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Common Sense Pathology

A REGULAR CASE-BASED SERIES ON PRACTICAL PATHOLOGY FOR GPs

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Assessing renal function

A JOINT INITIATIVE OF

 **RCPA**
The Royal College of Pathologists of Australasia

Australian
Doctor.

Dear Colleagues,

I am pleased to present to you an excellent article on the assessment of renal function, written by Prof. Michael Field. This is an unusually precise and clear article that is impossible to read without learning and understanding something new and useful about the subject.

After you have read it, perhaps twice, you may wish to consider the following:

- The case of an elderly patient whose renal function appears to be deteriorating clinically but whose creatinine has risen only slightly, in particular where the person is losing weight.
- The case where the urea is rising but the serum creatinine is not.
- The case where the serum creatinine is rising but the urea is not.
- The benefits, if any, of measuring blood urea.
- The concept of renal reserve, how that affects the relationship between serum creatinine and renal function, and how it makes management in the elderly generally different to that in the young.
- Why heart failure and anaemia can be harbingers of worsening renal function, particularly in the elderly.

Afterwards, I would suggest that you cut Prof. Field's article from its page and graft it within your reference library. .You will return to it someday.

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Assessing renal function

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Introduction

There are many reasons for GPs and other clinicians to know the level of renal function of their patients. These include explaining a range of presenting symptoms, establishing the involvement of the kidney in a systemic disease process (such as diabetes) and making appropriate judgments concerning prescription of drugs.

For the purpose of this article, renal function will be taken to mean the GFR, the single most important measure of overall renal performance in most situations. There will be no discussion of the many other forms of laboratory investigation that may help to diagnose various aspects of renal disease, such as tests of tubular function (including urinary concentration and acidification), urine microscopy and culture, or renal biopsy for the assessment of histopathological change in the renal parenchyma. Although isotopic imaging techniques and other infusion protocols can be used to determine the GFR, the focus here will be on the interpretation of the plasma creatinine and urea, which are by far the most commonly used indicators of global renal function.

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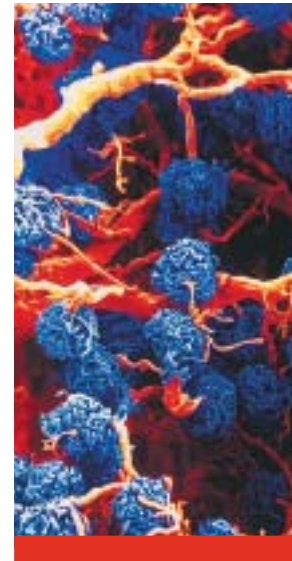
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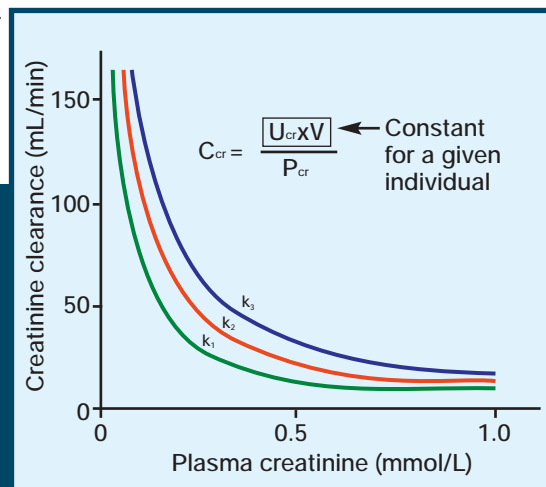
Creatinine and the GFR

The normal GFR in adults is 90-138mL/min (1.5-2.3mL/s). Although SI units are strictly in mL/s, mL/min is used more widely in clinical settings, and therefore will be used in the remainder of this article. Ideally the GFR estimate in a patient should be corrected for body surface area and expressed for a 'standard' surface area of 1.73m², but this requires measurement of a patient's height and weight, and the correction is not usually made in clinical practice. GFR declines with age, although the rate of decline is highly variable. It may thus be 'normal' or expected for the GFR to be reduced in elderly patients, but this should not be dismissed without appreciating the implications of the impaired renal function for fluid and electrolyte metabolism and the pharmacokinetics of administered drugs. Renal impairment is generally considered mild for GFRs in the range 60-90mL/min, moderate for 30-60mL/min, and severe if less than 30mL/min.

Because it is impossible to obtain a direct measurement of the haemodynamics of glomerular filtration in intact subjects, the clearance concept is used to estimate this important parameter indirectly. It can easily be shown¹ that for a substance that is freely filtered by the glomerulus, but neither reabsorbed nor secreted by the renal tubules, the clearance of that substance (calculated as the ratio of the rate of excretion of the substance divided by its plasma concentration, or $U_{cr}V/P_{cr}$) provides an indirect measure of the rate of glomerular filtration. While several chemical markers act as ideal substances for this purpose, creatinine, a metabolite of the muscle compound creatine, behaves approximately in the way described (although there is some tubular secretion at high plasma concentrations). Creatinine is released endogenously by skeletal muscle at a steady rate in proportion to muscle mass, so an estimate of GFR can be obtained by collecting a timed urine specimen (typically over 24 hours) with a plasma sample, both for creatinine estimation, in this period. Since for a given subject, the muscle mass and the urinary creatinine excretion rate ($U_{cr}V$) is constant, it follows that in a steady state the plasma creatinine is inversely proportional to the GFR, estimated by the creatinine clearance.

This analysis gives rise graphically to the relationship between GFR and plasma creatinine shown in figure 1. The figure shows the curves for this relationship in three subjects of different body weight, showing the shift in position of the hyperbolic function as muscle mass increases.

Figure 1. Relationship between creatinine clearance and plasma creatinine in three subjects.



- C_{cr} — creatinine clearance
- U_{cr} — urine creatinine concentration
- V — urine flow rate
- P_{cr} — plasma creatinine concentration
- k_1 — curve for a small-average patient
- k_2 — curve for heavier patient
- k_3 — curve for heaviest of the three patients

Interpreting the plasma creatinine

Several important consequences follow from the relationships just discussed. The usual reference intervals given for plasma (or serum) creatinine concentration are shown in table 1.

Table 1. Typical reference intervals for plasma creatinine²

Child < 12 years	0.04 – 0.08mmol/L
Adult: female	0.05 – 0.11mmol/L
Adult: male	0.06 – 0.12mmol/L



In general terms, there is dependence both on age and (in adults) on sex, but a close inspection of figure 1 shows care needs to be taken to interpret an isolated value for plasma creatinine in relation to body skeletal muscle mass, itself closely related to age and sex. For a given plasma creatinine (eg, 0.1mmol/L), the underlying GFR might be significantly reduced in a patient of low-muscle mass (curve k_1) or quite normal for a higher muscle mass (curves k_2 and k_3). A second implication of the curves in figure 1 is that small increases in plasma creatinine in the upper part of the reference interval indicate sharp reductions in GFR. This makes the test powerful because an initial increase in plasma creatinine represents a major decrease in GFR. Put another way, a substantial fall in GFR is necessary to shift the baseline plasma creatinine in a new steady state of renal function (although the impact of laboratory imprecision in this range is also proportionately greater).

The Cockcroft-Gault equation

Given the difficulties in deducing the GFR level from the plasma creatinine alone, and the inconvenience and inaccuracy of timed urine collection studies for determining creatinine clearance, use is generally made of empirical formulae that relate creatinine clearance to plasma creatinine, taking into account body weight, age and sex. Most of these formulae are derived from the original equation published by Cockcroft and Gault³ and are increasingly widely used, especially because they have been incorporated in calculators built into desktop computer software. In its best-known form, the equation is:

$$\text{estimated GFR (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{814 \times \text{plasma creatinine (mmol/L)}}$$

In this form the equation applies to men; the result should be multiplied by 0.85 for women to allow for the relatively lower proportion of body weight, which is muscle. Three factors to remember in using the equation: it assumes stable renal function; is unreliable at extremes of renal function (very high and very low GFR); and is unlikely to be accurate when normal body composition is disturbed (such as with marked oedema, obesity, pregnancy and severe muscle wasting).

The following case examples show the importance of these factors in interpreting the plasma creatinine.

Case one

A 24-year-old man weighing 86kg is assessed for an episode of macroscopic haematuria shortly after an episode of acute viral pharyngitis. A diagnosis of mesangial IgA nephropathy is suspected, and a renal biopsy is planned. To determine whether GFR is impaired, a plasma creatinine is requested, and the result is 0.13mmol/L.

Question: Is renal function impaired in this patient?

Clearly the creatinine result appears slightly above the usually quoted reference interval so the GFR may be assumed to be reduced. Inserting this data into the Cockcroft-Gault equation reveals the GFR is 96mL/min, which is normal.

In this case, the young age, male sex and high body-mass, largely due to muscle, means the moderately high plasma creatinine does not necessarily reflect reduced GFR.

Case two

A 79-year-old woman weighing 53kg is admitted to hospital with suspected DVT. She is treated with enoxaparin (Clexane), and a check of renal function is performed because the dose of this medication should be reduced when glomerular filtration rate is impaired. A plasma creatinine of 0.12mmol/L is obtained.



Question: Is any adjustment of the drug dose required in relation to renal function?

Again, in this case the creatinine is barely above the reference interval for women (refer page 3) and the assumption might be made that GFR is almost normal. Inserting the data into the Cockcroft-Gault formula (and allowing for 0.85 multiplier for female sex) reveals her GFR is markedly reduced at 30mL/min, and the dosing regime for enoxaparin would need to be significantly modified downwards.

These two examples show the importance of taking patient factors into account in interpreting the plasma creatinine. The comparison between these cases shows that the patient with the higher creatinine had the better preserved GFR.

Appropriate use of the Cockcroft-Gault formula will identify more patients as having impaired GFR than would otherwise be apparent from considering plasma creatinine values which are outside published reference intervals. This observation has been put to dramatic effect in a recent epidemiological study seeking to define the prevalence of impaired renal function in a defined patient population⁴. In specific at-risk patient groups, such as those with diabetes, systemic lupus erythematosus and glomerulonephritis, an early indication of glomerular involvement may be obtained by judicious use of the formula. A second important application of the formula is to guide the dosing regime to be employed with drugs that are renally excreted, where the dose must be reduced in proportion to the degree of renal impairment to avoid drug accumulation and adverse effects. Three prominent drugs in this category are digoxin, gentamicin and (as in the example above) enoxaparin. In the case of drugs that are themselves capable of producing nephrotoxicity, dose reduction or drug avoidance may also be appropriate where GFR is already impaired. A good example would be the non-steroidal anti-inflammatory drugs, including COX-2 inhibitors.

It is possible to construct tables showing the estimated GFR corresponding to a given level of plasma creatinine for patients of both sexes at several specific weight levels. Such charts (see table 2 below) are sometimes produced by hospital pharmacies, and their prominent display in drug treatment areas draws attention to the need for care in interpreting plasma creatinine results.

Table 2. Extract from chart for estimating GFR (mL/min) (age 70 only shown)

		Plasma creatinine 0.10mmol/L				
Age	Sex	Weight				
		50kg	60kg	70kg	80kg	90kg
70 years	M	43	52	60	69	77
	F	37	44	51	58	66

		Plasma creatinine 0.15mmol/L				
Age	Sex	Weight				
		50kg	60kg	70kg	80kg	90kg
70 years	M	29	34	40	46	52
	F	24	29	34	39	44

		Plasma creatinine 0.20mmol/L				
Age	Sex	Weight				
		50kg	60kg	70kg	80kg	90kg
70 years	M	21	26	30	34	39
	F	18	22	26	29	33



One unusual circumstance affecting plasma creatinine should be mentioned. The assay can detect creatinine absorbed from ingested animal muscle, so unexpectedly elevated levels obtained from subjects who have recently eaten a large meat meal should be repeated at a later time.

Plasma urea

Urea has been used for many decades as a marker of renal function because, like creatinine, it accumulates in states of reduced glomerular filtration. Unlike creatinine, it undergoes about 50% reabsorption during passage through the nephron. The clearance of urea is about half the GFR, and plasma urea varies inversely with the GFR.

Urea is less valuable as a measure of GFR than creatinine for several reasons. First, urea reabsorption is increased in conditions of dehydration and low-urine flow rate. Plasma urea is influenced not only by the GFR but also by the state of hydration. Second, hepatic urea production is related to intestinal protein absorption, and the protein catabolic rate. A high dietary protein intake, or factors such as sepsis and steroid therapy, will lead to an increased plasma urea without implication of reduced GFR. Third, because urea is produced in the liver, its production is reduced in cases of advanced liver failure, making it misleading as an index of renal function under those circumstances.

Table 3 summarises the separate factors that cause an increase in plasma creatinine and plasma urea concentrations. These factors need to be kept in mind in the interpretation of the next two clinical cases.

Table 3. Principal factors causing an increase in plasma creatinine and urea

Creatinine	Urea
Decreased GFR	Decreased GFR
Increased skeletal muscle mass	Decreased hydration/urine flow rate
	Increased protein intake:
	- diet
	- gastrointestinal bleeding
	Increased protein catabolism:
	- sepsis
	- steroid therapy
	- some tetracycline antibiotics

Case three

A 29-year-old woman is brought into a rural hospital after being lost in the bush for 48 hours. In this time she ran out of water and became very thirsty, although she did not collapse.

Results for plasma taken on her arrival are shown below, and the results after 48 hours of intravenous rehydration are given for comparison (all in mmol/L).

	Admission	48 hours later
Urea	17.4	8.5
Creatinine	0.12	0.11

Question: What accounts for the greatly different extent of change in the plasma urea and plasma creatinine results?

In this patient the plasma creatinine was initially at the upper limit of normal, and fell minimally after 48 hours of rehydration. Although information to allow estimation of the GFR is not given, there may have been GFR impairment on arrival with a modest increase in filtration after two days in hospital. The marked reduction in urea reflects, in addition to any GFR change, a dramatic improvement in patient hydration. The fall in plasma urea has been brought about to a minor extent by the increase in GFR, but to a major extent by the increased urine flow rate with its concomitant effect in enhancing urea clearance.

This differential effect of hydration state on urea versus creatinine has given rise to use of the urea/creatinine ratio as a means of assessing the extent of 'pre-renal' (hypovolaemia- and hypotension-related) factors in contributing to oliguria in patients with acute renal insults.

Case four

A 62-year-old man is admitted to hospital with an acute neurological disorder requiring treatment with corticosteroids. He is given prednisone in a daily dose of 100mg orally, with evidence of response in his condition. After five days of treatment he has an episode of melaena indicative of upper gastrointestinal bleeding. His plasma urea and creatinine results on admission and on the day of the GI bleeding episode are shown below (all in mmol/L).

	Admission	Five days later
Urea	6.5	17.2
Creatinine	0.12	0.11

Question: What factors have differentially influenced his plasma levels of urea and creatinine?

In this case there appear to have been movements in opposite directions in these two markers of renal function. The slight fall in plasma creatinine may represent a small degree of enhancement in the GFR, which is a known effect of corticosteroid administration (for haemodynamic reasons, even in the absence of intra-renal inflammation). The dramatic increase in plasma urea cannot be due to GFR impairment in this case, and other factors must be contributing. In this patient the culprits would be: (a) the prednisone administration, with its catabolic effects on protein metabolism; and (b) the GI bleeding, which leads to a 'meal' of protein-rich blood in the GI tract, which is effectively absorbed and metabolised as protein.

It is obvious that a clear understanding of the different factors that can influence plasma concentrations of urea and creatinine is essential in interpreting pathology results in situations such as those illustrated here.

Summary

Plasma creatinine is an excellent marker of renal function, in that it is influenced by changes in the GFR and little else in the short term. Its interpretation must take into account factors influencing the patient's skeletal body mass, namely the age, weight and sex. The use of the Cockcroft-Gault formula effectively does this and provides a rapid estimate of GFR and a practical guide to clinical decision-making.

The plasma urea is influenced by several factors other than the underlying GFR. With knowledge of these factors, additional information can be deduced by comparing changes in plasma urea and creatinine levels in a given patient under changing clinical conditions.

References

1. Field MJ, Pollock CA, Harris DC. *The Renal System*. Churchill Livingstone, Edinburgh 2001.
2. Royal College of Pathologists of Australia. *Manual of Use and Interpretation of Pathology Tests* (2nd edn). RCPA Sydney 1997.
3. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16:31–41.
4. Cumming RG, Mitchell P, Craig JC, Knight JF. Renal impairment and anaemia in a population-based study of older people. *Internal Medicine Journal* 2004; 34:20–23.





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