Assessment of kidney function in adults

Edmund Lamb

Abstract

Kidney function is typically assessed by measuring glomerular filtration rate (GFR), and many approaches have been used. Accuracy demands complex techniques involving the use of exogenous filtration markers (e.g. inulin, iohexol, ^{99m}Tc-diethylenetriaminepentaacetic acid, ^{51}Cr-ethylenediaminetetraacetic acid). For most clinical purposes, accuracy is sacrificed to practicality, and the blood marker creatinine (whose concentration has an inverse relationship to GFR) is used instead. Serum (or plasma) creatinine has many limitations as a kidney function test, being affected by a variety of non-renal and analytical factors. Serum cystatin C measurement has been proposed as an alternative marker. Application of creatinine-based GFR-estimating equations facilitates the detection and management of chronic kidney disease and allows disease to be categorized according to an international staging system. In addition to using GFR, the detection and classification of kidney disease involves measurement of urinary albumin (or protein) concentration. The use of urinary albumin:creatinine (or protein:creatinine) ratios obviates the need for 24-hour urine collections.

Keywords Albuminuria; chronic kidney disease; creatinine; cystatin C; glomerular filtration rate; MRCP; proteinuria

Key points

- Initial assessment of kidney function and classification of kidney disease requires assessment of glomerular filtration rate (GFR) and testing for albuminuria or proteinuria
- Creatinine-based equations enabling an estimation of body surface area-adjusted GFR from a blood sample are widely used: for clinical purposes, the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation is currently recommended in preference to the Modification of Diet in Renal Disease (MDRD) equation for reporting estimated GFR
- GFR estimation using cystatin C, alone or in combination with creatinine, can be used to further refine creatinine-based estimates and improve prognostication; formal estimation of GFR using complex infusion techniques is, however, still required in certain clinical situations
- Caution should be exercised before basing drug dosage adjustments on estimated GFR in individuals of extreme body size or when using drugs with a narrow therapeutic index
- Kidney damage is typically detected by the presence of albumin (or total protein) in the urine; expressing the urinary albumin (or protein) concentration as a ratio to creatinine corrects for variation in urinary flow rate and obviates the need for timed collections

Introduction

Although the kidney has numerous functions, the initiating step in many of these processes is glomerular filtration. The glomerular filtration rate (GFR) is directly related to the number of functioning nephrons in the kidney, and this number declines in all forms of progressive kidney disease. The accumulation of nitrogenous waste products and other uraemic toxins is inversely related to GFR. The integrity of the glomerular filtration barrier can also be compromized in kidney disease, and albuminuria (or proteinuria) has historically been regarded as the cardinal sign of kidney disease.

The international classification system for chronic kidney disease (CKD) uses GFR and albuminuria to categorize patients (see Table 1 in Management of chronic kidney disease, *Medicine* 2019; **47**(9)). Detection of CKD using GFR estimation is advocated in the 'at-risk' population.[1,2] Furthermore, changes in GFR, as reflected by changes in blood creatinine concentration, are the basis for the diagnosis of acute kidney injury. GFR is widely accepted as the best overall measure of kidney function, and this chapter focuses on approaches to measurement of GFR.

The kidney also has a variety of other functions (e.g. urinary acidification and concentration, electrolyte homeostasis, activation of vitamin D, synthesis of erythropoietin), which can be assessed using specific tests.

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Glomerular filtration rate

The concept of clearance

Clearance is defined as 'the volume of plasma from which a given substance is completely cleared by glomerular filtration per unit time'. It is normally expressed in ml/minute and is measured by quantifying the clearance of an exogenous or endogenous substance (S) by the kidneys. Provided that S is in stable concentration in the plasma, physiologically inert, freely filtered at the glomerulus, and neither secreted, reabsorbed, synthesized nor metabolized by the kidney, the amount of S filtered at the glomerulus is equal to the amount excreted in the urine. The amount of S filtered at the glomerulus equals GFR multiplied by plasma concentration of S (PS): GFR $\times$ PS. The amount of S excreted equals the urine concentration of S (US) multiplied by the urinary flow rate (V, volume excreted per unit time, normally in ml/minute). Because filtered S = excreted S:

$$\text{GFR} \times PS = US \times V$$

Approaches to GFR measurement shown in an approximate hierarchy

Most accurate

- Inulin (continuous-infusion technique)
- Inulin (single-bolus method)
- Iohexol, ^{51}Cr-EDTA, ^{125}I-iothalamate, ^{99m}Tc DTPA
- 3-hour creatinine clearance with cimetidine
- Estimated GFR (MDRD, CKD-EPI)
- Serum cystatin C
- Serum creatinine
- 24-hour creatinine clearance

Least accurate

CKD-EPI, Chronic Kidney Disease-Epidemiology Collaboration; DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediaminetetraacetic acid; GFR, glomerular filtration rate; MDRD, Modification of Diet in Renal Disease.

Table 1

Which rearranges to:

$$GFR = (US \times V)/PS$$

Correction for body size – GFR varies with body size so, to enable comparisons of GFR between individuals, it has become standard practice to normalize GFR to a measure of body size, usually body surface area (BSA). The DuBois and DuBois equation shown below is widely used, although other equations (e.g. Haycock) have been recommended.[3]

$$BSA\ (m^2) = [weight^{0.425}\ (kg) \times height^{0.725}\ (cm)] \times 0.007184$$

GFR is commonly corrected to a BSA value of 1.73 m^2, representing the average BSA of adults aged 25 years. This can, however, result in overestimation of GFR in small individuals, a critical issue when using GFR to determine drug dosage. Widely used GFR-estimating equations (e.g. the Modification of Diet in Renal Disease (MDRD) study and Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equations – see below), report GFR corrected for BSA.

Measurement of GFR using exogenous substances

The urinary or plasma clearance of several exogenous markers has been used to provide an accurate measurement of GFR. However, even with these reference procedures, there is within-individual, between-day biological variation in GFR (commonly cited as approximately 8%). Other factors such as recent dietary intake and exercise also affect GFR and should be standardized as far as possible before testing.[3]

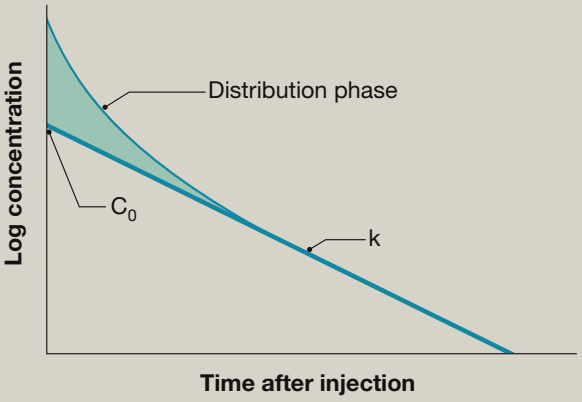
Constant-infusion (urinary clearance) or single-bolus injection (plasma clearance) methods can be used. In the constant-infusion technique, an intravenous loading dose of marker is followed by a constant infusion of a given quantity of marker per minute for 3 hours. After equilibration for 1 hour, blood is taken, and urine samples are collected at hourly intervals for 3 hours. The subject remains supine throughout the study and adequate hydration must be maintained.

Single-bolus plasma clearance methods have obvious practical advantages. A single dose of the marker is injected, and venous blood samples are collected at timed intervals (typically 120, 180 and 240 minutes after the start of the injection). The GFR can then be calculated using the slope intercept approach (Figure 1). Recent guidelines have suggested that single-sample approaches can also be clinically acceptable.[3]

Inulin: the fructose polymer inulin (molecular mass around 5 kDa), found in certain plants (e.g. Jerusalem artichokes), most closely satisfies the criteria of an ideal marker of GFR (although even inulin has some extra-renal clearance, equivalent to nearly 6 ml/minute for a 70 kg human). Inulin clearance using a constant-infusion urinary clearance approach has long been regarded as the gold standard measure of GFR. Single-bolus plasma clearance approaches are also used. However, lack of availability of simple laboratory methods of measurement remains an impediment to universal usage and, in practice, several other approaches to the measurement of GFR are commonly used (Table 1).

Iohexol: the X-ray contrast agent iohexol has the advantage of being used in a non-radioisotopic form, enabling analysis to be delayed and the procedure to be undertaken outside nuclear medicine facilities. Single-bolus plasma clearance of iohexol

Principle of glomerular filtration rate measurement using a single bolus plasma clearance technique



The GFR is calculated using knowledge of the amount of marker injected and the decrease in marker concentration (activity) as a function of time. Elimination of the marker is described by a two-compartment model: this comprises an initial equilibration or distribution phase (shaded), while the marker mixes between the vascular and extravascular space while also being cleared from the plasma by the kidney. The distribution phase can last 2–8 hours, depending on the individual's size, the distribution volume of the molecule (e.g. longer in oedematous patients) and the GFR (the lower the GFR, the longer the distribution phase). This gives rise to a bi-exponential clearance curve. However, GFR is normally calculated using single-exponential analysis by plotting log marker concentration against time. The half-life is calculated from the slope (k) and the volume of distribution (C_0) of the marker just after injection. Because this model ignores the distribution phase, GFR is overestimated. Various mathematical corrections (e.g. Brochner–Mortensen correction) can be used to adjust for this.

Figure 1

demonstrates excellent agreement with constant-infusion urinary inulin clearance.

Radioisotopes: various radioisotopes have been used (e.g. ^{99m}Tc-diethylenetriaminepentaacetic acid (DTPA), ^{125}I-iothalamate, ^{51}Cr-ethylenediaminetetracacetic acid (EDTA)) to measure GFR; all have relative advantages and disadvantages.

Measurement of GFR using endogenous substances

Although the clearance of infused markers provides an accurate assessment of GFR, these procedures are costly and cumbersome and are only generally used in selected secondary care situations. Creatinine and certain low molecular weight proteins (e.g. cystatin C, β-trace protein) have been used as endogenous markers of GFR. The use of urea in this context is of limited value and will not be discussed in detail. Serum urea measurement is occasionally useful in situations where there is a suspicion that the creatinine result is misleading (e.g. muscle-wasting disorders) and no alternative methods are available to assess GFR.

Creatinine: the most widely used endogenous marker of GFR is creatinine, expressed as either its serum or plasma concentration or its renal clearance. It is freely filtered at the glomerulus, and its concentration is inversely related to GFR. It is convenient and cheap to measure but is affected by a variety of non-renal influences (Table 2) and has poor sensitivity for CKD. Thus, although an increased serum creatinine concentration generally equates to impaired kidney function, a normal serum creatinine does not necessarily imply normal kidney function. This is a particular problem among older people, in whom reduced muscle mass can result in serum creatinine concentrations within the reference range even when kidney function is impaired.

Most laboratories use modifications of the Jaffe method to measure creatinine, although more specific and accurate enzymatic and isotope dilution-mass spectrometry methods are available. Measurement of creatinine, especially using the Jaffe reaction, suffers from many limitations (Table 2), and it is recommended that serum creatinine concentration alone should not be used to assess kidney function. Increasingly, serum creatinine is used to generate estimates of GFR using equations (see below), although the equations themselves are susceptible to many of these same limitations.

Limitations of serum creatinine concentration as a marker of GFR

Type of limitation	Examples	Notes
Non-renal influences	Gender	Male individuals have relatively high serum creatinine for the same GFR level
	Ethnicity	African-Caribbean individuals have relatively high serum creatinine for the same GFR level
	Recent dietary intake	Cooked meat and fish contain creatinine, which is readily absorbed
	Drugs — *in vivo* effect	For example, cimetidine and trimethoprim block tubular secretion of creatinine. Typically, 7—10% of creatinine excretion is from tubular secretion but this is increased in renal insufficiency
	Muscle mass	Creatinine is derived from muscle; consequently, serum concentrations reflect muscle mass. This is a particular limitation in patients with muscle-wasting disorders or amputees
	Extra-renal clearance	Becomes more significant in patients with CKD because of degradation as a result of bacterial overgrowth in the small intestine
Clinical utility	Poor sensitivity for CKD	Serum creatinine concentration remains within the reference interval until significant renal function has been lost. Does not detect patients with stage 2 CKD and fails to identify many patients with stage 3 CKD
	Not useful in acute kidney injury	There is a temporal delay between change in GFR and the resulting change in serum creatinine concentration
Analytical problems	Non-specificity	'Pseudo-chromogens' (e.g. protein, ketones, ascorbic acid, glucose, pyruvate, guanidine, blood-substitute products, cephalosporins) give false-positive reactions in the Jaffe assay
	Drugs — analytical effect	e.g. Metamizole causes falsely increased creatinine concentrations in the Jaffe assay, and phenindione causes falsely low creatinine results in some enzymatic assays
	Spectral interferences (icterus, lipaemia, haemolysis)	Can give falsely negative or positive results for creatinine depending on the precise assay conditions
	Methodological variation	Results differ between laboratories

Table 2

Creatinine clearance: because creatinine is endogenously produced and released into body fluids at a constant rate, its clearance can be measured as an indicator of GFR. However, this requires a timed urine collection, which is inconvenient and introduces inaccuracies. In adults, the within-individual biological day-to-day coefficient of variation for repeated measures of creatinine clearance exceeds 25%. Tubular secretion further undermines the theoretical value of creatinine as a marker of GFR, with creatinine clearance usually equalling or exceeding inulin GFR in adults by a factor of 10–40% at clearances >80 ml/minute. However, as GFR falls, the tubular secretion of creatinine rises disproportionately, and creatinine clearance values can reach nearly twice those for the true GFR. Hence, creatinine clearance provides at best only a crude index of GFR.

Estimated GFR: equations that estimate GFR have been derived, using serum creatinine corrected for some or all of gender, body size, race and age. These produce a better estimate of GFR than serum creatinine alone. The Cockcroft and Gault, MDRD and CKD-EPI equations have been widely used in adults (Table 3).

GFR-estimating equations in widespread use

The forms of the equations shown are for use when the serum creatinine concentration is expressed in SI units (micromol/litre). To convert serum creatinine concentration in micromol/litre to mg/dl, multiply by 0.011312.

Cockcroft and Gault equation

Creatinine clearance (ml/min) = [(140 − age (years)) × weight (kg)/(0.814 × serum creatinine] × (0.85 if female)

MDRD study equation[a]

GFR (ml/min/1.73 m^2) = 175 × [serum creatinine × 0.011312] −1.154 × [age]−0.203 × [1.212 if black] × [0.742 if female]

CKD-EPI Collaboration creatinine equation

GFR (ml/min/1.73 m2) = 141 × min([serum creatinine × 0.011312]/κ, 1)α × max([serum creatinine × 0.011312]/κ, 1)−1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black] where κ is 0.7 for female individuals and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of serum creatinine/κ or 1, and max indicates the maximum of serum creatinine/κ or 1

CKD-EPI Collaboration cystatin C equation

GFR (ml/min/1.73 m^2) = 133 × min(*Scys*/0.8, 1)$^{-0.499}$ × max (*Scys*/0.8, 1)$^{-1.328}$ × 0.996 Age [× 0.932 if female], where *Scys* is serum cystatin C, min indicates the minimum of serum creatinine/κ or 1, and max indicates the maximum of *Scys*/κ or 1

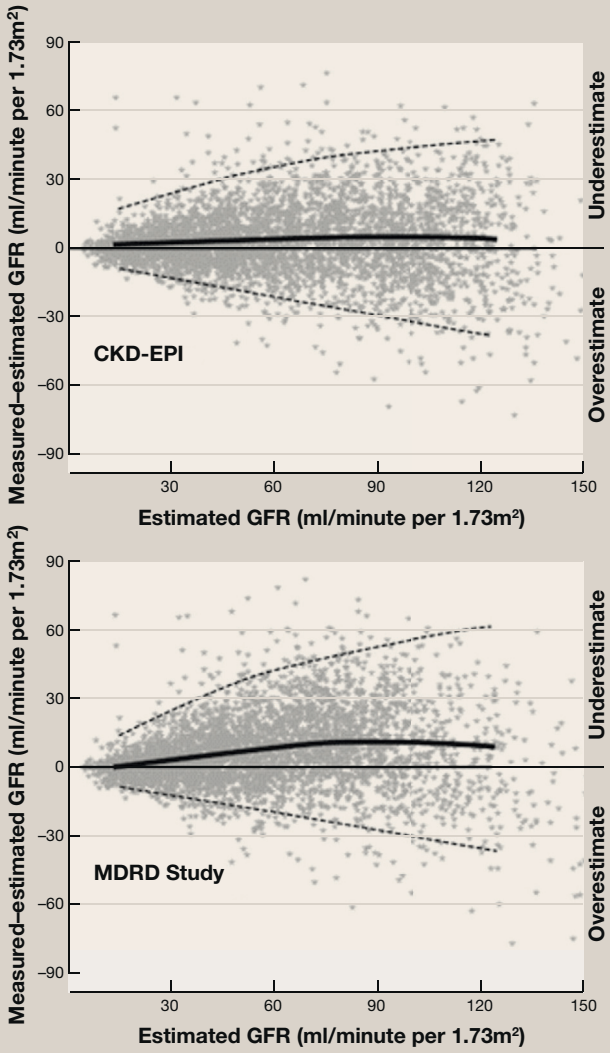
CKD-EPI Collaboration combined creatinine and cystatin C equation

GFR (ml/min/1.73 m^2) = 135 × min([*Scr* x 0.011312]/κ, 1)$^{\alpha}$ × max([Scr x 0.011312]/κ, 1)$^{-0.601}$ × min(*Scys*/0.8, 1)−0.375 × max(*Scys*/0.8, 1)−0.711 × 0.995 Age [× 0.969 if female] [× 1.08 if black], where *Scr* is serum creatinine, *Scys* is serum cystatin C, κ is 0.7 for female individuals and 0.9 for males, α is −0.248 for females and −0.207 for males, min indicates the minimum of *Scr*/κ or 1, and max indicates the maximum of *Scr*/κ or 1

[a] The so-called 'simplified' (four-variable) isotope dilution-mass spectrometry (ID–MS) traceable form of the MDRD equation is shown, for use when serum creatinine is measured with a reference (ID–MS) procedure.

Table 3

After its publication in 1999, the MDRD study equation was widely used as a practical and accurate estimate of GFR. However, the equation demonstrates increased negative bias and imprecision as GFR increases towards the physiological range (Figure 2). The CKD-EPI equation offers some advantages in this respect and is now recommended for use in clinical practice guidelines.[1,2] Both equations enable an estimate of GFR to be produced without knowledge of patient weight – a limitation of the Cockcroft and Gault equation – with the estimate being corrected for BSA and for African-American race. The inaccuracy of all estimating equations



Both panels show the difference between measured and estimated versus estimated GFR. A smoothed regression line is shown, with 95% confidence intervals (dotted lines). Note that the underestimation of GFR using the MDRD equation is somewhat ameliorated by use of the CKD-EPI equation, particularly at higher levels of GFR.

Figure 2 Source: Reproduced from Levey AS, Stevens LA, Schmid CH et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med* 2009; **150:** 604–12 with the permission of American College of Physicians, Inc.

should be appreciated: at best 90% of individuals have an estimated GFR within 30% of the true value. None of the above estimating equations is suitable for use in children, for whom alternative equations (e.g. Counahan–Barratt, Schwartz) exist.

There are several clinical situations in which more accurate knowledge of GFR is important. These include: certain chemotherapies (e.g. carboplatin); the use of any drug that is nephrotoxic or renally excreted and has a narrow therapeutic margin; the assessment of potential living related kidney donors; and the assessment of GFR in patients with muscle-wasting disorders, including spina bifida and paraplegia. When accurate GFR information is required, reference methods may be preferred.

Cystatin C: lower molecular weight (<30 kDa) proteins are relatively freely filtered at the glomerulus and either reabsorbed (and metabolized) in the proximal tubule or excreted into the urine. As they are entirely eliminated from the circulation, they have the potential to be used as GFR markers. Cystatin C is a low molecular weight (12.8 kDa) cysteine protease inhibitor synthesized by all nucleated cells. It offers a more sensitive and specific means of detecting CKD than serum creatinine.

GFR-prediction equations based on cystatin C have also been proposed, including equations that incorporate both cystatin C and creatinine (Table 3).[4] Although these equations show only modest improvements in accuracy of GFR estimation compared with creatinine-based equations, there is increasing evidence that use of cystatin C outperforms creatinine in risk stratification. A further advantage is that GFR estimation based on cystatin C is less influenced by age, dietary intake and race, and can be of benefit in situations where the relationship between muscle mass, creatinine and GFR is compromized (e.g. muscle-wasting disorders, amputees).

Proteinuria

Proteinuria is a common finding and an important prognostic indicator in patients with kidney disease. It is increasingly accepted that proteinuria is not just a consequence of, but also directly contributes to, progression of kidney disease. In health, albumin constitutes approximately 25% of total urinary protein. At higher levels of proteinuria, the relative contribution of albumin progressively increases, and when loss exceeds 1 g/day, most (typically >90%) is albumin. It is increasingly accepted that, in most situations, albuminuria reflects proteinuria and is the preferred method of detecting proteinuria.[5]

'Microalbuminuria' is a misleading historical term referring to the loss of albumin in the urine in amounts that are abnormally increased but below the limit of detection of conventional urine reagent strip ('dipstick') tests (approximately 300 mg/litre). Use of the terminology is now discouraged.[1,2]

Higher molecular weight proteins, the size of albumin and larger, are mostly retained within the circulation by the glomerular filter. Lower molecular weight proteins are more freely filtered, reabsorbed by proximal tubular cells and then catabolized within the tubular cells. Any increase in the filtered load (glomerular damage, increased glomerular vascular permeability, increased circulating concentration of low molecular weight proteins) or decrease in reabsorptive capacity (tubular damage) can result in proteinuria. Consequently, the appearance of significant amounts of protein in the urine suggests kidney disease. Proteinuria is commonly classified as glomerular, tubular or overflow proteinuria (Table 4). However, in nearly all cases there is also albuminuria. If significant non-albumin proteinuria is suspected, specific assays for tubular proteins should be used (e.g. α_1-microglobulin, monoclonal heavy or light chains (Bence Jones protein)). Total protein assays are insensitive in the detection of isolated tubular proteinuria.[5]

Sample collection and interpretation: historically, the 24-hour urine sample was regarded as the definitive means of demonstrating proteinuria. However, this is an imperfect reference method, and measurement of the albumin:creatinine (or protein:creatinine) ratio in a spot urine sample is now accepted as a

Characterization of proteinuria

Type of proteinuria	Causes	Examples of proteins seen
Glomerular	Increased glomerular permeability (e.g. from immune complex deposition)	Progressively increasing loss of higher molecular weight proteins as permeability increases (e.g. albumin, immunoglobulin G)
Tubular	Proximal tubular damage: decreased tubular reabsorptive capacity and/or release of intracellular components (e.g. caused by nephrotoxic drugs or heavy metals, anoxia)	Predominantly lower molecular weight proteins (e.g. α_1-microglobulin, β_2-microglobulin, retinol-binding protein, kidney injury molecule-1, neutrophil gelatinase-associated lipocalin) and enzymuria (e.g. *N*-acetyl-β-D-glucosaminidase, alkaline phosphatase, α-glutathione-*S*-transferase)
	Decreased nephron number from progressive CKD: increased filtered load per nephron	As above
	Distal tubular damage	Tamm–Horsfall glycoprotein π-Glutathione-*S*-transferase
Overflow	Increased plasma concentration of relatively freely filtered protein • Multiple myeloma • Rhabdomyolysis	Bence Jones protein Myoglobin

Table 4

more practical alternative. Expressing the albumin concentration as a ratio to creatinine enables correction for urinary dilution. An early morning urine sample is preferred because it correlates well with 24-hour protein loss and is required to exclude the diagnosis of orthostatic (postural) proteinuria. However, a random urine sample is acceptable if no early morning sample is available. Samples should be collected in the absence of urinary tract infection or acute metabolic crises.

Albumin:creatinine ratios <3.0 mg/mmol require no further investigation until the patient's next clinical review. For patients demonstrating ratios above, or equal to, this cut-off, urine samples should be sent to the laboratory for confirmation on at least one further occasion (ideally within 1 month). Patients demonstrating increased albumin:creatinine ratios in further samples have albuminuria. In the international classification of CKD, three categories of albuminuria are recognized: A1 (normal to mildly increased, <3 mg/mmol creatinine, approximately equivalent to <30 mg/day); A2 (moderately increased, 3–30 mg/mmol); and A3 (severely increased, ≥30 mg/mmol) ((see Table 1 in Management of chronic kidney disease, *Medicine* 2019; **47**(9)). In the absence of reduced GFR, CKD may still be identified in some individuals by the presence of albuminuria (or proteinuria). ◆

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TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online here.

Question 1

A 25-year-old man with Duchenne muscular dystrophy presented for a regular review appointment. His condition was stable. He was known to be a regular user of cannabis, which he thought improved his symptoms.

Investigations

- Serum creatinine 15 micromol/litre (64–104) using an enzymatic assay
- Estimated glomerular filtration rate (GFR) (using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation) was 235 ml/minute/1.73 m^2 (90–120)

What is the most likely explanation for these results?

A. Low muscle mass
B. Hyperfiltration is a usual feature of muscular dystrophy
C. Use of cannabis
D. Laboratory error in the creatinine measurement
E. An information system error in the estimated GFR calculation

Question 2

A 56-year-old man presented for annual medical review. Apart from some recent tiredness, he felt well. He had a 5-year history of type 2 diabetes mellitus managed by diet.

On clinical examination, his heart rate was 75 beats/minutue, and blood pressure 145/90 mmHg. Urine reagent strip testing was negative for protein and glucose.

Investigations

- Blood haemoglobin 140 g/litre (130–180)
- Serum creatinine 90 micromol/litre (64–104)
- Estimated GFR (using the CKD-EPI equation) 82 ml/minute/1.73 m^2 (>60)
- Blood HbA_{1c} 33 mmol/mol

What is the most important next investigation?

A 24-hour urine protein
B Urinary albumin:creatinine ratio
C Blood glucose concentration
D Plasma parathyroid hormone concentration
E Inulin clearance studies