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Diabetes monitoring – albuminuria

Frequently asked questions

I am treating this man's blood glucose, blood pressure and blood fats already. Why check for microalbuminuria if it won't change my management?

Detecting microalbuminuria is important for two reasons. The onset of microalbuminuria marks a major increase in the risk of morbidity and mortality (*Figure 1*). Microalbuminuria does not indicate early renal damage, it is just the earliest indicator we have. By the time microalbuminuria occurs renal biopsy would show widespread glomerular damage. Moreover, just as the endothelium of the glomerular has been so significantly damaged that it now 'leaks' albumin, so the endothelium of many other vascular beds is disrupted.

These two facts – that microalbuminuria indicates considerable renal damage and not the onset and that microalbuminuria is a marker of widespread vascular endothelial injury – explain why the presence of microalbuminuria greatly increases the likelihood of renal and cardiovascular morbidity and mortality.

The onset of microalbuminuria is a signal that management needs to be revised. If we were truly unable to change our management, then the 'bad news' of microalbuminuria would worry both us and the patient, to no good end.

The STENO-2 trial¹ showed that even if we are providing high quality diabetes care, 'trying harder' on all fronts dramatically improves outcomes – roughly halving cardiovascular events from 45 to 25% and progression to nephropathy from 40 to 20% over 7 years (*Figure 2*).

In a general practice of a 1000 patients there will be 30 patients with known diabetes and 10 of these will have microalbuminuria. 'Trying harder' in these 10 patients will prevent one cardiovascular event or one progression to nephropathy every 2 years.

The clinical significance of albuminuria and its implications for treatment explain why The Royal Australian College of General Practitioners guidelines suggest, and the Service Incentive Payment (SIP) cycle requires, assessment of albuminuria every year.²

Which specimen should I use for microalbuminuria – spot, first voided, 24 hour, timed overnight?

Albumin is usually increased by:

- food – protein metabolism increases glomerular filtration and thus albumin filtration
- exercise – especially vigorous exercise, increases blood pressure, glomerular pressure and albumin filtration, and
- erect posture – especially in young people, may cause the kidney to descend in the abdomen, kink the renal vein and increase glomerular pressure and albumin excretion.

The urine specimen that best represents the usual albumin excretion is one that is produced while the person is fasting, not exercising, and supine (overnight or first voided) (see *Patient education*). The best samples are:

- first voided specimen for albumin creatinine ratio (mg/mmol), or
- a timed overnight specimen for albumin excretion rate ($\mu\text{g}/\text{min}$).

The albumin excretion rate provides a more reliable estimate of albuminuria, if the timing is accurate, as a laboratory only measures one substance. However, the albumin creatinine ratio is much easier for patients to collect and is the usual sample, even though a laboratory measures two substances

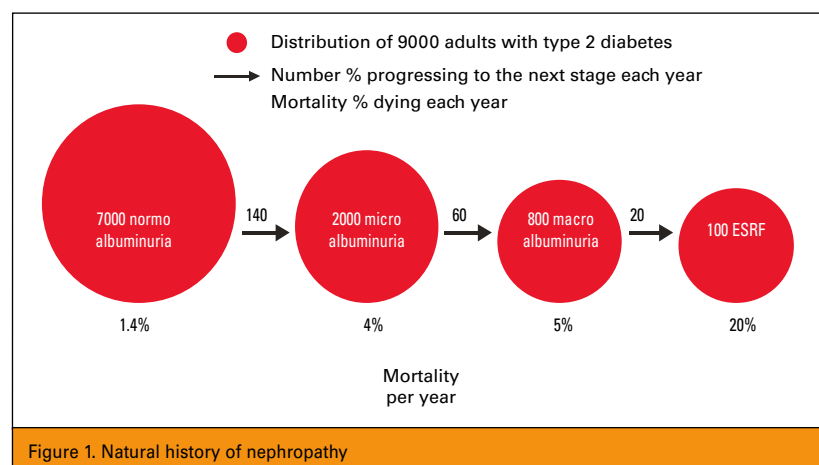


Figure 1. Natural history of nephropathy

and the two results increase the potential for variability.

Albumin is measured as a concentration or as a total quantity in the specimen. It is necessary for the overall concentration of the urine or for the duration of the collection. Otherwise 'normal' people could have apparently abnormal results because of very concentrated urine or a prolonged collection. This scaling is done by:

- creatinine for albumin concentration, or
- timing for albumin excretion rate.

The amount of creatinine we all produce and excrete is determined by our muscle mass. Creatinine is a breakdown product of creatine that acts as an energy reservoir in muscle. The more muscle we have, the more creatinine we produce. Hence men, generally having a larger muscle mass, have higher plasma creatinine values and urine creatinine excretion than women.

The albumin creatinine ratio (ACR) scales the albumin concentration according to the creatinine concentration and allows for concentration or dilution of the urine. Values for women are higher than men because creatinine excretion

(the denominator) is lower.

In timing the urine collection scales for duration, the person voids before bed and notes the starting time of the collection. Overnight all the urine produced is collected. On rising the person voids, collecting the urine and noting the time of completion. The laboratory calculates the duration and scales the amount of urine in the specimen by time – albumin excretion rate (AER $\mu\text{g}/\text{min}$). Results are recorded as normo-, micro- or macro-albuminuria (Table 1). Microalbuminuria can only be detected by a laboratory or by a special urine dipstick (Micral™). Macroalbuminuria corresponds to proteinuria ($\geq 500 \text{ mg/L}$ of protein) and is the lower limit of proteinuria with the usual urinalysis dipstick.

Once macroalbuminuria occurs, proteinuria is considered more indicative of overall kidney function. The corresponding specimens for protein are:

- protein creatinine ratio (PCR) on a spot urine specimen (preferably first voided), or
- 24 hour urine protein excretion (for a timed specimen).

My patient is very frustrated, and so am I. Specimen collection is correct but there is microalbuminuria one day and not a week later. What's going on?

Even when specimens are correctly collected there is considerable intra-individual variability.³ You will remember that the intra-individual variability is expressed as a coefficient of variation (CV_i) which is the standard deviation (SD) divided by the mean value of the measurement. The CV_i for microalbuminuria can be different at different levels but typically is approximately 40%. This means that for a mean value of 40 $\mu\text{g}/\text{min}$ (microalbuminuria as it is over 20 $\mu\text{g}/\text{min}$) the SD is 16 $\mu\text{g}/\text{min}$ (40% of 40) and the 95% range for measurement is 8–72 $\mu\text{g}/\text{min}$ (mean $\pm 2 \text{ SD}$). Microalbuminuria can indeed be 'here today and gone tomorrow'. This is well recognised by laboratories which recommend that microalbuminuria on one specimen be confirmed by a second before taking any clinical action. If the second specimen is negative, it is recommended that a third decide the presence or absence of microalbuminuria. This reduces the risk of reacting to a false positive result, particularly at values close to a decision threshold between normo- and micro-albuminuria and micro- and macro-albuminuria where a small change could cross a threshold with important clinical implications. The alternative is to take multiple measurements and use the mean value. Unfortunately it may take a large number of measurements to reduce the variability of this mean to <10%.

There may also be concern that real microalbuminuria might be missed by a falsely negative result. Fortunately, it is likely that if microalbuminuria is missed this year it would be detected next year and generally diabetic nephropathy does not progress so rapidly that potentially important renal damage will be missed, unless blood pressure is uncontrolled.

If I treat microalbuminuria, will retesting tell me if the treatment is working?

There is evidence that reducing microalbuminuria by controlling hypertension and using medications affecting the renin angiotensin aldosterone (RAS) system reduces progression of micro- and macro-albuminuria.^{4,5} As a rough guide, halving albuminuria doubles the time to end stage

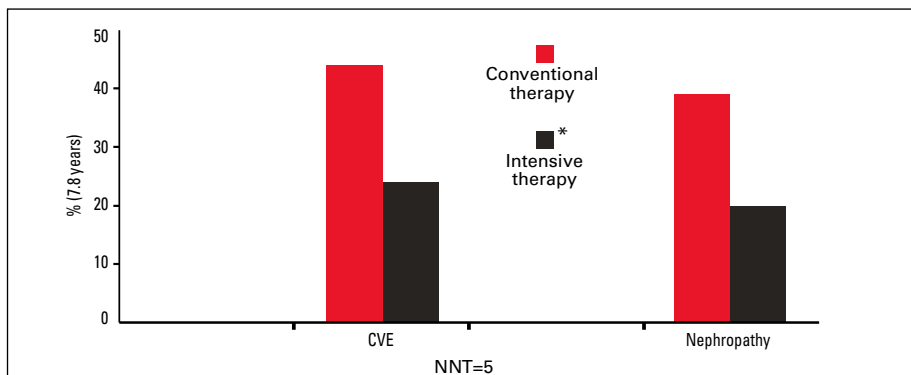


Figure 2. 'Tying harder' – the STENO-2 study

Table 1. Urine specimen results²

	Women	Men
Albumin creatinine ratio (mg/mmol)		
Specimen: first voided morning urine		
Normal	0–3.5	0–2.5
Microalbuminuria	3.6–35.0	2.6–25.0
Macroalbuminuria	>35.0	>25.0
Urinary albumin excretion ($\mu\text{g}/\text{min}$)		
Specimen: timed overnight urine collection		
Normal	<20	<20
Microalbuminuria	20–200	20–200
Macroalbuminuria	>200	>200

renal failure. This is part of the justification for monitoring albuminuria. After all, if the important clinical decision was to bring blood pressure on to target and use medications blocking the RAS system, there would be little point in making subsequent measurements which would not affect clinical decisions.

The target is to reverse, stabilise or slow progression of renal damage. If albuminuria were to progress rapidly this might prompt a comprehensive review and/or specialist referral to exclude a second or complicating problem. However, because of the high CV_i of albuminuria, repeat measures may give misleading information about progress. There are two general approaches to dealing with this variability:

- perform several measures at one point of time (eg. yearly) to reduce variability, or
- perform several measures at different times (eg. 6–12 months) to provide information about trends.

Within the microalbuminuria range, glomerular filtration rate (GFR) and plasma creatinine do not change⁶ and albuminuria is the only monitor of renal function. Once overt nephropathy (macroalbuminuria/proteinuria) occurs, GFR falls more quickly than usual. For example, in a person without diabetes, GFR declines by 1 mL/min/year over the age of 40 years. For a person with type 1 diabetes and overt nephropathy the decline is 11 mL/min/year.⁷

Conflict of interest: none declared.

References

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Patient education

A guide to collecting urine specimens for the laboratory

It is important to collect the correct urine specimen, otherwise misleading results can occur.

- If you have any questions, ask your doctor or the laboratory for guidance
- Make sure you know what to do before you collect the urine specimen
- Many people, especially women, find it convenient to pass the urine into a large clean container, washed out with water (not detergent). This makes it easier to pour it into the laboratory bottle.

First voided specimen

- When you get out of bed in the morning, empty your bladder, collecting the first part of the urine in the urine specimen bottle
- The first voided urine collection is now complete. Take the specimen and the laboratory form to your doctor's surgery or to the laboratory
- If you make a mistake, wash the bottle out with clean water and repeat the collection correctly the following morning.

Overnight specimen

- Just before you go to bed and to sleep, empty your bladder into the toilet and note the time.
- Collect any urine you pass during the night into the laboratory bottle
- When you get out of bed in the morning, empty your bladder and collect all the urine. Note this time as well
- The overnight urine collection is now complete. Take the specimen and the laboratory form to your doctor's surgery or to the laboratory
- If you make a mistake, wash the bottle out with clean water and repeat the collection correctly the following night.

24 hour urine

- When you get out of bed in the morning of the day you are collecting the urine, empty your bladder into the toilet and note the time
- Collect any urine you pass during that day and night into the laboratory bottle
- The next morning, get out of bed at the same time as the day before and collect the urine
- This completes the 24 hour urine collection. Take the specimen and the laboratory form to your doctor's surgery or the laboratory
- If you make a mistake, wash the bottle out with clean water and repeat the collection correctly the following day.