Microalbuminuria screening in diabetes

In this second article in the ‘Test tips’ series, Dr Iona Galloway and Professor Gerry McKay outline what microalbuminuria is, why we should screen those with diabetes for it, which test to perform, who should be screened, how to interpret the results, and practical points to consider.

Introduction
Diabetic nephropathy is the leading cause of chronic kidney disease and end-stage renal failure. The development of microalbuminuria is an early risk marker for diabetic nephropathy, defined as a level of albumin detected in the urine of 30–299mg/day.1 This early marker of diabetic nephropathy is potentially modifiable through lifestyle changes and pharmacological interventions targeting blood pressure, specifically through the renin angiotensin system, and blood glucose.

Microalbuminuria is also considered to be a marker of vascular risk, particularly relevant given the increasing numbers of individuals being diagnosed with type 2 diabetes mellitus.

What is microalbuminuria and why screen for it?
Microalbuminuria in those with diabetes mellitus has been the subject of research since the late 1970s.2,3 This research has centred upon microalbuminuria as a risk factor in the development of overt diabetic nephropathy and as a marker of increased cardiovascular risk. Current evidence has demonstrated that only a small percentage of those with microalbuminuria will progress to overt nephropathy and end-stage renal disease.4 The UKPDS study demonstrated the prevalence of microalbuminuria was 24.9% at 10 years and 28% at 15 years post diagnosis of type 2 diabetes.3 However, the prevalence of elevated creatinine or renal replacement therapy was only 0.8% at 10 years and 2.3% at 15 years, suggesting that those who develop microalbuminuria do not necessarily progress to the development of chronic kidney disease.4 Microalbuminuria has been shown to regress in patients both spontaneously and also through optimisation of blood pressure and glycaemic control.5 The presence of microalbuminuria with normal renal function is not indicative of underlying diabetic nephropathy, but acts as a risk marker for possible progression and identifies patients who may benefit from targeted intervention.1

The presence of microalbuminuria does not only indicate potential renal involvement, but it is also associated with increased cardiovascular risk.6 The HOPE study evaluated cardiovascular outcomes in patients with or without diabetes and the effect of ramipril upon these. A sub-study (MICRO-HOPE) in patients with both type 1 and type 2 diabetes evaluated the effect of ramipril on microvascular outcomes along with cardiovascular outcomes. An analysis was performed on the results from both studies to assess the incidence of cardiovascular outcomes in patients with or without microalbuminuria. The presence of microalbuminuria was shown to be associated with an increase in the

Vignette 1
A 62-year-old man attended for his annual type 2 diabetes review at his general practice. He was diagnosed six years previously and is now on metformin, gliclazide and sitagliptin. His past medical history includes hypertension and ischaemic heart disease for which he is prescribed amloidipine 5mg, ramipril 2.5mg, aspirin 75mg and simvastatin 40mg.

On review his BP was 146/85mmHg, his feet were screened as moderate risk and recent retinal screening showed background diabetic retinopathy in both eyes. His most recent HbA1c was 85mmol/mol. An early morning urine sample was sent for albumin:creatinine ratio along with serum urea and electrolytes and lipid profile. His albumin:creatinine ratio was elevated at 40mg/mmol, urea 3.2mmol/L, creatinine 96µmol/L and cholesterol 6.3mmol/L.

What does his albumin:creatinine ratio indicate? How should he be managed?

The urinary albumin:creatinine ratio should be repeated, but this man is at high cardiovascular risk and there should be no delay in titrating up the dose of his ramipril and optimising his glycaemic control. His BP should be optimised to <130/80mmHg and consideration should be given to improve his lipid profile through both lifestyle and pharmacological approaches.

Vignette 2
A 26-year-old female with type 1 diabetes was reviewed in the hospital outpatient clinic. She was diagnosed at eight years old and has been managed on a basal bolus regimen with carbohydrate counting and prandial dose adjustment. She had several years’ history of sub-optimal glycaemic control in her late teens/early 20s. She has no other significant past medical history and is on no regular medications except from her insulin. She is a smoker of 20 cigarettes/day.

Her updated HbA1c was 70mmol/mol; her BP was 130/74mmHg. On retinal screening she had observable diabetic retinopathy in the right eye only. Her albumin:creatinine ratio was elevated at 13mg/mmol, urea 4.5mmol/L and creatinine 82µmol/L. She had two previous elevated albumin:creatinine ratio samples in the preceding year.

What does her albumin:creatinine ratio indicate? Does she need treatment? When should a repeat sample be obtained?

This lady has an abnormal albumin:creatinine ratio on repeat sampling and should be considered for the addition of an ACE inhibitor if there are no contraindications. In this situation the main one might be that she may wish to become pregnant at some point. Smoking cessation is of course an important part of her management. Repeat sampling should take place some three to six months after starting treatment.
Test tips

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Incidence of myocardial infarction, stroke or cardiovascular death (23.1% versus 13.8%), all-cause mortality (18.2% versus 9.4%), and hospitalisation due to heart failure (6.9% versus 2.2%). An increased risk of adverse cardiovascular outcomes was demonstrated in all patients irrespective of a diagnosis of diabetes mellitus.

**Which test to use?**

The most basic screening tool available for microalbuminuria is dip-stick testing of a spot urine sample. Currently available tests include Micral-Test and Albustix. These quick and simple methods only give a semi-quantitative result. The Micral-Test provides a colour change which groups results into 0, 20, 50 and 100mg/L ranges. It has been shown to have an 89–100% sensitivity and 91–98% specificity. False positive results can occur due to the concentration of urine sample tested. Dipstick testing has been replaced for most routine outpatient clinical practice with the downside being that routine evaluation of urine for microscopic haematuria and ketones is no longer available and sometimes this could be clinically relevant.

Testing for microalbuminuria involves either timed or non-timed urine sample collection. For patients, timed samples can be more onerous than spot samples and can result in incomplete sampling. An overnight timed urine collection of 8–12 hours may also be used; however, this sampling method has constraints similar to 24-hour collection. From these samples either the albumin excretion rate, albumin concentration or albumin:creatinine ratio can be measured.

A spot sample of urine for measurement of either urinary albumin concentration, albumin excretion rate or albumin:creatinine ratio is the most commonly used method in clinical practice and this methodology has been validated against timed samples, as have protein:creatinine ratios. An additional advantage is that it is more acceptable to patients. The timing of sample collection is important in the interpretation of results when solely measuring albumin concentration. Diurnal variation in albumin excretion results in higher levels of albumin excretion during the day. The preferred time for collection is early morning; however, if this is not possible then consistent timing of sample collection for the patient should be adopted. Urine albumin samples are stable for approximately two days at room temperature. Patients should be advised that samples should be refrigerated if obtaining three consecutive early morning specimens until they can be transported to the laboratory for analysis.

**Who should be screened for microalbuminuria?**

Routine screening should begin in those with diabetes over the age of 12. In individuals with type 1 diabetes, screening is not routinely required within the first five years of diagnosis. For type 2 diabetes, screening should commence at the time of diagnosis. The disparity between time to commencing screening between type 1 and type 2 diabetes exists due to the often asymptomatic initial stage of type 2 diabetes prior to diagnosis.

According to both NICE and SIGN guidance those with diabetes mellitus should be screened at least annually. If a positive sample is obtained, a further two samples should be sent within a three to six-month period to confirm the result. This group should then have repeat testing performed on a six-monthly basis.

**How to interpret the results?**

Each of the sampling methods described has a different microalbuminuric range; these are listed in Table 1. Results higher than those in the table fall into the proteimuric range and confirm nephropathy.

<table>
<thead>
<tr>
<th>Test</th>
<th>Microalbuminuria range</th>
</tr>
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<tbody>
<tr>
<td>Albumin excretion rate</td>
<td>30–300mg/day 20–200µg/min</td>
</tr>
<tr>
<td>Albumin:creatinine ratio</td>
<td>2.5–25mg/mmol</td>
</tr>
<tr>
<td>Albumin:creatinine ratio (United States)</td>
<td>30–300mg/g</td>
</tr>
<tr>
<td>Albumin concentration</td>
<td>30–300mg/L</td>
</tr>
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**Table 1. Sampling methods and their microalbuminuric ranges**

**Box 1. The common causes of false positive samples**

There is wide variability between sampling, dependent on a range of factors. False positive and false negative results can occur due to many different reasons. Box 1 summarises the common causes of false positive samples, which include exercise, urinary tract infections, febrile illness and dehydration. To confirm the presence of microalbuminuria, three samples should be obtained in total with two positive samples confirming microalbuminuria. These samples should be obtained within three to six months of each other. In clinical practice it is perhaps easier to consider the presence of microalbuminuria as an abnormally raised albumin and use this as a prompt to take action.

Once microalbuminuria (or abnormally raised urinary albumin) is confirmed the individual with diabetes should be commenced on an angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) if not contraindicated. Optimisation of other cardiovascular risk factors including stopping smoking, blood pressure, glycaemic control and lipid profile should be addressed; these have been demonstrated in several studies to impact upon microalbuminuria. The DCCT/EDIC trial demonstrated that strict glycaemic control was associated with a
lower incidence of microalbuminuria and increased regression of pre-existing microalbuminuria.17

Conclusion
Screening for the presence of microalbuminuria remains a central part of the annual assessment of those with both type 1 and type 2 diabetes mellitus. A spot sample, ideally an early morning collection, should be assessed for albumin:creatinine ratio.

The mainstay of management of patients with microalbuminuria (abnormally raised urinary albumin) include introduction of ACEI/ARB, optimisation of blood pressure, improving glycaemic control, and addressing other cardiovascular risk factors.

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Declaration of interests
There are no conflicts of interest declared.

References

POEMS

Screening for pre-diabetes: neither HbA1c nor fasting glucose results are very accurate

Clinical question
Are screening tests for pre-diabetes accurate?

Reference

Study design: Meta-analysis (other) Funding source: Foundation Setting: Various (meta-analysis)

Synopsis
The authors conducting this systematic review and meta-analysis searched several databases for all research papers that evaluated the diagnostic accuracy of laboratory-based (not clinic-based) glycated haemoglobin (HbA1c) or fasting blood glucose tests to identify impaired glucose tolerance, using an oral glucose tolerance test as the reference standard for diagnosis. Heterogeneity among the studies was high, probably due to the differences in populations and settings.

Across all studies the prevalence of impaired glucose tolerance was 27% but varied by study, which will make predictive values bounce around. For HbA1c tests, the sensitivity was 0.49 (95% CI 0.4–0.58) and the specificity was 0.79 (0.73–0.84). For fasting blood glucose tests, the sensitivity was 0.25 (0.19–0.32) and the specificity was 0.94 (0.92–0.96). In other words, neither is very good at predicting oral glucose tolerance test results.