Monitoring kidney function in diabetes

Frequently asked questions

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If microalbuminuria is the earliest indicator of diabetic nephropathy why measure plasma creatinine?

Both microalbuminuria and increasing plasma creatinine (P-creat) are nonspecific measures of overall renal damage. Microalbuminuria reflects the overall 'leakiness' of the glomeruli. The increased permeability results in abnormal amounts of a protein, albumin, which normally doesn't 'leak' enough to be detected in the urine. P-creat mostly reflects the balance between:

- creatinine production (dependent on muscle mass), and
- excretion (mostly dependent on glomerular filtration rate [GFR]). At low GFR the contribution of renal tubular and gastrointestinal movements of creatinine become significant and P-creat becomes a less reliable measure of GFR.

In an individual, P-creat is largely dependent upon GFR, which is a general overall measure of renal function. After all, the kidney is there to filter the blood and excrete water soluble wastes and toxins.

In diabetes microalbuminuria is the earliest indicator of diabetic nephropathy where hyperglycaemia directly or indirectly damages the glomerulus and causes albumin 'leakage'. Renal damage can also occur in diabetes for other reasons (*Figure 1*) and can decrease GFR without causing microalbuminuria.[1] At least 30% of those with decreased GFR have normoalbuminuria.[2]

Diabetes is often associated with hypertension, dyslipidaemia and macrovascular disease (*Figure 1*). The kidney receives 25% of the cardiac output and flow is reduced by atherosclerosis affecting the renal arteries. Diabetes is also associated with diabetic neuropathy, which may affect bladder function increasing urinary back pressure on the kidney and also with reduced resistance to infection predisposing to significant and recurrent urinary tract infections. Other problems with diabetes may be treated with nephrotoxic agents. Finally, diabetes usually occurs in the second half of life and renal function declines after the age of 40 years. Microalbuminuria might be the earliest indicator of a nephropathy specifically caused by diabetes, but P-creat (and GFR) can also be reduced by the other problems that affect renal function.

Should I measure P-creat or estimate GFR? If GFR, which of the 50 formulas should I use?

Both: measure and estimate. Use any formula, but an estimated GFR (eGFR) is now reported by pathology laboratories with urea, creatine and electrolyte measurement. In an individual the eGFR is age and gender adjusted and gives an overall index of renal function.

Measuring GFR directly is technically demanding (inulin or radioactive tracer clearance) or inherently limited (creatinine clearance). In Australia an equation, originally developed as part of the Modification of Diet and Renal Disease (MDRD) study, is used to calculate eGFR based on P-creat. (The eGFR formula can be downloaded at http://kidney.org.au).

As noted, P-creat is affected by creatinine production and therefore muscle mass. Creatine phosphate is the high energy compound that provides instant energy to the muscle. A certain amount of creatine is broken down to creatinine each day. The more muscle, the more creatine, the more creatinine production. Similarly, the more cooked meat (muscle) eaten, the more creatinine to be excreted. Some medications and metabolites affect P-creat levels without actually affecting GFR but by decreasing tubular secretion or by interfering in the assay (*Table 1*).

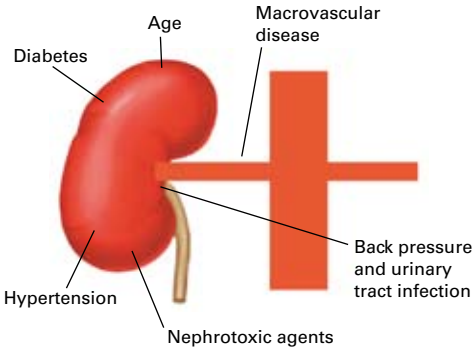

Figure 1. Kidney killers in diabetes

The major influence apart from GFR on P-creat is the muscle mass, hence the effect of gender, age, ethnicity and nutrition. Similarly, remember that extreme diets, some medications and some unusual metabolic disturbances can affect P-creat without affecting renal function.

I started an ACE inhibitor for Joan and 1 week later the P-creat had increased from 100 to 125 (range 50–120 umol/L) so I stopped it. Would an ARA have the same effect?

The National Prescribing Service recommends checking P-creat a week or so after starting an angiotensin converting enzyme (ACE) inhibitor or angiotensin receptor antagonist (ARA) or after changing doses. Many doctors don't but there are situations where it really is a wise precaution.

The ACE inhibitor and ARA can be expected to decrease GFR – their therapeutic effect is to decrease the action of angiotensin II. Angiotensin dilates the afferent and constricts the efferent arterioles of the glomerulous. This increases glomerular pressure and glomerular filtration. This is part of the physiological response to a decrease in blood pressure which otherwise would decrease GFR.

A change of >15% is more than expected from the variability of the P-creat in the individual and Australian guidelines suggest that a change of >30% within the first 2 months of therapy should prompt review of the use and/or dose of the ACE inhibitor or ARA. A nephrologist may be able to offer advice.[3]

In Joan's case the increase is 25% and is most likely to be clinically significant rather than attributable to P-creat variability. Although Joan's P-creat has increased from within to outside the reference range the increase is <30% and doesn't preclude the use of an ACE inhibitor or ARA. However, it might be wise to think twice before increasing the dose.

The effects of ACE inhibitors and ARAs on P-creat is especially marked when the renin, angiotensin, aldosterone system is 'revved up' in response to decreased cardiac output (eg. heart failure) decreased extracellular volume (eg. dehydration, diuretics) renal artery stenosis or other causes of decreased renal arterial pressure. Such patients may be tipped into acute renal failure. If an ACE inhibitor or ARA is indicated 'starting low and going slow' is good advice. Low doses of a short acting agent, will reduce the likelihood and duration of any adverse effect. For example, in some situations the pharmacist may prepare a dilute solution of a short acting agent such as captopril so that 'starting low and going slow' is made more practical.

Table 1. Factors affecting plasma creatinine

Creatinine availability	Muscle mass – age, gender, ethnicity, diet
Creatinine secretion	Medications – fenofibrate (not gemfibrozil), trimethoprim, cimetidine
Creatinine assay	Some 'sporin' antibiotics, ketosis

Table 2. The nine nephrotoxic nasties

Nephrotoxic	Radiocontrast agents: use low ionic agents, avoid dehydration
	NSAIDs*: use paracetamol
	ACE inhibitors: check renal function
Needs adjustment if GFR is reduced	Allopurinol – 100 mg/day/30 mL/min of GFR
	Digoxin: check levels
	Sulphonamides: half dosage if GFR is <30 mL/min
Not used if GFR <30 mL/min	Some hypoglycaemics – glibenclamide, glimepiride, metformin
	Potassium sparing diuretics – amiloride, triamterene, spironolactone
	Tetracyclines

* Including COX-2 'specific' NSAIDs

Now Joan's P-creat is high, which medication doses should I change?

The dangerous drugs in renal impairment are those that might further reduce renal function and those whose clearance may be affected (*Table 2*).[4] It is important to note that dosage adjustment is based on the patient's actual GFR and not their eGFR which is adjusted for body surface area. Actual GFR can be calculated using medical software or using a simple formula:

For women: [(140 – age) x healthy body weight (kg) ÷ P-creat (umo/L)]

For men: multiply by 1.25

(As a rough guide healthy body weight [kg] = height [cm] – 100. For Joan, aged 68 years and 150 cm tall; = 72 x 50 ÷ 125 = 29 mL/min).

This estimate as well as the eGFR is subject to the limitations of *Table 1* as both depend on creatinine availability, secretion and assay.

One of the more dangerous medication combinations for renal function is the 'triple whammy' of an ACE inhibitor or ARA, a nonsteroidal anti-inflammatory drug (NSAID) and a diuretic. Many patients will take a combination of ACE inhibitor/ARA diuretic preparation and should be warned not to take any medication (prescribed, over-the-counter, alternative) for pain or arthritis without discussing the medication with a doctor or pharmacist.

Conflict of interest: none declared.

References

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