

Microalbuminuria: Screening and management in type 2 diabetes

Julia Arundale

Introduction

In many diabetes units, patients with type 1 or type 2 diabetes are screened for proteinuria. Screening for microalbuminuria is well established for patients with type 1 diabetes, but in type 2 diabetes it remains an area for debate. A major reason for this is that most patients routinely receive treatment that as a secondary effect addresses microalbuminuria anyway. This article looks at microalbuminuria screening and how it can be used clinically (for example in the adjustment of blood pressure targets) and also explores its management.

In many diabetes units, people with type 1 and type 2 diabetes are screened for macroalbuminuria (also known as 'proteinuria') by dipstick urinalysis, but they are not routinely screened for microalbuminuria. The evidence for the benefits of screening and managing microalbuminuria in patients with type 1 diabetes is well established (e.g. Diabetes Control and Complications Trial Research Group, 1993; Parving, 1996). However, there is some debate within diabetes regarding the screening for microalbuminuria in type 2 diabetes and, if microalbuminuria is detected, its management. Most of the debate centres on the use of angiotensin-converting enzyme (ACE) inhibitors in patients with microalbuminuria, which, unless contraindicated, most patients with type 2 diabetes are routinely prescribed anyway (National Institute for Clinical Excellence [NICE], 2002; Department of Health [DoH], 2003). Therefore, the detection of microalbuminuria would not alter the management of the patient, but would have associated costs.

Microalbuminuria

Microalbuminuria is defined by an albumin excretion rate of 30–300 mg/day. (The normal albumin excretion rate is 0–30 mg/day; proteinuria is defined as an albumin excretion rate greater than 300 mg/day.) Microalbuminuria can be detected using measurement of the albumin:creatinine ratio (ACR) or urinary

albumin concentration.

In describing diabetic nephropathy, Williams (2002) writes that 'The earliest clinically detectable sign of nephropathy is microalbuminuria.' Screening for diabetic nephropathy at an early stage of the disease is important for identifying those patients affected and for provision of the appropriate management. The most accurate test is a urine sample on the first morning as albumin urinary excretion is affected by fluid intake and exercise. However, the renal unit is relying on the patient to remember to perform the sample and bring it with them to the clinic. And, in fact, the method most commonly used in renal units is measurement of ACR, which is performed by the patient while attending the clinic.

Measuring ACR at a random time during the day is generally believed to be accurate as a measure of albumin excretion. If albuminuria is present it is confirmed by two further samples within the next 3–4 months. A diagnosis of diabetic nephropathy rather than other glomerular disease is usually made if the patient has retinopathy, and there are typical features that can help (such as the length of diabetes and other medical complications). However, in type 2 diabetes there is a greater chance of non-diabetic renal disease being present than in type 1 diabetes, and a renal biopsy may be needed if there are atypical features. Also, not all people with diabetes who have

ARTICLE POINTS

- 1** Screening for microalbuminuria in type 2 diabetes has been much debated.
- 2** Screening would allow an important cardiovascular risk to be identified.
- 3** But people with diabetes are routinely prescribed treatments such as ACE inhibitors that are of benefit in microalbuminuria anyway.
- 4** Other treatments, though, may be of greater benefit and could be prescribed.
- 5** Screening could be of major use in giving an early indication of more serious kidney disease.

KEY WORDS

- Microalbuminuria
- Screening
- ACE inhibitors
- Blood pressure targets
- Angiotensin II receptor antagonists

Julia Arundale is a Clinical Nurse Specialist in Renal Diabetes at the Renal Unit, University Hospital Birmingham NHS Foundation Trust, Birmingham.

PAGE POINTS

1 Screening people with type 2 diabetes could allow the patient and professional to be aware of the increased cardiovascular risk.

2 People with type 2 diabetes are routinely prescribed treatments to prevent certain diabetic complications that will also be of benefit in microalbuminuria anyway.

3 It is possible that other types of antihypertensive drugs will be of more use in the treatment of microalbuminuria.

4 The UKADS was designed to apply the UKPDS findings to the care of people of Asian ethnicity.

nephropathy have diabetic nephropathy; this is an important distinction to make as both management and prognosis may differ.

Once patients have been screened and identified as having microalbuminuria (indicating diabetic nephropathy), provision of the appropriate treatment can, as well as protecting the renal function, reduce cardiovascular risk. Dinneen and Gerstein (1997) state that 'Patients with Type 2 diabetes and microalbuminuria have a two-fold increased risk of cardiovascular morbidity and mortality,' compared with patients with type 2 diabetes without microalbuminuria.

ACE inhibitors

One important reason for not screening for microalbuminuria is that people with type 2 diabetes are routinely prescribed treatments to prevent certain diabetic complications that will also be of benefit in microalbuminuria anyway. ACE inhibitors are the first-line treatment in diabetes for reducing the risk of cardiovascular disease, as concluded from the Heart Outcome Prevention Evaluation (HOPE) study and MICRO-HOPE sub-study (Hope Study Investigators, 2000).

The HOPE study looked at the benefits of the ACE inhibitor ramipril in 9541 patients who were aged 55 or older, had a previous cardiovascular event or at least one other cardiac risk factor such as diabetes, and had no clinical proteinuria. These patients were not taking an ACE inhibitor. The results of this study showed a 22% reduction in risk in those patients predisposed to cardiovascular disease. The MICRO-HOPE sub-study looked at urine samples collected from 3500 of the patients in the HOPE study and concluded that the risk reduction for progression to overt nephropathy was 24%, which also demonstrated the renoprotective effect of ramipril.

The results of both these studies are very important for treating patients with microalbuminuria or increased albuminuria. However, ramipril versus placebo was the only comparison made, meaning that the benefit of other ACE inhibitors was not demonstrated. (In some diabetes and renal units, a number of ACE inhibitors are prescribed on top of ramipril.) Also, people

who have uncontrolled hypertension – which is a traditional indication for an ACE inhibitor – were excluded from the study.

As discussed, the HOPE study and MICRO-HOPE sub-study only investigated ramipril, so do other ACE inhibitors have the same renoprotective effect? Remuzzi and Bertani (1998) write that the pathophysiology of ACE inhibitors is known, and they are renoprotective in their effect.

It is possible that other types of antihypertensive drugs will be of more use in treating microalbuminuria, as discussed below.

The UKPDS

The United Kingdom Prospective Diabetes Study (UKPDS) was a multicentre study of 5102 people with type 2 diabetes that assessed the long-term effects of persistent hyperglycaemia and hypertension on the development of both microvascular and macrovascular complications. This is a very high-profile study in type 2 diabetes. Watkins (2003), in writing about the UKPDS, reported benefits of reducing blood pressure but found that the benefits were achieved regardless of the drugs used to reach the required level of blood pressure.

The UKADS

The United Kingdom Asian Diabetes Study (UKADS; personal communication, Dr W Hanif, 2005) was designed to apply the UKPDS findings to the care of people of Asian ethnicity, who constitute one of the most at-risk groups of patients with type 2 diabetes in primary care. One of the major findings was that a large proportion (40%) of Asians had normal blood pressure (<140/80 mmHg) but had microalbuminuria or proteinuria.

The study was community based, had large patient numbers and showed that healthcare interventions can be organised effectively by working with primary care teams. Interestingly, the study showed no change in HbA_{1c} between the intervention and control group, and one of the two principal conclusions from the UKPDS was that intensive blood glucose control is worthwhile (Gray et al, 2002).

However, the UKADS does report that 'In practice greater effort, time and resource may be required to produce a change in HbA_{1c} than to produce a reduction in blood pressure or cholesterol' (UKADS, personal communication, Dr W Hanif, 2005). Another important conclusion from the UKADS is that the prevalence of microalbuminuria is much greater in South Asians with diabetes and so routine screening for microalbuminuria should be mandatory in this group. But why should South Asians be singled out? It could be argued that all patients with type 2 diabetes should be screened for microalbuminuria, regardless of whether their blood pressure is above or within target.

This study used a small number of patients, was based in primary care and used extra resources of Asian link workers, as well as practice nurses and community diabetes specialist nurses, to achieve the targets. It is important to ask whether the approach used in the small UKADS can produce similar results to those in the UKPDS over a larger Asian patient population.

Blood pressure targets

The targets and treatment for a person with type 2 diabetes with microalbuminuria are different for a person with type 2 diabetes but without microalbuminuria. The MICRO-HOPE sub-study (HOPE Study Investigators, 2000) stated that ACE inhibitor treatment should be extended to normotensive patients with high cardiovascular risk. Microalbuminuria is a cardiovascular risk that could be screened for. Once microalbuminuria has been identified, blood pressure targets can be reduced accordingly.

NICE states that people with a higher-risk urine albumin excretion should maintain blood pressure below 135/75 mmHg (NICE, 2002). Microalbuminuria is stated as a higher-risk albumin excretion. Screening people for microalbuminuria would allow their blood pressure target to be set at 135/75 mmHg or lower rather than 140/80 mmHg or lower, which is the target

set by NICE for people with lower-risk urine albumin excretion. NICE (2002) also states in the guidance that urinary ACR or albumin concentration – the screening tests for microalbuminuria – should be performed yearly.

The UKPDS suggests that the blood pressure target should be 140/80 mmHg or lower, while the British Hypertensive Society gives 140/80 mmHg or lower as the optimal blood pressure target for people with diabetes, except in the presence of nephropathy, where it should be 130/80 mmHg or lower (Ramsay et al, 1999). The Renal Association (2002) blood pressure target is 130/80 mmHg for those with proteinuria-associated renal disease and stable renal function, while for patients with progressive renal disease (diagnosed if an individual has increasing serum creatinine and increasing ACR) the target is lower, at 125/75 mmHg. Through screening initially for microalbuminuria and then performing ongoing measuring of albumin excretion, progressive renal disease can be diagnosed and the blood pressure target reduced to 125/75 mmHg. The National Service Framework (NSF) for diabetes recommends that all people with diabetes should receive regular surveillance for renal complications. Should these tests reveal that a person has microalbuminuria or proteinuria, the NSF guidelines state that he or she should be treated with an ACE inhibitor unless contraindicated (DoH, 2003). The blood pressure targets are lower in all the standards in type 2 diabetes with albuminuria.

In writing about the minimum recommended levels of blood pressure control, Ramsay et al (1999) state that 'Despite best practice, it may not be achievable in some treated hypertensive patients.' It is not always possible for some patients to reach blood pressure targets because of side effects such as dizziness or a general unwell feeling linked to the reduction in blood pressure.

Finally, recommendations are only worthwhile if they are followed, and in those patients who can tolerate blood pressure targets, these targets can and should be met.

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1 The prevalence of microalbuminuria is much greater in South Asians with diabetes and so routine screening for microalbuminuria should be mandatory in this group.

2 The targets and treatment for a person with type 2 diabetes with microalbuminuria are different for a person with type 2 diabetes but no microalbuminuria.

3 In those patients who can tolerate blood pressure targets, these targets can and should be met.

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1 The IRMA2 study evaluated the effects of irbesartan on microalbuminuria in patients with hypertension and type 2 diabetes.

2 Angiotensin II receptor antagonists are well tolerated and have a lower incidence of cough and angioedema.

3 There have not been any formal studies on the use of both ACE inhibitors and angiotensin II receptor antagonists in type 2 diabetes.

4 Screening for microalbuminuria could be of major importance in patients with type 2 diabetes as an early indication of more serious kidney disease.

Angiotensin II receptor antagonists

Much of the literature and research about the treatment of type 1 and type 2 diabetes discusses the use of ACE inhibitors (Lewis et al, 1993). However, the IRbesartan in patients with type 2 diabetes and MicroAlbuminuria (IRMA2) study evaluated the effects of irbesartan on microalbuminuria in patients with hypertension and type 2 diabetes (Kassianos, 2002). Irbesartan is an angiotensin II receptor antagonist and, like ACE inhibitors, reduces the pressure inside the glomerulus, which can be renoprotective as well as cardioprotective.

This study assessed the effects of irbesartan in 590 hypertensive patients with type 2 diabetes, microalbuminuria and normal renal function when measured on serum creatinine. The study duration was 2 years and the primary outcome was the time to onset of diabetic nephropathy, defined as persistent albuminuria. Patients were randomised to once-daily therapy with irbesartan 150 mg, irbesartan 300 mg or placebo. Antihypertensive agents (excluding ACE inhibitors, other angiotensin II receptor antagonists and dihydropyridine calcium-channel blockers) were added to help achieve similar blood pressure reductions in each patient group. By doing this, the investigators were trying to remove the possibility of the blood pressure-lowering effect contributing to any observed benefit, so that the benefit could be attributed to the drug independent of this effect.

The results of the study showed that the irbesartan 300 mg group demonstrated a relative risk reduction of 70% in progression to nephropathy. This was found to be equivalent to needing to treat ten patients with type 2 diabetes and microalbuminuria to prevent one person from developing more advanced renal disease. The irbesartan 150 mg group demonstrated a relative risk reduction of 39% compared with the control group. Lewis et al (2001) carried out a study assessing the effects of irbesartan 300 mg and amlodipine 10 mg in people with type 2 diabetes, which led to the same conclusion.

The IRMA2 study also demonstrates the

improved effect of the maximum dose of irbesartan compared with the smaller dose. This finding can be put into clinical practice by demonstrating the necessity of checking albuminuria loss by ACR once commenced on irbesartan and increasing the dose if albuminuria has not decreased.

It is important to remember that there is limited experience with angiotensin II receptor antagonists compared with ACE inhibitors. It is known, though, that angiotensin II receptor antagonists are well tolerated and have a lower incidence of cough and angioedema compared with ACE inhibitors (See, 2001), which may make them more suitable for addressing microalbuminuria.

Nephrologists are also beginning to discuss the possible benefits of using both an ACE inhibitor and an angiotensin II receptor antagonist, but there have not been any formal studies on the use of ACE inhibitors and angiotensin II receptor antagonists in type 2 diabetes. In type 1 diabetes, the Candesartan And Lisinopril Microalbuminuria (CALM) study looked at the benefits of dual treatment and found that dual use was more effective in reducing blood pressure and albuminuria than single therapy (Mogensen et al, 2000).

End-stage renal disease

Screening for microalbuminuria could be of major importance in patients with type 2 diabetes as an early indication of more serious kidney disease. Williams (2002) writes that 'Diabetic nephropathy develops in up to 40% of patients with type 2 diabetes and is now a leading cause of end stage renal failure in the western world.' Once patients have developed microalbuminuria – even when their blood pressure meets goals and an ACE inhibitor or angiotensin II receptor antagonist is being used – there is a risk of the development of proteinuria, which could lead to nephropathy and end-stage renal failure. Renal disease that progresses to end-stage renal failure is a great burden on the individual, his or her family and the National Health Service. Thus, there is a great need for investigations to identify therapies that can halt or slow down the progression of diabetic renal disease. Adler

et al (2003) explain that the burden of nephropathy will increase in the future as the incidence of diabetes increases and the age of onset declines, although the effects may be reduced by the use of recognised therapies. As a result of these therapies, some of which have been discussed, people with diabetes are living longer. And there are better treatments available for the highest-risk complication of diabetes: cardiovascular disease.

Empowerment

The NSF for diabetes covers the empowerment of people with diabetes. The NSF states that people need to be given the knowledge, skills and motivation to assess their risks and understand what they will gain from changing their behaviour (DoH, 2003). Patients need to know why we are screening for microalbuminuria and the risks and benefits of long-term treatment. Many patients are empowered in that they ask for their blood pressure and cholesterol readings and are aware of their target readings for these. But we need to aim for patients to ask for and understand the result and implications of their ACR.

Conclusion

We screen for eye disease in diabetes, and it is a much simpler procedure to carry out preliminary screening for diabetic kidney disease, although the cost-effectiveness of this must be evaluated. ■

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