The significance of microalbuminuria in clinical practice

Anthony Barnett

Article points

1. Microalbuminuria is an independent risk factor for CV events and renal disease in people with diabetes.
2. Recent evidence suggests that microalbuminuria should be treated more aggressively with ACE inhibitors or ARBs, even where BP is normal.
3. It is both desirable and possible to achieve the separate targets for BP and microalbuminuria.
4. Paramount is the need to identify microalbuminuria as early as possible in order to inform treatment choice and preserve as much kidney and heart function as possible.

Key words

- Microalbuminuria
- Nephropathy
- Cardiovascular risk

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Detection of microalbuminuria in people with diabetes has been established as a useful marker of clinical nephropathy and increased cardiovascular (CV) risk. It is also a reason to treat hypertension and other CV risk factors aggressively. However, many GPs are still unsure about the value of testing and have mixed opinions on whether it will alter the management of individual patients. In this article, Anthony Barnett outlines the background to GPs' hesitancy and examines the case for testing and treatment in order to improve morbidity and mortality in people with diabetes.

The term microalbuminuria refers to small quantities of albumin in the urine above the normal level. It is diagnosed when 30–300 mg albumin is excreted into the urine in 24 hours (or 20–200 µg albumin/min) or when the urinary albumin:creatinine ratio is 30–300 µg creatinine (Yuyun et al, 2005). A positive diagnosis requires two of three urine collections to meet these criteria. The albumin:creatinine ratio is usually, but not necessarily, from the first morning sample (*Table 1*).

The prevalence of microalbuminuria is relatively high in people with types 1 or 2 diabetes and in those without diabetes. For example, the Heart Outcomes Prevention Evaluation (HOPE) study (Gerstein et al, 2000) involved more than 9000 individuals aged 55 years or older with a history of cardiovascular disease (CVD) or with diabetes plus at least one other CV risk factor. The study found microalbuminuria to be present in 32.2% of people with diabetes and in 14.7% of those without diabetes.

The prognostic value of testing

Microalbuminuria is well established as the earliest indicator of diabetic kidney damage, reported in 1982 as a predictor of clinical nephropathy and death in type 1 diabetes (Parving et al, 1982) and in 1984 in type 2 diabetes (Mogensen, 1984). More recent evidence has corroborated findings of the earlier studies that showed, for example, a risk of atherosclerotic vascular disease 2.5 times greater in people with raised urinary albumin excretion (Deckert et al, 1996), confirming that microalbuminuria is predictive of CVD and all-cause mortality. These findings relate to people with diabetes or hypertension as well as to the general population, independently of the classic risk factors (Gerstein et al, 2001).

The HOPE study went on to show that 25% of individuals with diabetes and microalbuminuria died from myocardial infarction, stroke or CVD within the study period, compared with 13.9% of people without both diabetes and microalbuminuria. Figures for all-cause mortality were 18.6% and 9.3%, respectively (Gerstein et al, 2001).

In 2003, a detailed review of seven studies reporting on the relationship between microalbuminuria and CV events in people with diabetes and hypertension found the relative risk of CV end points to be at least twice and up to eight times as high in the presence of microalbuminuria (Park et al, 2003).

Furthermore, studies also suggest that albuminuria levels below the conventionally

Table 1. Definitions of normoalbuminuria and microalbuminuria.

Measure	Normoalbuminuria	Microalbuminuria
Albumin excretion rate	<30 mg/24 h <20 µg/min	30–300 mg/24h
Albumin : creatinine ratio	<30 mg/g	30–300 µg : 1 mg

recognised threshold of microalbuminuria are also significantly associated with CV morbidity and mortality (Klausen et al, 2004).

Given that CVD accounts for up to 70% of all deaths due to diabetes (International Diabetes Federation, 2003), this wealth of evidence suggests that screening for microalbuminuria in primary care should highlight those at increased risk of CVD and who are, therefore, in need of aggressive treatment to reduce all CV risk factors such as hypertension and blood glucose levels.

Treatment of microalbuminuria

The UK Prospective Diabetes Study (UKPDS) demonstrated that tight control of blood glucose levels and hypertension can reduce the progression of diabetic nephropathy (UKPDS Group, 1998). Studies also confirm that reducing albuminuria should be a treatment target independent of lowered blood pressure (Laverman et al, 2005).

Established current treatment of microalbuminuria is by lowering of blood pressure and using drugs with an independent effect on the renin-angiotensin-aldosterone system (RAAS). Most commonly used are angiotensin-converting enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs).

In recent years, several trials have identified the effects of ACE inhibitors and ARBs on the progression on nephropathy independent of their effects on blood pressure. The Irbesartan Diabetic Nephropathy Trial (IDNT) was one such trial (Lewis et al, 2001). A total of 1715 people with diabetic nephropathy were randomised to either the ARB irbesartan, the calcium-channel blocker amlodipine or placebo, with blood pressure controlled to target levels by drugs excluding ACE inhibitors or calcium-channel blockers. Participants assigned to the ARB group showed a 20% reduction in risk of renal disease progression versus placebo and a 23% risk reduction compared to those taking calcium channel blockers. Those randomised to the ARB showed a significantly increased risk of time to doubling of serum creatinine versus placebo and versus amlodipine. In addition, the study showed that irbesartan use was also linked with decreased amounts of protein in the urine.

Similar results were found by the Reduction of Endpoints in Non-insulin-dependent diabetes mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study (Brenner et al, 2001) among 1513 people with diabetic nephropathy from type 2 diabetes. This study compared the ARB losartan with placebo, with blood pressure controlled to target levels by the use of calcium-channel blockers, among other agents. Treatment with losartan was associated with a 16% reduction in the primary endpoint (composite of doubling of serum creatinine, end stage renal disease or death) and a significant reduction in the degree of proteinuria. These results from RENAAL further demonstrated the positive effects of ARBs in nephropathy due to type 2 diabetes.

In contrast to these studies in people with diabetes and overt renal disease, the IRbesartan in patients with type 2 diabetes and MicroAlbuminuria (IRMA-2; Parving et al, 2001) study was carried out in people whose kidneys were functioning normally, but who exhibited microalbuminuria. A total of 590 participants were randomised to either 150 mg or 300 mg irbesartan or placebo. Those taking 300 mg irbesartan daily showed a 70% reduction in relative risk of developing diabetic nephropathy, measured by changes in the amount of albumin excreted. Treatment with irbesartan showed a strong dose-dependent relationship to the risk of developing nephropathy at similar blood pressures. The authors extrapolated that treating 10 people with hypertension and type 2 diabetes with 300 mg irbesartan daily for 2 years would prevent

Page points

1. Microalbuminuria is an independent risk factor for CV disease and mortality from all causes in people with diabetes or hypertension as well as in the general population.
2. In people with diabetes and hypertension, microalbuminuria at least doubles the risk of having a CV event.
3. Screening for microalbuminuria in primary care highlights those at increased risk of vascular disease and therefore in need of aggressive treatment to reduce all CV risk factors.
4. Studies confirm that reducing albuminuria should be a treatment target independent of lowered BP.

one case of diabetic nephropathy.

All three studies provided evidence of the benefits of ARBs in slowing the progression of renal disease independently of their blood pressure-lowering effects. For example, in IRMA-2, average blood pressure was similar throughout the study between the irbesartan 150 mg/day, 300 mg/day and placebo groups (143/83 mmHg, 141/83 mmHg and 144/83 mmHg, respectively). This indicates that slowing the progression of diabetic kidney disease by irbesartan in hypertensive people with type 2 diabetes has a protective effect in addition to the blood pressure-lowering effect of the drug.

Another study, MIcroalbuminuria, Cardiovascular, and Renal Outcomes (MICRO)-HOPE, evaluated whether the ACE inhibitor ramipril could lower CV and renal disease risk in people with diabetes. A total of 3577 people with diabetes were randomised to either ramipril (10 mg) or placebo. Those on ramipril had a 25% reduced incidence of CV events (myocardial infarction, stroke or death) independent of ramipril's effects on lowering blood pressure (HOPE Study Investigators, 2000).

Reporting in 2004, the Prevention of REnal and Vascular ENdstage Disease Intervention Trial (PREVEND IT) showed that treating microalbuminuria with an ACE inhibitor in the absence of either hypertension or hypercholesterolaemia can reduce CV and renal events by 44% over a 4-year period. In addition, trial participants randomised to the ACE inhibitor fosinopril experienced a 23% decrease in urinary albumin excretion (Asselbergs et al, 2004).

Blood pressure and albuminuria targets

Despite the fact that PREVEND IT and other trials suggest that a more aggressive approach to treatment of microalbuminuria is needed, the condition often remains overlooked or considered minimally significant by many GPs. This occurs, in particular, when dealing with patients with microalbuminuria and normal blood pressure because the amount of albumin present in the urine is so small. Many GPs remain unlikely to treat microalbuminuria on its own, even though it is associated with increased CV and renal risks and treatment of these patients is likely to have a positive impact on survival.

The important question when assessing the value of microalbuminuria testing in primary care is whether a positive result would influence clinical practice. Patients testing positive for microalbuminuria are recommended for first-line RAAS intervention to preserve kidney function and reduce their blood pressure. However, microalbuminuria testing has additional benefits in people with diabetes as it monitors response to therapy. In some people blood pressure may respond to treatment but the urinary albumin levels may not. This scenario would require an additional therapy to achieve target levels.

We already know from the studies mentioned that reducing microalbuminuria has CV benefits independent of lowering blood pressure and that treating people with diabetes with ACE inhibitors or ARBs is likely to improve urinary albumin excretion in its own right. Now, there is also evidence to suggest that it is desirable and possible to achieve the independent targets for blood pressure and microalbuminuria. For example, Laverman et al (2005) indicated that an absence of blood pressure response to the ARB losartan does not preclude a reduction in albuminuria and that optimal reduction of albuminuria may require titration beyond the predefined blood pressure target.

Page points

1. National guidance on diabetes includes testing for microalbuminuria and subsequent treatment with an ACE inhibitor or ARB where necessary.
2. There is much evidence now to suggest that more aggressive treatment options should be considered for those with microalbuminuria.
3. Responses to ACE inhibitors or ARBs may vary between patients.

What GPs need to know

Testing for microalbuminuria and subsequent treatment with an ACE inhibitor or an ARB is included in both the NICE guidance on diabetes (NICE, 2002) and the Quality and Outcomes Framework (DoH, 2003). GPs are awarded points for testing for microalbuminuria in the previous 15 months, followed by further points for treatment of those found to have microalbuminuria with ACE inhibitors or ARBs. This is a result of the wealth of evidence demonstrating preservation of kidney function and reduction of CV risk with treatment of microalbuminuria.

There is much evidence now to suggest that more aggressive treatment options should be considered for those with microalbuminuria. The evidence for the renoprotective effects of ACE inhibitors and ARBs, independent of their blood pressure-lowering effects, is strong. For people whose blood pressure responds to treatment without changes in the level of microalbuminuria, the use of ACE inhibitors and ARBs as dual inhibition of the RAAS should be considered.

Conclusion

Microalbuminuria is undeniably a useful and easy-to-test indicator of increased risk of CV and renal complications in people with diabetes. Those testing positive for microalbuminuria should be treated with an ACE inhibitor or ARB.

However, as with blood pressure, patients should be treated to a target albumin level in diabetes. Not all people will respond to ACE inhibitor or ARB treatment in the same way: one individual's albumin level may change with blood pressure unaffected, whereas another's blood pressure may respond but with their albumin level remaining high. For this reason, the level of urinary albumin should continue to be an important marker in diabetes and a target for treatment in those at increased CV and renal risk.

Above all is the need to identify microalbuminuria as early as possible in order to inform treatment choice in an effort to preserve as much kidney and heart function as possible. ■

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