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Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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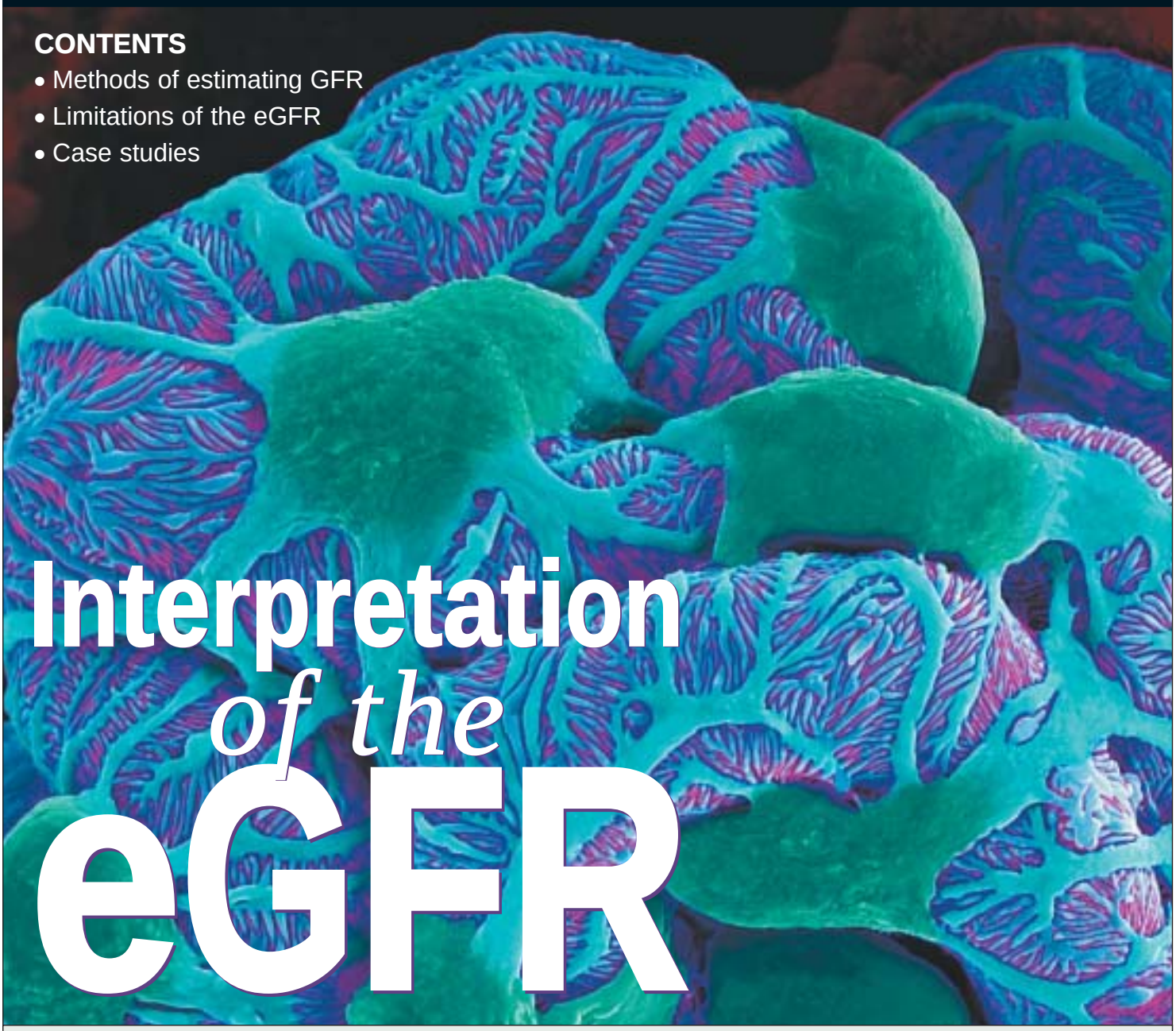

Interpretation *of the* eGFR

A JOINT INITIATIVE OF RCPA The Royal College of Pathologists of Australasia Australian Doctor.

Interpretation of the eGFR


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Introduction

During the past 1.5 years, pathology laboratories have started reporting the eGFR (estimated glomerular filtration rate) with every request for a serum creatinine in adults. The eGFR is an estimate of the GFR, calculated from the serum creatinine and the patient's age and sex, and has been introduced to improve the recognition of reduced renal function, such as occurs in chronic kidney disease (CKD).

The eGFR is proving to be a reliable estimate of renal function with accuracy equal to, or better than, any easily available alternative. However, as with all tests, there are strengths and weaknesses to this calculation. Its key strengths are the easy availability and the proven accuracy across both sexes and a wide range of body shapes and ages. Its limitations include its dependence on the measurement of the serum creatinine, the lack of current validation in all racial groups and concerns over its use for making drug-dosing decisions. Like any pathology test, the eGFR is only as good as the interpretation and the actions that are based on it. In this article, we provide some background to the test and some clinical cases to illustrate its use in patient management.

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The importance of GFR

The GFR is the single most important parameter of renal function for identifying and classifying CKD (table 1). Normal renal function is present when the GFR is more than 90mL/min/1.73m^2 but function may be considered normal for age at levels less than this, particularly when the age exceeds about 60. Age-related GFR reference intervals have not been established. At a GFR of 60-90mL/min/1.73m^2 (and even when it is more than 90mL/min/1.73m^2) CKD is said to be present if there is ancillary evidence of kidney damage, most commonly proteinuria. Importantly, a GFR less than 60mL/min/1.73m^2 on two occasions more than three months apart defines the presence of CKD.

A diagnosis of CKD is of great significance for patients with regard to both morbidity and mortality, being associated with a poor quality of life due to fatigue, anaemia and risk of progression to end-stage disease, as well as increased mortality mainly due to cardiovascular disease. The aim of early identification of CKD is to institute the relevant investigations and management in order to prevent these complications.

Methods of estimating GFR

The eGFR, calculated using the MDRD formula (named after the Modification of Diet in Renal Disease study where it was developed), is only one of several tools for estimating the GFR. The various ways of estimating GFR are listed in table 2 and each method has its strengths and weaknesses.

> *A rise in serum creatinine of 20%, especially in the acute setting, should trigger investigations as to the cause, even if the serum creatinine remains within the population reference interval.*

Serum creatinine alone is difficult to convert to an estimate of GFR without a formal calculation and is not recommended for the purpose of assessing severity of reduction in renal function. However, the most sensitive indicator of minor reductions in GFR is a rise in serum creatinine compared with the patient's own previous result. A rise in serum creatinine of 20%, especially in the acute setting, should trigger investigations as to the cause, even if the serum creatinine remains within the population reference interval.

The eGFR calculated using the MDRD formula is the most accurate of any of the creatinine-based calculations and should be used unless there are specific reasons to the contrary such as extremes of body size or in amputees. Its ready availability without the need for additional calculations ensures that any marked reductions in GFR are easily apparent.

The Cockcroft and Gault equation is the recommended tool for drug-dosing decisions in commonly available material such as *MIMS*,

Table 1. Classification of chronic kidney disease (CKD)

Stage	GFR (mL/min/1.73m^2)	Description	Comment
1	≥90	Kidney damage with normal or increased GFR	CKD only if other signs of kidney damage, eg, proteinuria, haematuria or scarred kidneys, seen on imaging
2	60-89	Kidney damage with mildly decreased GFR	CKD only if other signs of kidney damage, eg, proteinuria, haematuria or scarred kidneys, seen on imaging
3	30-59	Moderately decreased GFR	CKD if persistent for ≥3 months
4	15-29	Severely decreased GFR	CKD if persistent for ≥3 months
5	<15	Kidney failure	CKD if persistent for ≥3 months

Australian Medicines Handbook and *Therapeutic Guidelines*. This is due, at least in part, to historical reasons and to the lack of resources to formally consider the use of the MDRD equation for this purpose. It is our belief that, for most outpatient settings, in the absence of extremes of body composition, the eGFR is probably sufficient for making drug-dosing decisions.

The measurement of creatinine clearance, requiring a 24-hour urine collection, is the most cumbersome of the creatinine-based tests. It is the least accurate but remains a useful test in patients with abnormal body composition (eg, very low or high proportions of body fat or muscle). Formal measurement of GFR in a nuclear medicine laboratory is usually reserved for specialised centres.

Limitations of the eGFR

While the eGFR is the preferred method for the estimation of kidney function in most circumstances, it has a number of limitations. In each clinical case, the limitations need to be considered in the light of any possible alternative tests. The following issues should be borne in mind:

- *Accuracy* The eGFR is accurate to about plus or minus 30%. Therefore, a result of 60mL/min/1.73m^2 may represent a true value between 42 and 78mL/min. While this is not ideal, the eGFR has higher accuracy than any of the alternative creatinine-based methods.
- *Racial groups* The eGFR has not yet been validated for any racial groups found in Australia other than Caucasians. It is known from the original study that a modification of the formula is needed for African-Americans. As it is likely that any differences are related to body composition, care should be taken with its interpretation in any person of extreme muscularity, obesity or emaciation regardless of race, and race alone should not preclude the use of the test.
- *Creatinine measurement* All the formulae mentioned above are based on serum creatinine. Potential pitfalls are interferences in creatinine assays that may occur due to, for example, recent cooked meat ingestion and interference from some drugs such as cephalosporins. Only the eGFR has been derived using current standardised creatinine assays.
- *Acute changes* Very rapid deterioration in kidney function may be underestimated by the eGFR.

Table 2. GFR estimation tools

Method	Requirements	Comment
Serum creatinine	Serum creatinine	Difficult to convert to GFR
eGFR	Serum creatinine, age and sex eGFR = 186 × (SCr x 0.0113)$^{-1.154}$ × (age)$^{-0.203}$ [× 0.742 if female]	Most readily available result
Cockcroft and Gault	Serum creatinine, age, sex and weight C&G = (140-age) × weight / (0.81 × SCr) [× 0.85 if female]	Recommended for drug-dosing decisions
Creatinine clearance	Serum creatinine and timed 24-hour urine creatinine	For extremes of body composition
Measured GFR	Nuclear medicine test	"Gold standard" Expensive and time-consuming

Notes about the formulae
SCr: Serum creatinine concentration in µmol/L; age in years; weight in kg.
eGFR: the coefficient 186 is to be replaced with 175 for assays aligned with the international reference method.
Results expressed in mL/min/1.73m^2.
Cockcroft and Gault: This is an estimate of creatinine clearance. Results expressed in mL/min. An ideal body weight, estimated from the patient's height, is commonly recommended in place of actual body weight for overweight or obese subjects. Ideal body weight can be calculated as follows: Males (kg) = 50kg plus 0.9kg for every cm of height >152cm; Females (kg) = 45.5kg plus 0.9kg for every cm of height >152cm.

This is because serum creatinine takes some time to accumulate after a sudden fall in GFR. Therefore in this circumstance both serum creatinine and eGFR may underestimate the severity of the renal impairment. Awareness of the rate of change of either provides a clue to the severity of the condition. However, this type of rapid change is rare outside the emergency situation.

Case study 1

JD, a 35-year-old healthy female with a family history of CKD, sees you with multiple bruises two days after a minor car accident.

Her blood chemistry (never done before) taken at the time of her presentation revealed the following results:

Serum creatinine	120µmol/L (reference interval 40-90µmol/L)
eGFR	47mL/min/1.73m^2

Does JD have CKD?

The definition of CKD requires demonstration that the abnormalities have persisted for more than three months. This is to ensure that acute changes are not wrongly classified. In clinical practice, if there are no obvious causes for an acute deterioration in kidney function and the abnormality persists for more than a few days, it is usually reasonable to conclude that CKD is present. However, acute kidney disease should always be considered and promptly followed.

Is JD's kidney function impairment important?

Yes. At the age of 35, the 'normal' GFR is about 90mL/min. Cohort studies have shown that the long-term complications associated with reduced GFR begin to appear at levels less than 60mL/min. Drug handling by the kidney will clearly be affected at this level of GFR. If JD had previously donated one kidney, the GFR could be expected to be in this range (that is, about half the normal value).

Should you correct the eGFR for her body surface area to make it an actual GFR?

No. The grading of severity of the reduced GFR is based on the value corrected for a standardised body surface area as part of the eGFR equation. This is why the results are reported as a rate (mL/min) per 1.73m^2 (a standardised body surface area). The only requirement for using an actual GFR result that is 'uncorrected' for body surface area is for making drug-dosing decisions in patients with abnormal body composition, for which the Cockroft and Gault equation is recommended.

> *Simple bruising alone, even if extensive, does not elevate the serum creatinine concentration.*

Could the bruises have contributed to the elevated serum creatinine concentration?

No. Simple bruising alone, even if extensive, does not elevate the serum creatinine concentration.

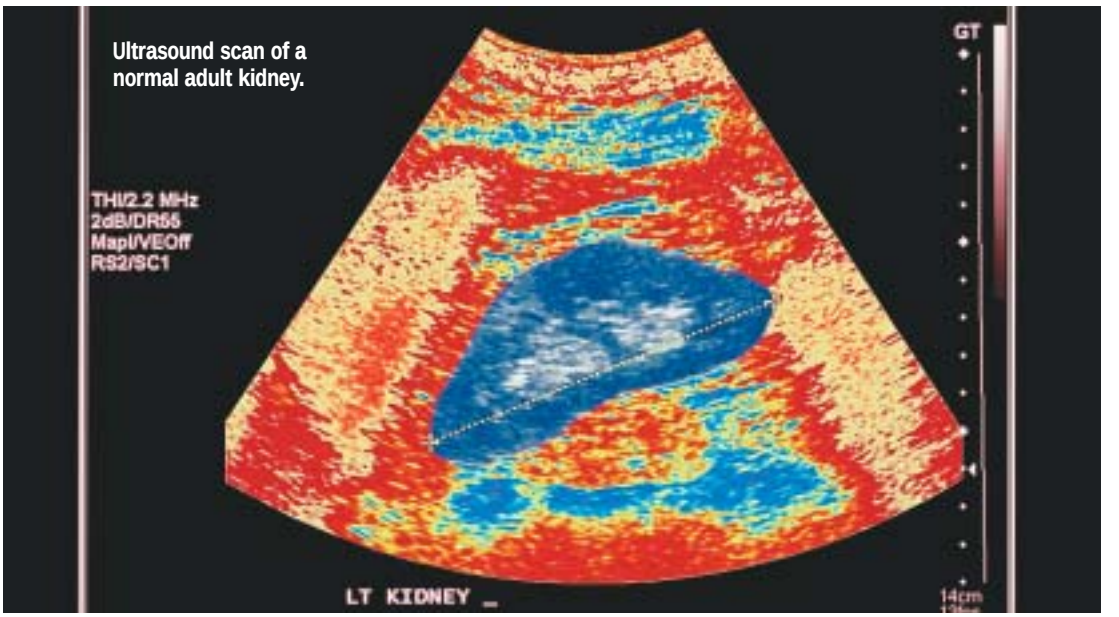
With severe muscle injury, such as occurs in compartment syndrome or with rhabdomyolysis, excess creatine is released from muscles and is metabolised to creatinine, which can cause a mild temporary increase in serum creatinine concentration.

Does JD require further investigations? If so, what initial investigations would you perform?

Yes, as these findings suggest either acute kidney disease or CKD. First, however, a careful clinical history and full physical examination, focusing on CKD, should be performed. Investigation should follow even if history and physical exam are non-contributory.

The first investigation is a urine dipstick for protein and blood. The sensitivity of the dipstick is such that a negative result for blood excludes microscopic haematuria. Haematuria, if present, should be pursued by sending a fresh urine specimen for phase-contrast microscopy to determine red blood cell morphology.

A negative result for protein means that, at most, microalbuminuria may be present. Protein-



uria, if present, should be quantified. The presence of more than 1g/day of proteinuria is associated with a reduced prognosis.

In all cases of CKD, an ultrasound of the kidneys and bladder should be performed to exclude obstruction, establish the presence of two kidneys and allow an assessment of the renal parenchyma for scars.

JD's repeat tests confirmed the original eGFR, her ultrasound was normal and the urine showed dysmorphic red cells (glomerular red blood cells) and a protein/creatinine ratio of 150mg/mmol (normal is ≤25mg/mmol), which is equal to a 24-hour urine protein of 1.5g. What is the likely cause of her kidney disease?

The combination of glomerular bleeding and the significant amount of protein in her urine together with the reduced GFR indicate renal parenchymal damage, most likely due to glomerulonephritis which may be familial. Other causes of serious kidney disease at her age include reflux nephropathy and vasculitis.

Should she be referred to a nephrologist?

Yes and the referral should be achieved without delay. Acute treatable kidney disease (such as vasculitis, SLE or acute proliferative glomerulonephritis) has not been excluded. Renal biopsy is indicated and is likely to be performed within a day or so of referral.

Comment

The car accident in this case study led to the chance finding of stage 3 CKD and follow-up investigations revealed findings consistent with parenchymal damage, most likely due to glomerulonephritis.

JD's serum creatinine concentration of 120µmol/L may well have been overlooked in the past as being within the reference interval. Reference intervals in Australian laboratories are not uniform and many laboratories do not use a gender-adjusted interval. The reference interval recommended for laboratories using a standardised creatinine measurement is likely to be about 40-90µmol/L for women and 60-110µmol/L for men. The automatic reporting of eGFR assists greatly in highlighting the significant reduction in kidney function, as is evident in this case study.

Case study 2

HR, an 81-year-old female, visits you for a repeat prescription of the antihypertensive medications she has been taking for 15 years. A recent biochemistry test showed:

Serum creatinine	98µmol/L (reference interval 40-90µmol/L)
eGFR	50mL/min/1.73m^2

Does HR have CKD?

Yes. A previous serum creatinine concentration from one year ago confirms the current finding, consistent with the diagnosis of stage 3 CKD. There are currently no adjustments for age made to the eGFR when defining the stages of CKD. However, GFR does decline with age, although it is uncertain whether this decline is associated with 'healthy' ageing or represents kidney damage (eg, secondary to vascular disease) that occurs more frequently with advancing years.

Is this level of reduced GFR clinically important at her age?

Yes. While a reduction of eGFR to 50mL/min/1.73m^2 is not uncommon in 80-year-olds in our population, it remains potentially significant with regard to the late complications of CKD (such as progression to end-stage kidney disease and anaemia). However, a recent large study has failed to show a significant independent association with mortality in the elderly for eGFR values more than 45mL/min/1.73m^2. For patients older than 70 with an eGFR between 45 and 59mL/min/1.73m^2, once other risk factors have been assessed, it may be appropriate to treat conservatively. Of course, this reduction in eGFR remains important when making drug-dosing decisions.

What investigations should you perform?

At a minimum, HR should have a urinalysis including dipstick for protein and blood and an ultrasound of her kidneys and bladder. The biochemistry should be repeated in about six months to reassess the stability of her GFR.

On review, HR's results showed a normal ultrasound and negative urinalysis for blood and protein and confirmed the eGFR reduction. Should management be altered in view of these findings?

The management plan, because of her age, could in effect be that of stage 2 CKD rather than stage 3. Careful attention should be paid to cardiovascular risk reduction and modification of drug doses appropriate to this level of kidney function. Otherwise, a wait-and-watch approach is appropriate with six-monthly reviews.

If the ancillary investigations show abnormalities, use clinical judgment to assess the need for further investigations and specialist referral.

Comment

HR has a serum creatinine concentration in the 'normal' range yet still has significant impairment of kidney function (stage 3 CKD). It is likely that this would have been missed without the automatic reporting of eGFR. Her management plan needs to be altered by this finding and appropriate attention paid to drug dosing and cardiovascular risk reduction commensurate with her age of more than 80.

Case study 3

RT is a 58-year-old businessman who exercises regularly, doesn't smoke and drinks wine most nights. His hypertension has been controlled for 10 years on two medications. He has requested a "kidney health check" after seeing advertising that led him to believe he was at high risk of CKD.

His urinalysis was negative.

Serum creatinine	104µmol/L (reference interval 60-110µmol/L)
eGFR	68mL/min/1.73m^2

Does RT have CKD?

No. Without other evidence of kidney damage, an eGFR of less than 60mL/min/1.73m^2 is needed to make this diagnosis.

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Why have laboratories begun to report actual figures in the range of 60-89mL/min/1.73m², such as in the case of RT?

This change has been made since laboratories have achieved greater accuracy in measuring serum creatinine concentration, which has allowed more accurate estimates of eGFR in this range.

What is the significance of a reduced GFR in the range 60-90mL/min?

From a clinical viewpoint, if the eGFR is stable in the 60-90mL/min range over time, and is not associated with other evidence of kidney damage, there appears to be little clinical consequence.

Does RT require further investigation of his kidneys?

Provided that his urinalysis is repeated and is again normal, he is asymptomatic and his blood pressure remains well controlled, no further investigations should be performed.

Is the management of RT altered by his reported eGFR?

No. His hypertension and age place him in a high-risk group, so annual screening of his serum creatinine concentration and urinalysis is indicated. The finding of an eGFR of 68mL/min/1.73m² is compatible with normal health and the ability to handle usual doses of renally cleared drugs.

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