare in *Henry VI, Part 2*) was the answer that Pyrrhus, king of Epirus, received when he asked about making war with Rome: "I assert that you can conquer the Romans/the Romans can conquer you." The lesson is clear: listen carefully to those whom you consult—they may not be saying what you would like them to say. It is a lesson that seems to have been forgotten.

The word consult comes from the Latin verbs consulere (supine consultum) and consultare, both of which mean to apply to someone for advice or information. Consultare also means to consult an oracle. The *Oxford English Dictionary* gives several definitions for "consult," including "to have especial respect or beneficial reference to (a person's good, interest, convenience, etc.) in forming plans; ... To ask advice of, seek counsel from; to have recourse to for instruction, guidance, or professional advice ... to seek permission or approval from (a person) for a proposed action."

My concern that modern methods of consultation do not conform to this description received another dig in the ribs recently when an organisation enthusiastic to introduce author pays, "open access" publishing, and institutional repositories (with apparently little regard for the various deleterious effects that these policies may have (*BMJ* 2005;330:759) including damage to learned societies that publish their own journals) proclaimed that it would "discuss with the learned societies ways in which they can adapt to and exploit new models of publication." To me this is rather like a doctor telling her patient that she will see him through his terminal illness, helping him to adapt to the inevitable. The patient may have consulted the doctor, but the doctor has not consulted the patient.

One way of getting the answer you want is to ask the right question. My local council (a word, incidentally, that comes from concilium; not to be confused with counsel), keen to introduce charges for allowing me to park outside my own house, recently sent me a consultation questionnaire. Did I agree that there should be a consistent policy about such charges throughout the city? My gut reaction was "yes," because surely consistency is desirable. Well actually it isn't always. What is good and necessary in some parts of town may be harmful in others. So, should the same policy be applied throughout? I answered "no," but it won't do any good—I suspect that they have already decided what they're going to do.

All too often today consultation seems to mean, as Paul Glasziou suggested to me when we discussed it, "This is what we intend to do; tell us how much you agree." I therefore propose a novel Likert scale for responding to modern consultations: Agree/Agree strongly/Agree very strongly/Agree enthusiastically/Couldn't agree more.

I also note that another meaning of the Latin word consulere, listed in the *Oxford Latin Dictionary*, is "[with *male*, *duriter*, and similar] to plan harm (to), act mischievously, prejudicially, etc (towards) … [and with *contra*] to take steps against."

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We welcome articles up to 600 words on topics such as *A memorable patient, A paper that changed my practice, My most unfortunate mistake,* or any other piece conveying instruction, pathos, or humour. Please submit the article on http://submit.bmj.com Permission is needed from the patient or a relative if an identifiable patient is referred to. We also welcome contributions for "Endpieces," consisting of quotations of up to 80 words (but most are considerably shorter) from any source, ancient or modern, which have appealed to the reader.