Chapter 2
Measuring Kidney Function

Quantifying Glomerular Filtration from Laboratory Tests

Abstract In this chapter we explain:

- How serum creatinine is related to glomerular filtration rate (GFR)
- The limitations of creatinine as a measure of GFR
- How GFR is estimated from serum creatinine and cystatin C
- Common errors made when using eGFR
- How to interpret urea and creatinine together

How Can Kidney Function Be Measured?

To assess someone's kidney function, one would really like to measure their glomerular filtration rate (GFR). This can be done using a radioisotope tracer that is cleared from the blood solely by glomerular filtration, such as Cr-51 EDTA or Tc-99m DTPA. This technique is useful for research and when precise measurements of GFR are required. But it is impractical for routine repeated measurements.

Instead of measuring the clearance of an artificial tracer, routine assessment of kidney function uses the concentration of a substance produced by the body, creatinine, urea or cystatin C. Their concentration is determined by the balance between the rate of production and the rate of excretion.

When production and excretion have been stable for more than 24 h, an equilibrium concentration is reached. In equilibrium, the concentration is not affected by the volume of body water in which the substance is dissolved. Patients who are chronically fluid overloaded do not have a lower concentration due to dilution. The higher concentration found with dehydration is due to reduced kidney function, not haemoconcentration.

Creatinine would be the ideal choice for measuring kidney function if it was produced at a constant rate, freely filtered by the glomeruli, and neither reabsorbed nor secreted by the tubules. Unfortunately, it does not pass all these tests.

Creatinine is released into the bloodstream at a fairly constant rate from the breakdown of creatine in healthy skeletal muscles and is freely filtered by the glomeruli. In addition, 10–20 % of normal total creatinine excretion is by secretion into the tubules. As GFR declines that proportion increases and so serum creatinine does

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not increase as much as predicted from filtration. This is shown by comparing simultaneous measurements of serum creatinine and GFR using the gold standard inulin clearance technique (see Fig. 2.1).

The curved relationship between creatinine and GFR makes changes in serum creatinine hard to interpret correctly. Figure 2.2 shows a graph of serum creatinine against time in a man with declining kidney function. The shape of the line suggests that the rate of loss of kidney function accelerates over the years.

If we now add in GFR values, it is clear that kidney function has actually declined at a constant rate over the whole period (see Fig. 2.3).

Because of the inverse curved relationship between GFR and creatinine, the drop in GFR from 116 to 60 during the first 5 years causes a smaller increase in serum creatinine than the decline from 60 to 30 over the next 3 years.

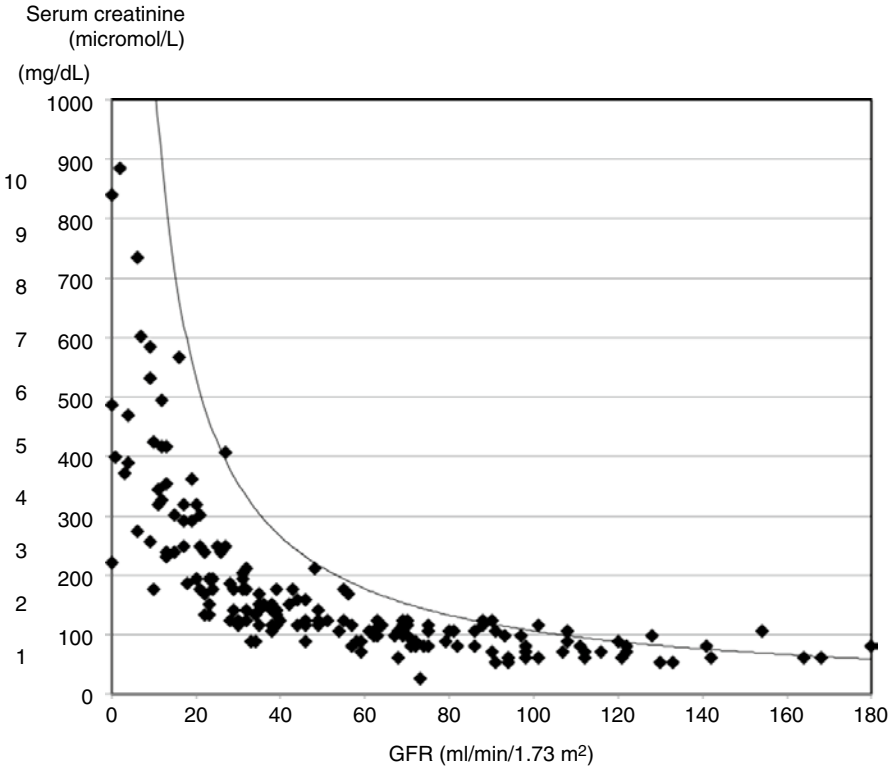

Fig. 2.1 Simultaneous measurements of serum creatinine (*filled diagonal box*) and GFR by inulin clearance in over 100 individuals. The *continuous line* represents the relationship between serum creatinine and GFR that would be found if creatinine was only filtered by glomeruli and not modified by the tubules (Redrawn from Shemesh et al. [1]).

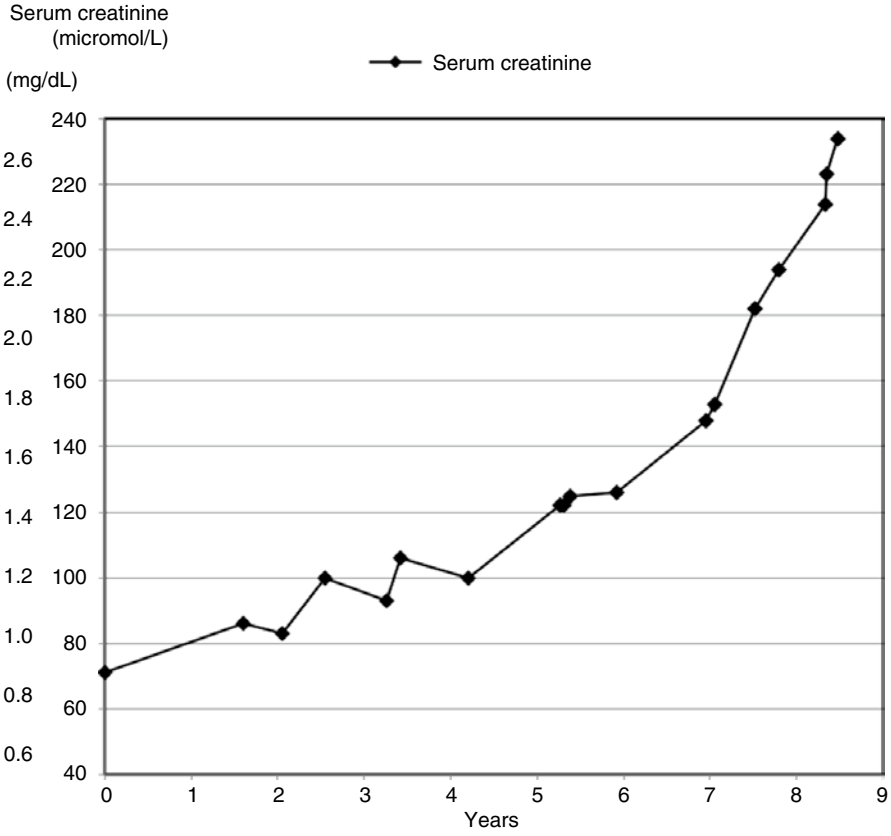

Fig. 2.2 A graph of serum creatinine against time in a man with declining kidney function

How Can GFR Be Estimated from Serum Creatinine?

To make serum creatinine results easy to interpret we need to convert them into estimates of the GFR (eGFR). Equations to do the conversion have been derived from databases containing simultaneous measurements of GFR, by a radioisotope clearance technique, and serum creatinine concentration. The four-variable MDRD equation was derived from measurements performed on adult patients with chronic kidney disease in the Modification of Diet in Renal Disease (MDRD) study [2].

eGFR values are standardised to a body surface area of 1.73 m^2 and so their calculation does not require the patient's body weight. This makes it possible for the laboratory to provide eGFR values automatically from the patient's age and sex.

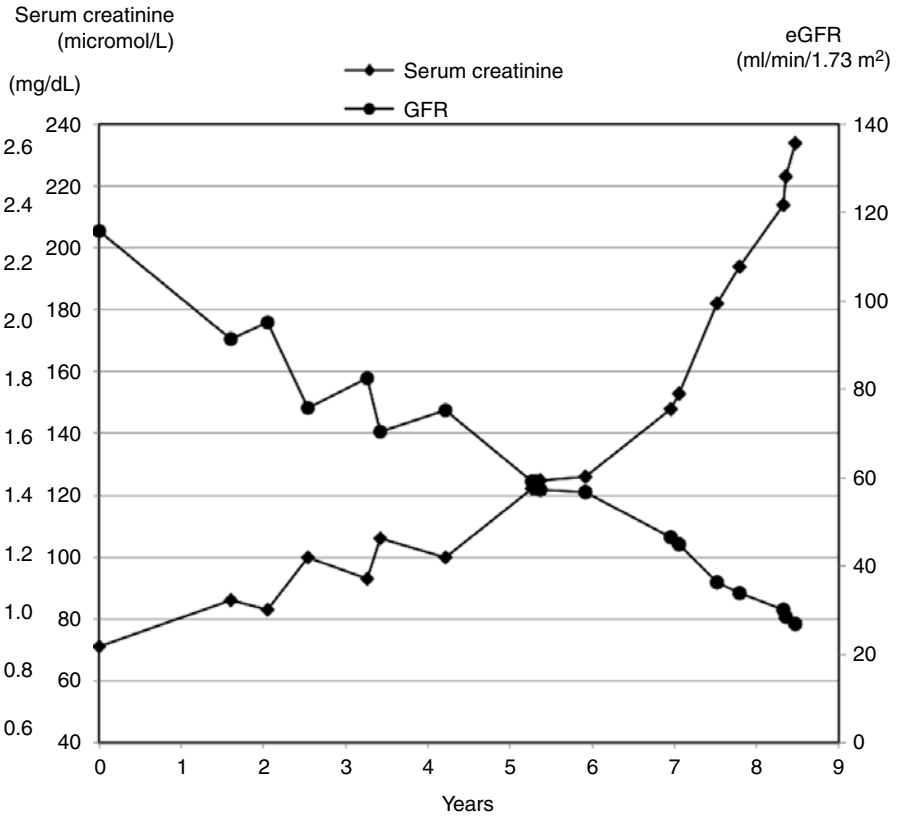

Fig. 2.3 A graph of serum creatinine and GFR against time in the same man as in Fig. 2.2

As the laboratory does not usually have reliable information about ethnicity, the adjustment for Afro-Caribbean race is done manually.

For children, different equations are available [3]. The commonest used is the Schwarz equation [4].

The Schwarz Equation [4]

$$\mathrm{GFR\,(ml/min/1.73\ m^2)} = (0.413 \times \mathrm{Height\,in\,cm} \times 88.4) / \mathrm{Creatinine\,in\,micromol/L}$$

$$\mathrm{GFR\,(ml/min/1.73\ m^2)} = (0.413 \times \mathrm{Height\,in\,cm}) / \mathrm{Creatinine\,in\,mg/dL}$$

$$\mathrm{GFR\,(ml/min/1.73\ m^2)} = 175 \times (\mathrm{Creat})^{-1.154} \times (\mathrm{Age})^{-0.203} \times (0.742\,\mathrm{if\ female}) \times (1.212\,\mathrm{if\ black\ race})$$

This equation uses serum creatinine values calibrated against isotope dilution mass spectrometry (IDMS).

Are These Estimates Accurate and Reliable?

The 90 % confidence intervals of the estimates are wide. Using the MDRD equation, 90 % of estimates are within 30 % of the directly measured GFR and 98 % within 50 %. In children using the Schwarz equation, 80 % of estimates are within 30 % of the measured GFR. The estimates are less accurate in people with very abnormal body composition, such as amputees and malnourished patients.

The MDRD equation was derived from patients known to have kidney disease and a raised serum creatinine. It is inaccurate for estimating GFR from serum creatinine values in the normal range, i.e. outside the dataset used to derive the formula, for example in pregnancy [5]. The eGFR is not appropriate for situations in which a more accurate measurement of GFR is required, such as in the assessment of a potential transplant donor.

Because the MDRD equation underestimates the true GFR when serum creatinine values are in the normal range, people are at risk of being labelled as having kidney disease based upon these estimates. To reduce this, guidelines recommend that laboratories use the more recently developed CKD-EPI equations [6]. CKD-EPI gives estimates that are closer to the measured GFR at lower levels of serum creatinine, applying a different equation when creatinine is in the normal range [7, 8].

It is best to use the eGFR estimate provided by the laboratory that analysed the blood sample as that will include appropriate adjustments for the creatinine assay.

The accuracy of GFR estimates is less relevant when they are used to follow an individual patient over time. Here it is the shape of the graph rather than the exact value that is of interest. There is a good correlation between the slopes of measured and estimated GFR values over time. Also, patient-related factors affect the measured and estimated GFR slopes in a similar way, so slopes can be compared between patients [9, 10].

One way to validate the use of eGFR graphs is to compare them with graphs of measured GFR in patients with similar pathological processes. Figure 2.4 shows sequential measurements of GFR from five patients with autosomal dominant polycystic kidney disease (ADPKD). The trajectory of GFR is linear, although the gradient varies between patients.

The CKD-EPI Equations [7]

Black
Female

Serum creatinine	
$\leq 62\ \mu mol/L (\leq 0.7\ mg/dL)$	$GFR = 166 \times (Scr/0.7)^{-0.329} \times (0.993)^{Age}$
$> 62 \mu mol/L (> 0.7\ mg/dL)$	$GFR = 166 \times (Scr/0.7)^{-1.209} \times (0.993)^{Age}$

Male

$$\leq 80 (\leq 0.9) \quad \text{GFR} = 163 \times (\text{Scr} / 0.9)^{-0.411} \times (0.993)^{\text{Age}}$$

$$> 80 (> 0.9) \quad \text{GFR} = 163 \times (\text{Scr} / 0.9)^{-1.209} \times (0.993)^{\text{Age}}$$

White or other ethnicity
Female

$$\leq 62 (\leq 0.7) \quad \text{GFR} = 144 \times (\text{Scr} / 0.7)^{-0.329} \times (0.993)^{\text{Age}}$$

$$> 62 (> 0.7) \quad \text{GFR} = 144 \times (\text{Scr} / 0.7)^{-1.209} \times (0.993)^{\text{Age}}$$

Male

$$\leq 80 (\leq 0.9) \quad \text{GFR} = 141 \times (\text{Scr} / 0.9)^{-0.411} \times (0.993)^{\text{Age}}$$

$$> 80 (> 0.9) \quad \text{GFR} = 141 \times (\text{Scr} / 0.9)^{-1.209} \times (0.993)^{\text{Age}}$$

CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration
Scr = serum creatinine in mg/dL (micromol/L/88.4)
Age in years for ≥18

Graphs of estimated GFR from patients with ADPKD also have linear trajectories (see Fig. 2.5).

Interpreting eGFR Values

eGFR equations for men and women are different because, on average, men contain proportionately more muscle than women. Body composition also changes with age, the proportion of muscle declining as people grow older. Including these factors, we can draw a family of graphs of estimated GFR versus serum creatinine (see Fig. 2.6).

Females have a lower eGFR than males for any given serum creatinine value (see Fig. 2.7).

To derive the correct eGFR, the laboratory must be provided with the correct sex and date of birth. Using an incorrect adjustment causes a significant error in the

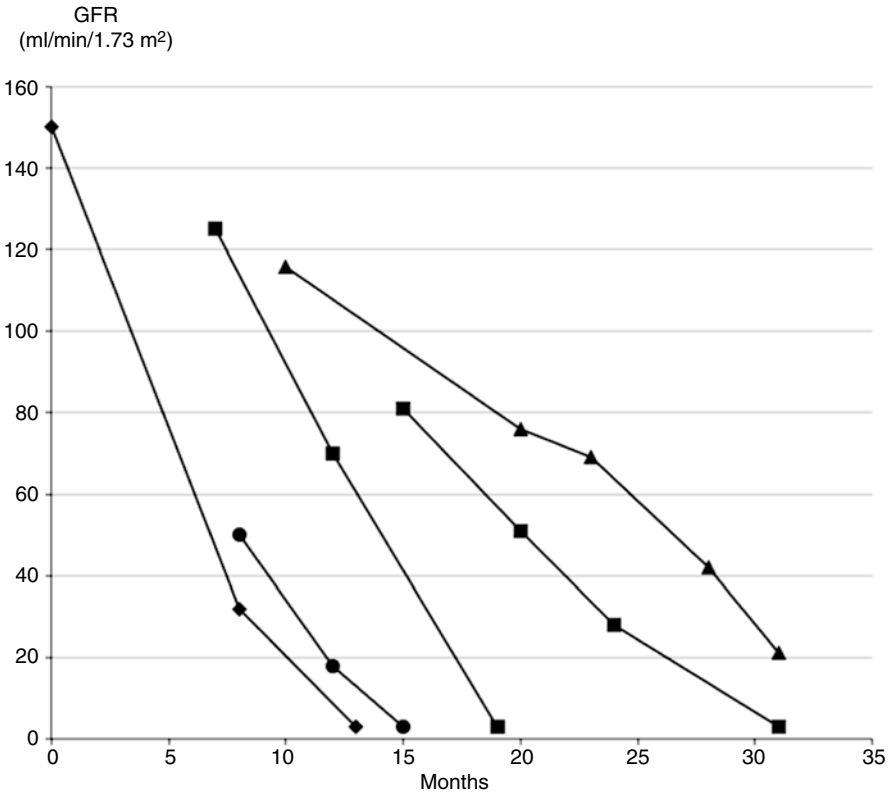

Fig. 2.4 Measurements of GFR using inulin or Cr-EDTA clearance from five patients with autosomal dominant polycystic kidney disease (ADPKD). The rate of decline is more rapid than found in most patients with ADPKD [11]

estimate, giving either false alarm or false reassurance, as shown by the following cases (Patients 2.1 and 2.2).

Patients with family names that are also used as first names are at particular risk of being labelled with the wrong sex (Patient 2.2).

The estimated GFR needs to be adjusted for Afro-Caribbean race but not for other ethnicities (see Fig. 2.10). This is because of genetically determined differences in skeletal muscle between racial groups. Compared to white Caucasians, black African people have 30–40 % higher activities of a number of enzymes involved in phosphagenic metabolic pathways, including creatine kinase [12].

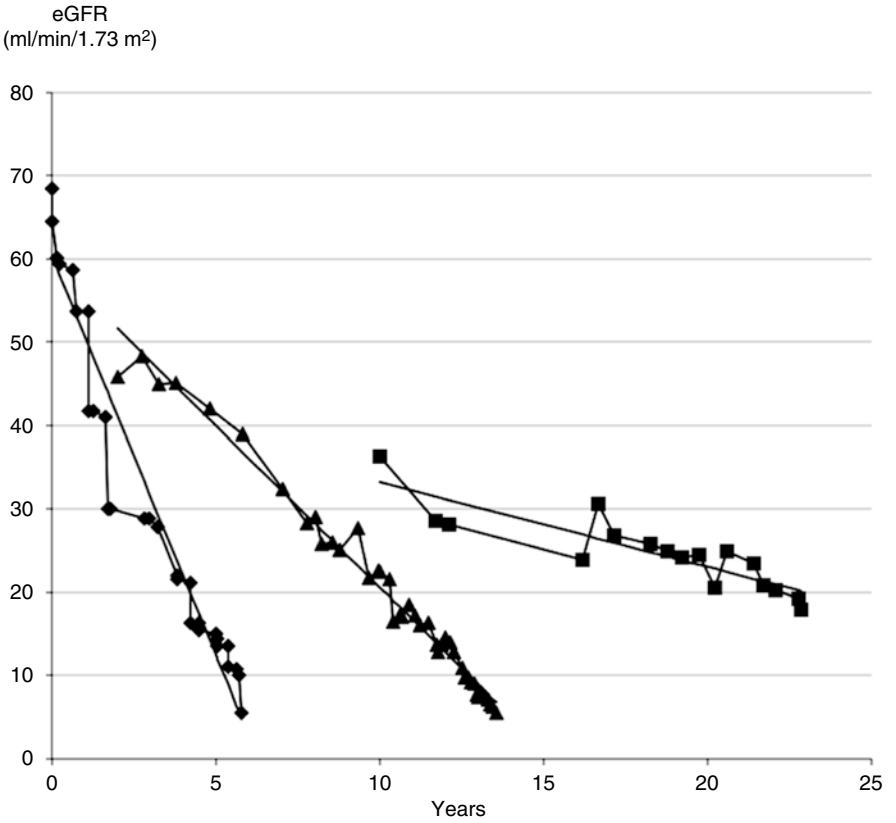

Fig. 2.5 eGFR graphs from three patients with ADPKD, chosen to show the wide variation in the eGFR gradient between patients

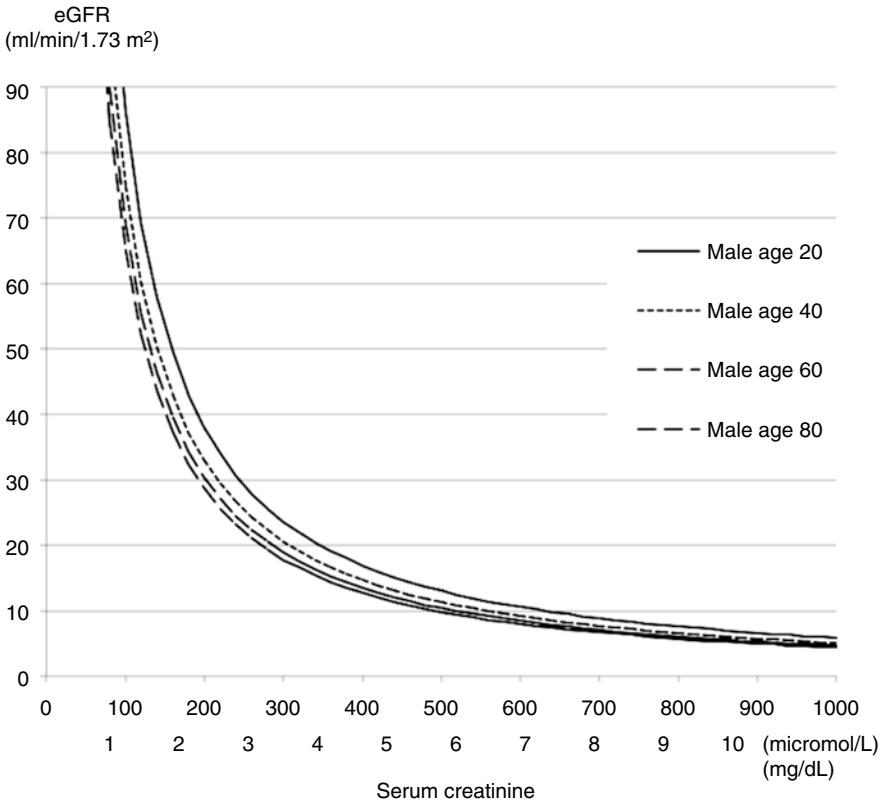

Fig. 2.6 A family of graphs of eGFR against serum creatinine, showing how the estimated GFR falls with age (MDRD equation)

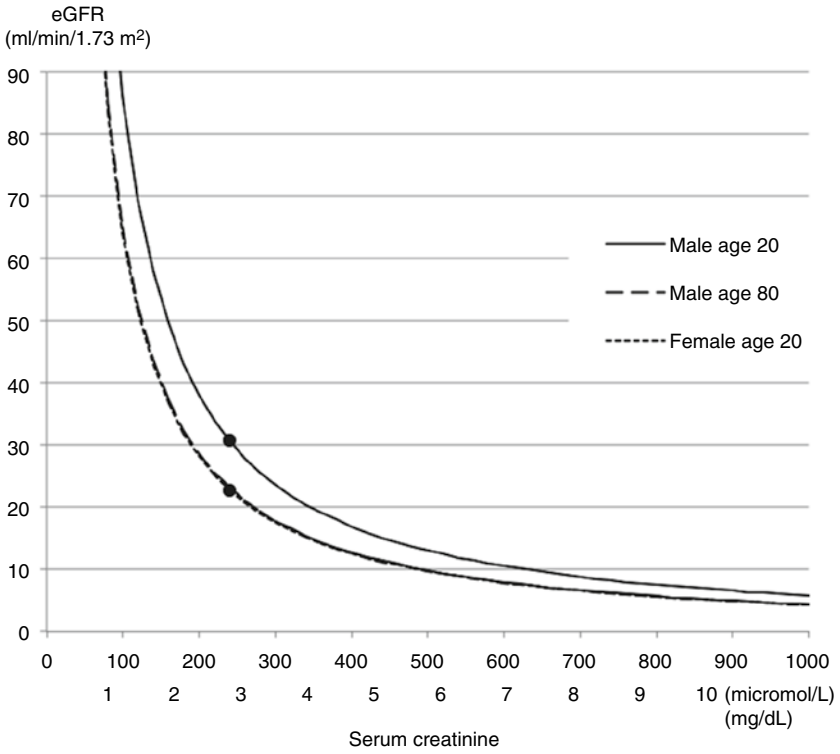

Fig. 2.7 eGFR calculated for a female aged 20 and males aged 20 and 80 years (MDRD equation). For a male with a serum creatinine = 240 micromol/L (2.7 mg/dL) altering the sex to female, or the age from 20 to 80 years, reduces the eGFR from 31 to 23 ml/min/1.73 m^2. The line for a male aged 80 is almost identical to that for a female aged 20 years

Patient 2.1: Biochemical 'Sex Change'

Mr Edwards was shocked to be told by his GP that he needed to go back to the kidney clinic and talk about possible dialysis because his kidney function had suddenly dropped from 25 to 18 (see Fig. 2.8).

Careful study of the laboratory report revealed the mistake:

```
Patient: 123456            John Edwards
Date of Birth 14/08/1948   Female
Sample  B,13.0763622  (BLOOD)    Collected  16  Jun  2013  08:00
Received 16 Jun 2013 12:00
Urea & Electrolytes
    Sodium                141     mmol/L     (133 - 146)
    Potassium             5.0     mmol/L     (3.5 - 5.3)
    Urea         *        19.6    mmol/L     (2.5 - 7.8)
    Creatinine     *      235     µmol/L     (50 - 98)
    Estimated GFR     *   18      ml/min/1.73m2
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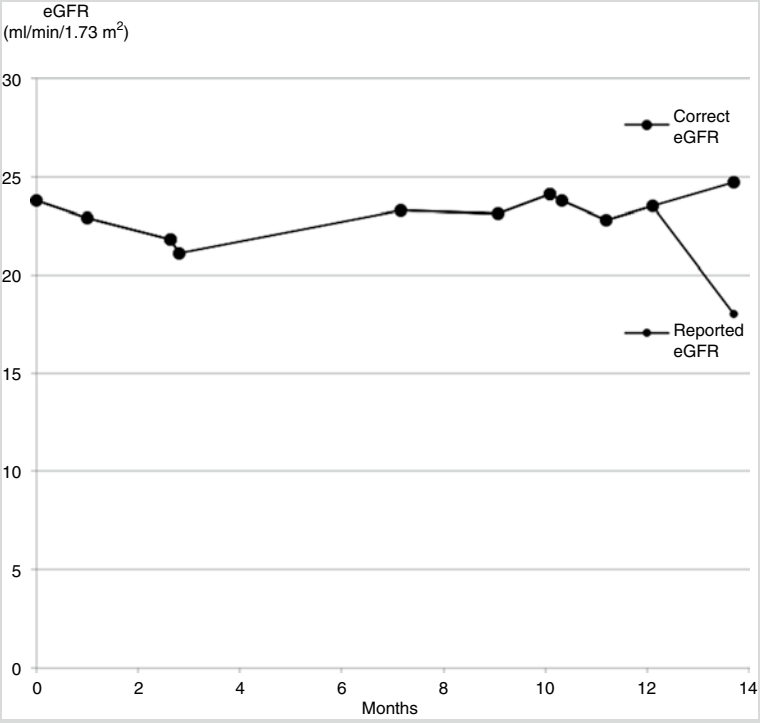

Fig. 2.8 Apparent drop in eGFR due to error on laboratory report

Patient 2.2: Biochemical 'Sex-Change'

Mrs Tracey Paul was delighted to be told at her routine diabetes clinic review that her kidney function had improved (see Fig. 2.9).

Unfortunately, the good news was an error; her kidney was declining after all. The error was picked up when a doctor questioned how serum creatinine and eGFR had both increased. Here is her laboratory report:

```
Patient: 234567          Tracey Paul
Date of Birth 02/07/1937     Male
Sample B, 13.0343712 (BLOOD)  Collected 15 Apr 2014 Received
15 Apr 2014 15:38
Urea & Electrolytes
    Sodium               139     mmol/L     (133 - 146)
    Potassium            4.9     mmol/L     (3.5 - 5.3)
    Urea         *       16.7    mmol/L     (2.5 - 7.8)
    Creatinine     *     144     µmol/L     (50 - 98)
    Estimated GFR    *   41      ml/min/1.73m2
```

Previous results:

Date	Sodium	Potassium	Urea	Creatinine	eGFR
15.01.2014	141	5.0	14.8	126	37

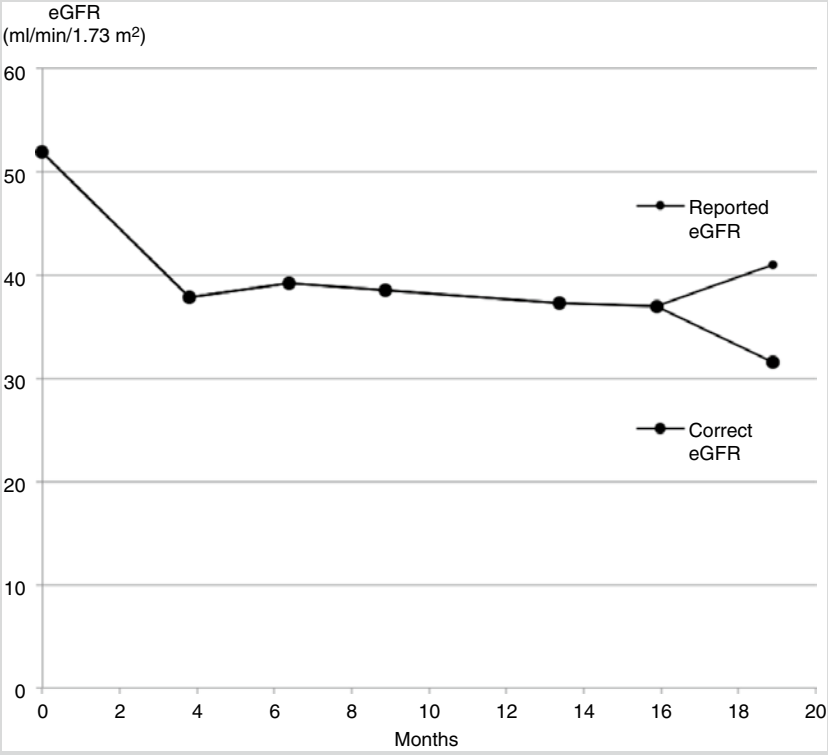

Fig. 2.9 Apparent rise in eGFR due to error on laboratory report

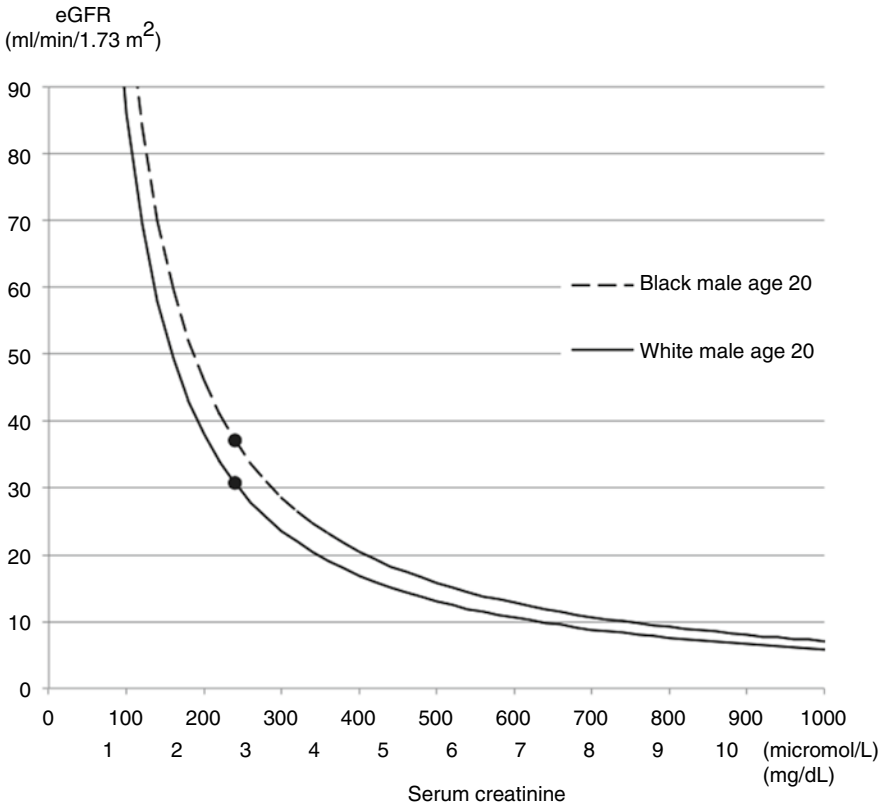

Fig. 2.10 eGFR (*filled circle*) calculated for white and black males aged 20 years (MDRD equation). For a man with a serum creatinine = 240 micromol/L (2.7 mg/dL), altering the race from white to black increases the eGFR by 21 %, from 31 to 37 ml/min/1.73 m^2

Not All Changes in Serum Creatinine Are Caused by Changes in GFR

Changes in serum creatinine do not necessarily indicate changes in glomerular filtration. Three other factors affect the serum creatinine concentration: dietary creatinine, muscle mass and secretion of creatinine by the tubules.

Dietary Creatinine

Little creatinine is absorbed from meat in a usual diet. However, meat that has been boiled, such as in goulash, leads to a rise in creatinine that lasts 8 h. Dietary supplements, such as protein shakes and creatine, do not alter GFR [13] but there can be a

transient increase in serum creatinine with excessive amounts. People who use these supplements do so to increase their muscle mass. Therefore it can be hard to work out whether a high serum creatinine level is due to the creatine supplements, a high muscle mass, reduced GFR, or a combination of all three.

In this situation, it is helpful to use an alternative maker of glomerular filtration to creatinine, namely cystatin C [14]. Cystatin C is a small protein comprising 120 amino acids that is produced by all nucleated cells, not just muscle. Its function is to inhibit enzymes that break down proteins, in particular extracellular cysteine proteases. It is freely filtered by glomeruli and then reabsorbed by the tubules; only small amounts are excreted in the urine.

Equations based upon cystatin C give a more accurate estimate of GFR when it is in the normal range and so are useful for distinguishing whether a raised serum creatinine is due to large muscle mass alone or a reduced GFR.

Patient 2.3: Big Muscles or Small Kidneys?

Emershan was a fit and healthy 33 year old black man. He had been a successful athlete, specialising in sprint distances. He had had his U&E's checked as part of a number of tests for chest pains, for which no cause was ever found. These were the results (Table 2.1).

Estimated GFR was 55 ml/min/1.73 m^2 (adjusted for black race)

His blood pressure was normal and urinalysis showed no blood or protein. Urinary albumin:creatinine ratio was 0.2 mg/mmol. A kidney ultrasound scan was normal.

He ate a normal diet with no creatine supplements.

He was anxious that he may have a kidney disease. To resolve the issue, serum cystatin C was measured. The result, 0.93 mg/L, gave an eGFR using the CKD-EPI Cystatin C (2012) equation of 95 ml/min/1.73 m^2. He was reassured.

Table 2.1 Emershan's blood results

Sodium	139 mmol/L	(133–146)		
Potassium	4.4 mmol/L	(3.5–5.3)		
Urea	4.3 mmol/L	(2.5–7.8)	BUN	12.0 mg/dL
Creatinine	130 micromol/L	(64–111)	Creatinine	1.47 mg/dL

Changes in Muscle Mass

Creatinine production is proportional to a patient's skeletal muscle mass. If a patient loses or gains a lot of muscle, the serum creatinine concentration will change independently of GFR. For example, patients who are seriously ill requiring care in an intensive therapy unit (ITU) can lose a substantial amount of body weight. As a result, their serum creatinine can be up to one-third lower after the illness. This reduces the apparent number of patients left with kidney damage on discharge from the ITU, and the severity of that damage as estimated from their serum creatinine [15].

Tubular Secretion of Creatinine

The equations used to estimate GFR take the tubular secretion of creatinine into account. However, problems arise when a patient is given a drug that blocks secretion of creatinine by the tubules. The most commonly used drug that does this is the antibiotic trimethoprim [16]. The anti-arrhythmic dronedarone has the same effect is some patients [17].

Treatment with these drugs will cause the eGFR to drop, even though the true GFR has not changed.

Patient 2.4: The Trimethoprim Effect

Rick, a longstanding kidney transplant patient receiving ciclosporin and prednisolone, was troubled by recurrent *Escherichia coli* urinary infections. These responded well to long-term treatment with alternating courses of trimethoprim and cephalexin. Each time Rick took trimethoprim the eGFR dropped and he was worried that his transplant was being damaged (Table 2.2).

The serum urea was the clue that the tubular effect of trimethoprim was causing a rise in creatinine. It did not rise with the serum creatinine, suggesting that the true GFR was unchanged.

Table 2.2 Sequential biochemical results in a kidney transplant patient receiving prophylactic antibiotics

Date	Urea (mmol/l)	Creatinine (micromol/L)	BUN (mg/dL)	Creatinine (mg/dL)	eGFR (ml/min/1.73 m^2)	Antibiotic
22 Oct 2013	13.3	168	37.3	1.90	40.2	TMP
05 Nov 2013	13.0	166	36.4	1.88	40.8	TMP
21 Jan 2014	12.6	136	35.3	1.54	51.5	Ceph
27 May 2014	11.7	167	32.8	1.89	40.4	TMP
26 Aug 2014	12.5	147	35.0	1.66	46.9	Ceph

TMP trimethoprim, *Ceph* cephalexin

Serum Urea and Creatinine – Different Measures of Kidney Function

Changes in serum urea can give useful additional information about what is happening to kidney function. Urea and creatinine are both filtered by the glomeruli but only urea can diffuse across cell membranes and be reabsorbed from the tubules.

The amount of urea reabsorbed is determined by the rate of flow of filtrate along the nephron. When the rate slows, more urea is reabsorbed and the rate of excretion falls (see Fig. 2.11).

How does this difference affect a patient's results? Consider two people: one with polycystic kidneys (ADPKD), the other with normal kidneys but low blood pressure due to prolonged diarrhoea. In the man with ADPKD, half of the nephrons have been affected by cysts and do not function – his GFR is half-normal. However, the rate of flow of filtrate in the functioning nephrons is normal and he produces a normal volume of urine per day.

In the man with low blood pressure, the nephrons are filtering at half the normal rate – his GFR is also half-normal. To compensate for the hypovolaemia, salt and water are reabsorbed from the tubules into the blood and the flow of filtrate along the nephrons is slow. Urine volume is reduced.

Because the glomerular filtration rate is halved, the concentration of creatinine is doubled in both patients. However, in the second patient, the slower flow of filtrate along the nephrons allows more urea to diffuse out of the tubules into the blood. As a result, the serum urea concentration is higher in the second patient than in the first.

Calculating the ratio of serum urea to serum creatinine shows this effect (Table 2.3).

A urea-to-creatinine ratio >100 (BUN-to-creatinine ratio >20) is often said to indicate dehydration but can occur in any situation in which the flow of filtrate along the nephrons is slowed. It is a marker of a pre-renal or, more precisely, pre-glomerular cause of kidney impairment.

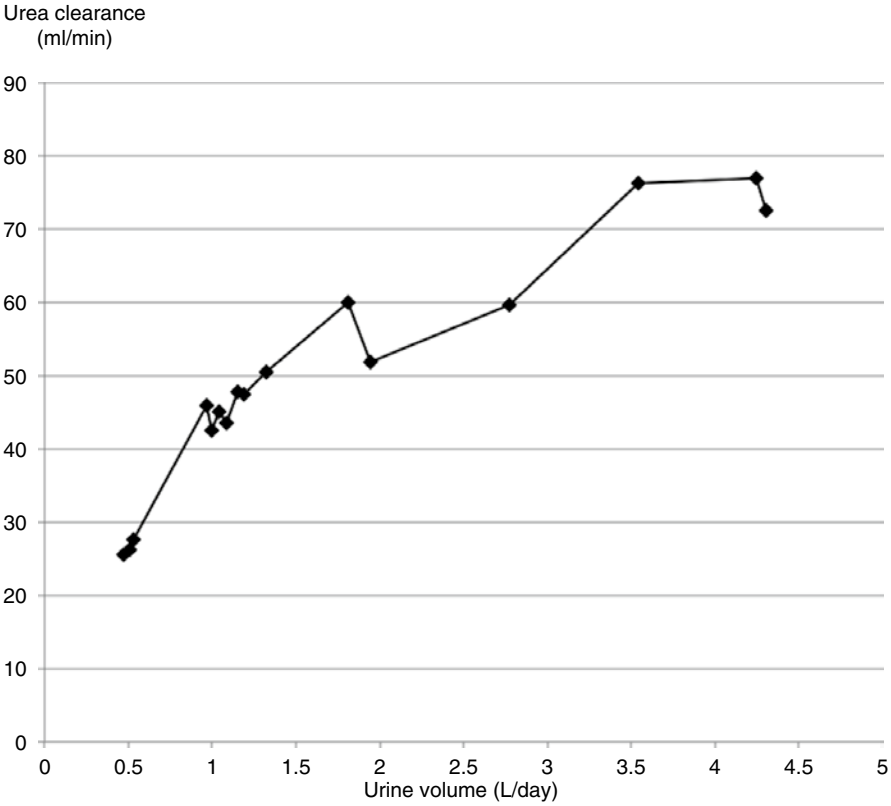

Fig. 2.11 Effect of urine volume on the rate of excretion of urea, calculated as the urea clearance. *Filled diagonal box* indicate measurements of serum creatinine (Redrawn from clearance values reported in [18]. Data are from samples taken from Harold Austin, published in 1921 [19])

Table 2.3 Calculation of the urea-to-creatinine ratio

	ADPKD	Low blood pressure
Urea (mmol/L) BUN (mg/dL)	10.2 28.6	33.5 93.8
Creatinine (micromol/L) Creatinine (mg/dL)	160 1.8	160 1.8
eGFR (ml/min/1.73 m^2)	38.9	38.9
Urea-to-creatinine ratio BUN-to-creatinine ratio	10,200 ÷ 160 = **63.8** 28.6 ÷ 1.8 = **15.9**	33,500 ÷ 160 = **209.4** 93.5 ÷ 1.8 = **51.9**

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