Game changers in type 2 diabetes

Microalbuminuria

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The diabetes complication of microalbuminuria indicates considerable renal damage and an increased risk of cardiovascular events. Its treatment involves improving all aspects of diabetes management and targeting the microalbuminuria itself.

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Confirmed microalbuminuria may be the first detectable sign of renal damage, well before glomerular filtration decreases and the plasma creatinine level increases, but it signifies considerable rather than minimal renal damage. The early signs of nephropathy are less obvious than those for retinopathy, where microaneurysms occur many years before the retinopathy progresses to proliferative diabetic retinopathy and its likely associated visual loss. Microalbuminuria is more like nonproliferative diabetic retinopathy, which warns that visual function is threatened and should prompt close monitoring and early preemptive therapy. Microalbuminuria warns that renal function is threatened and the risk of cardiovascular events is considerably higher than the risk predicted by traditional risk factors.[1]

The progression of the microvascular and macrovascular complications of diabetes, including that of microalbuminuria to nephropathy, can be reduced by better control of diabetes – that is, moving closer to the targets for glycosylated haemoglobin level, blood pressure and cholesterol level (Table).[2] The presence of microalbuminuria should, therefore, prompt GPs and patients to check whether the targets of type 2 diabetes management are being achieved, and if not, to try harder to reach the targets.

This article reviews the investigation of microalbuminuria and its natural history in people with diabetes, and suggests an evidence-based approach to its management. It is the second of a series of articles reviewing clinical situations that indicate a major change in the level of risk of diabetes-related complications and prompt the need for a major review of diabetes management.

INVESTIGATIONS

Testing for microalbuminuria is performed on either a timed overnight (for the albumin excretion rate; AER) or first voided early morning urine (for the albumin: creatinine ratio; ACR). As blood and products of inflammation can cause albumin to appear in urine, a routine urinalysis (looking for nitrites and blood) should be performed on the specimen to exclude contamination.

TABLE. THE ABCS OF DIABETES CARE[2]*

Factor	Target
A – Glycosylated haemoglobin (A_{1c})	<7.0%
B – Blood pressure	<130/80 mmHg
C – Cholesterol	<4 mmol/L
s – Smoking	0

* A further 's' (salicylate therapy) in the original ABCss is no longer routinely recommended for those people with diabetes and no known cardiovascular disease.

Small amounts of plasma proteins are filtered through the normal glomerular membrane and are reabsorbed in the proximal tubules. If glomerular pressure is increased, larger amounts of protein are filtered. Detection of low levels of albumin, the most abundant plasma protein, in the urine is the earliest test available for diabetic nephropathy.

To avoid false positive results when investigating possible microalbuminuria, it is important to test a urine specimen formed when glomerular pressure is expected to be normal. As glomerular pressure is increased by erect posture, eating and activity, urine formed overnight while the person is sleeping is the best specimen to use; a random specimen is quite likely to give a false positive result. Urine albumin is measured as the concentration or total quantity in the sample and the values need to be adjusted for the concentration of the urine or duration of the collection (a prolonged collection time may give abnormal results in people with normoalbuminuria). The albumin concentration determined in a first voided early morning specimen is adjusted by the creatinine concentration of the sample, giving the ACR (mg/mmol). The total albumin quantity determined in a timed overnight specimen is adjusted by time to give the AER (μg/min). Because men have a larger proportion of muscle mass than women and creatinine is formed from muscle creatine, creatinine excretion is generally higher in men than women. This means that the ACR reference range indicating microalbuminuria is lower in men than in women (2.5 to 25 mg/mmol *vs* 3.5 to 35 mg/mmol).

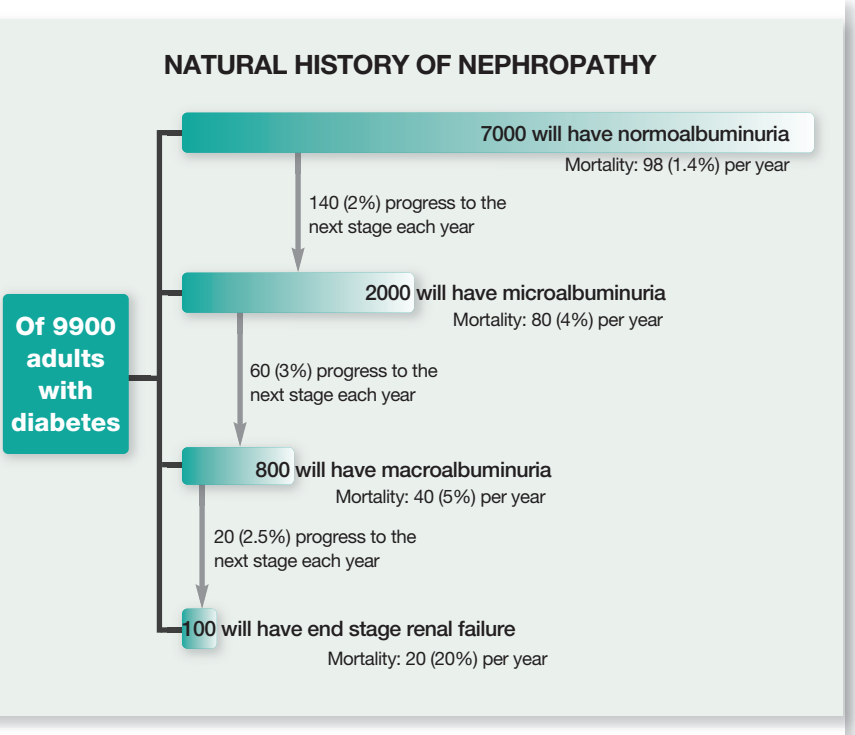


Figure 1. Natural history of nephropathy.[1] It is estimated from an extrapolation of UKPDS data that in a population of 9900 adults with type 2 diabetes, 2000 will have microalbuminuria, 800 will have macroalbuminuria and 100 will have end stage renal failure.[1,5] Of the 2000 with microalbuminuria, only 100 will progress to end stage renal failure (that is, one in 20), partly because many will die of cardiovascular events beforehand.

Microalbuminuria cannot be detected by routine urinalysis, which detects only macroalbuminuria (albumin concentration greater than 300 mg/L; equivalent to total protein greater than 500 mg/L). A microalbuminuria dipstick test is available, and can detect urinary albumin semiquantitatively at concentrations of 20, 50 and 100 mg/L (microalbuminuria, greater than 30 mg/L); however, it does not correct for any general urine concentration or dilution.

Unfortunately, urinary albumin and creatinine excretion is highly variable within the individual, with a coefficient of variation (CVi) of approximately 40%.[3] This means that:

- a positive test result on one specimen should be confirmed by a test on another specimen, and if that is negative then a third specimen should be tested
- changes over time need to be more

than 80% (2 x CVi) to be likely to be a real signal rather than the background 'noise' of variability.

The occurrence of microalbuminuria in a person with diabetes does not mean that it was necessarily caused by the diabetes. In the absence of significant diabetic retinopathy, a parallel microvascular complication of diabetes, an alternative cause should be suspected and sought. Causes of albuminuria not related to diabetes include:[4]

- contamination from extra urinary causes
- haematuria
- lower or upper urinary tract infection
- bladder obstruction
- nephritis (glomerular or interstitial)
- renovascular disease (arterial or venous).

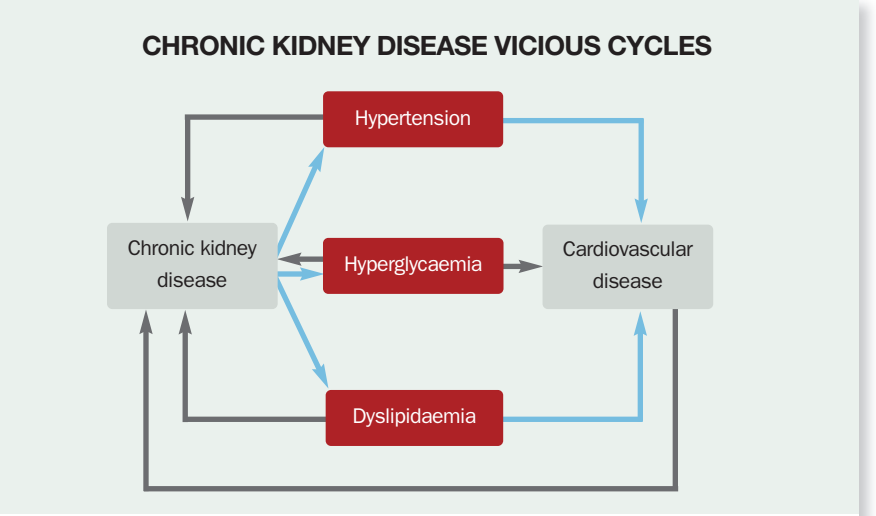


Figure 2. Vicious cycles in chronic kidney disease.[6] Chronic kidney disease is worsened by increased hypertension, hyperglycaemia and dyslipidaemia, and by progression of cardiovascular and renovascular disease.

MICROALBUMINURIA – NATURAL HISTORY

The onset of microalbuminuria predates progressive renal disease and excess cardiovascular events by some time. With progression of nephropathy, however, the plasma creatinine concentration increases (and glomerular filtration rate decreases), and excess cardiovascular events occur. Although microalbuminuria is an index of renal microvascular damage, most of the associated excess mortality is from cardiovascular disease. For every 20 people who develop microalbuminuria, only one will progress to end-stage renal disease, partly because many die of cardiovascular events beforehand (Figure 1).[1,5]

The high cardiovascular mortality associated with albuminuria is not well appreciated but becomes obvious when several vicious cycles initiated by renal damage are understood (Figure 2).[1,6] Progressive renal damage is associated with increasing blood pressure, which contributes to further renal damage. Renal damage also makes glycaemic control more difficult and hyperglycaemia also contributes to progressive renal damage. Finally, renal damage is associated with dyslipidaemia, which combines with hypertension to cause cardiovascular disease, including renovascular disease, completing yet another vicious cycle. If microalbuminuria is detected and stabilised early, these vicious cycles do not develop; however, once they have started it can be difficult to interrupt them.

MICROALBUMINURIA – MANAGEMENT

An evidence-based approach to the management of microalbuminuria is discussed below.

Blood glucose and blood pressure control

The United Kingdom Prospective Diabetes Study (UKPDS) showed decreases in blood glucose levels and blood pressure in patients with type 2 diabetes were associated with reduction in the onset and progression of microvascular and macrovascular complications, including microalbuminuria.

In the study of intensive blood glucose control (UKPDS 33), over 10 years, glycosylated haemoglobin (A_{1c}) was 0.9% lower in the intensive group than in the control groups (7.0% *vs* 7.9%).[5] In the study of tight blood pressure control (UKPDS 38), mean blood pressure during follow up was 10/5 mm/Hg lower in the tight control group than in the less tight control group (144/82 mmHg *vs* 154/87 mmHg).[7] Intensive blood glucose control and tight blood pressure control had an additive effect.[7] Figure 3 compares the progression of microalbuminuria with these treatments and conventional treatment.

A 'legacy effect' from the UKPDS was also shown 10 years later.[8] There was ongoing reduction of microvascular disease, cardiovascular events and mortality in the previous intensive therapy group, although A_{1c} level and blood pressure were similar at that stage in both groups.

Angiotensin blockade and multifactorial interventions

Renin angiotensin system blockade with an ACE inhibitor or angiotensin receptor antagonist is associated with decreased progression of microalbuminuria independently of blood pressure reduction.[1]

Prospective randomised controlled trials have assessed two general approaches

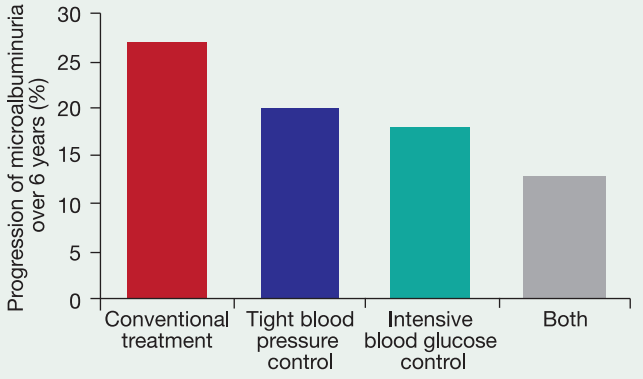


Figure 3. Slowing progression of microalbuminuria by intensive blood glucose control and tight blood pressure (BP) control – UKPDS 33 and UKPDS 38.[5,7] Reduction of BP (by 10/5 mmHg) and glycosylated haemoglobin (A_{1c}; by 0.9%) individually and together reduce progression to microalbuminuria. (Conventional treatment: BP target, below 154/87 mmHg; fasting blood glucose target, below 15 mmol/L by diet alone. Tight BP control: BP target below 144/82 mmHg. Intensive blood glucose control: fasting blood glucose target, below 6 mmol/L by sulfonylurea or insulin.)

to stabilising/slowing/reversing microalbuminuria, reducing the decline in GFR and reducing cardiovascular events and mortality:

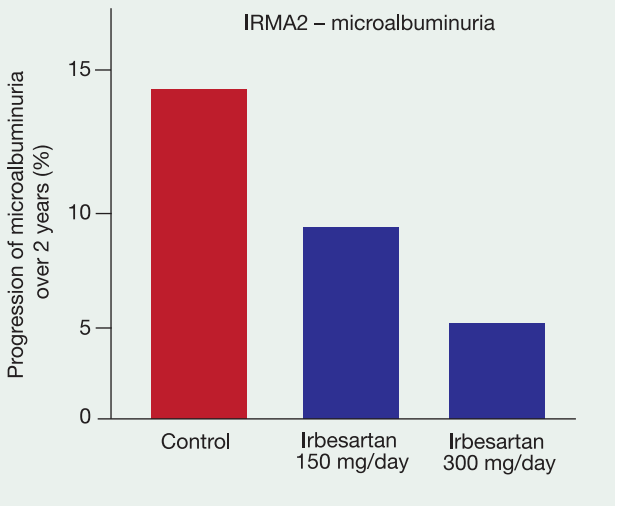
- one approach targets the microalbuminuria itself with an angiotensin receptor antagonist: the Irbesartan Microalbuminuria Type 2 Diabetes Mellitus in Hypertensive Patients (IRMA2) trial and the Irbesartan Diabetic Nephropathy Trial (IDNT)[9,10]
- the other approach aims to improve all aspects of diabetes management (lifestyle, self-care and medication): the Steno-2 trials, from the Steno Diabetes Centre in Denmark.[11,12]

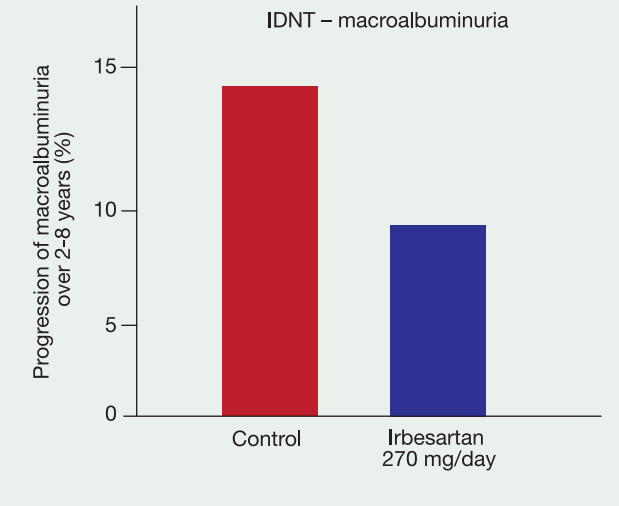
Angiotensin blockade

The IRMA2 trial and IDNT were conducted in hypertensive patients with type 2 diabetes and microalbuminuria. In these trials, the angiotensin receptor antagonist irbesartan reduced progression of microalbuminuria, especially at a dose of 300 mg/day (the IRMA2 trial), and reduced progression of macroalbuminuria to severe renal impairment and cardiovascular mortality (IDNT; Figures 4a and b).[9,10]

Lifestyle, self-care and medication

In the Steno-2 trial, progression of patients with type 2 diabetes and microalbuminuria to end-stage renal disease and cardiovascular events was halved over the seven years of the trial, and follow up some 10 years later showed a continuing effect of this period of intensive therapy.[12] This 'legacy' effect occurred





Figures 4a and b. Slowing progression to nephropathy by targeting microalbuminuria and macroalbuminuria – the IRMA2 trial and IDNT.[9,10] a (left). In the IRMA2 trial, irbesartan at a dose of 150 and 300 mg/day reduced progression of microalbuminuria. b (right). In the IDNT, irbesartan at a dose of 270 mg/day (the average dose, after titration from 150 to 300 mg/day) reduced progression of macroalbuminuria (to end stage renal failure or doubling of plasma creatinine).

despite equivalent management in both the intensive and control therapy groups after the trial.

Education and 'trying harder'

Another trial targeted patients with diabetes but without microalbuminuria and tested whether educating them about diabetes improved their own diabetes management and moved their risk factor profile closer to target, with the expectation that this would slow the progression of vascular complications.[13] In this 'active patients' trial, patients with type 2 diabetes, hypertension and hyperlipidaemia were educated about medical and lifestyle risk factors, therapies to lower them and therapeutic targets. They were also advised on how to interact and discuss treatment with their doctors. A clinically and statistically significant improvement in risk factors occurred with well-informed and motivated patients, as did a slowing of progression of microvascular disease (albuminuria and retinopathy).

In the 'active doctors' trial – the Steno-2 trial – doctors were encouraged to increase therapy and reduce the level of medical risk factors and patients were encouraged and supported to improve lifestyle risk factors.[11]

Of course, in both these 'active' trials doctors and patients were 'trying harder'. However, specifically targeting both the doctors and the patients might improve outcomes further than focusing on one group or the other (Figure 5).

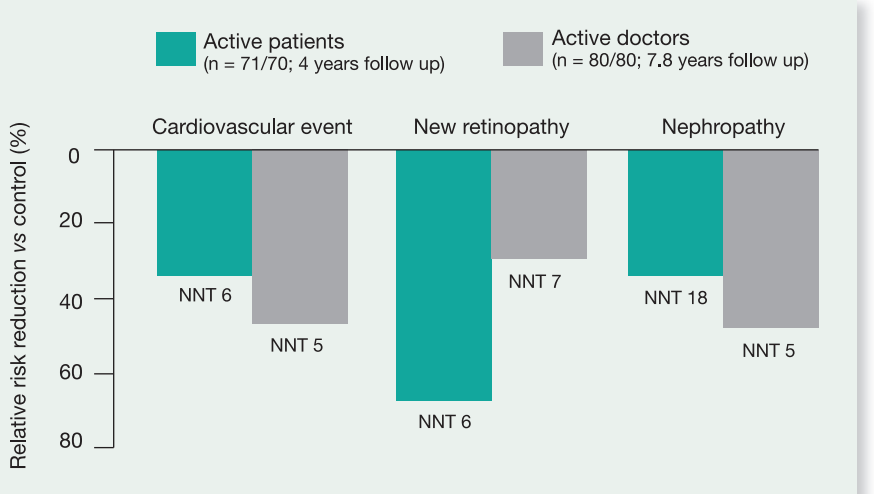


Figure 5. 'Active patients' and 'active doctors' and vascular complication reduction in type 2 diabetes.[11,13] Macrovascular and microvascular events were significantly lower in the intervention groups compared with the control groups, with small numbers needed to treat (NNT) to prevent one event.

Overview of management

Although the benefits discussed above occurred in clinical trial settings rather than in the real world, they make it clear that 'trying harder' and intensified treatment can improve clinical outcomes. The implications for practical management of microalbuminuria seem clear: doctors should 'try harder' in terms of angiotensin blockade, blood pressure and blood glucose management and other clinical aspects of diabetes management, and patients should 'try harder' to improve their self-care behaviours and become actively involved in trying to achieve risk factor targets.

The GP is clearly the most appropriate professional to co-ordinate such management and to recruit the team of medical, nursing and allied health professionals.

CONCLUSION

The detection of microalbuminuria in a patient with diabetes signals the presence and likely progression of clinically significant renal damage and cardiovascular risk. Testing for microalbuminuria is performed on either a timed overnight (albumin excretion rate) or first voided early morning urine (albumin:creatinine ratio), having excluded contamination with blood or inflammatory products by urinalysis. As microalbuminuria is highly variable (coefficient of variation within an individual of 40%), two positive specimens are required for diagnosis.

The natural history of albuminuria is of progressive renal damage and falling glomerular filtration rate, with increased cardiovascular risk. The cardiovascular risk is associated with several vicious cycles initiated by renal damage (hyperglycaemic, hypertensive, dyslipidaemic and vascular).

Control of blood glucose and blood pressure, the use of angiotensin blockade to treat albuminuria and more active therapy by doctors and patients have been shown to significantly delay the onset and progression of micro- and macroalbuminuria and to halve progression from microalbuminuria to end-stage renal disease and cardiovascular events.

GPs have a clear role in co-ordinating the evidence-based management of people with microalbuminuria and in reducing progressive renal impairment and the increased risk of cardiovascular events. MT

REFERENCES

References are included in the pdf version of this article available at www.medicinetoday.com.au.

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