MICROALBUMINURIA

1. Use

A. Diagnosis/Screening

Diabetes is the leading cause of end-stage renal disease in the US and Europe (231). Early detection of diabetic nephropathy relies upon tests for urinary excretion of albumin. Conventional qualitative tests (chemical strips or "dipsticks") for albuminuria do not detect the small increases of urinary albumin excretion seen in early stages of nephropathy. For this purpose, tests for "microalbuminuria"† are used. Microalbuminuria is defined (231) as excretion of 30 – 300 mg of albumin /24 h (or 20 – 200 μg/min or 30 – 300 μg/mg creatinine) (Table 7) on two of three urine collections.

Table 7: Definitions of Microalbuminuria and Clinical Albuminuria*

	mg/24 h	μg/min	μg/mg creatinine
Normal	< 30	<20	< 30
Microalbuminuria	30-300	20-200	30-300
Clinical albuminuria†	>300	>200	>300

†Also called "overt nephropathy"

*From ADA (14)

The ADA recommends periodic qualitative ("dipstick") testing for urine albumin in adults with diabetes (231). Positive tests represent "clinical albuminuria" or "overt nephropathy" in the ADA recommendations, corresponding to protein excretion > 300 mg/24 hours (> 200 μg/min or > 300 μg/mg creatinine) (Table 7). In these patients, quantitative measurement of urine protein excretion is used in the assessment of the severity of proteinuria and its progression, in planning treatment, and in determining the impact of therapy. Measurement of creatinine clearance as an index of glomerular filtration rate can be performed on the same timed (usually 12-h or 24-h) urine collection. Negative "dipstick" tests for "clinical proteinuria" (albumin excretion < 300 mg/day) should be followed with a test for microalbuminuria. For children with type 1 diabetes, testing for microalbuminuria is recommended to begin after puberty and after 5 years' duration of diabetes.

The recommendation to screen for microalbuminuria is based on expert opinion that considered such things as the natural history of diabetic nephropathy and the evidence from many randomized controlled clinical trials of benefit of treatment of those patients found to have microalbuminuria.

In the ADA algorithm for urine protein testing (231), the diagnosis of microalbuminuria requires the demonstration of increased albumin excretion (as defined above) on 2 of 3 tests repeated at intervals of 3 – 6 months, and exclusion of conditions that "invalidate" the test.

†Although the term microalbuminuria is recognized as a misnomer (the albumin is not small), the term is well entrenched and not likely to be replaced by alternatives (e.g., paucialbuminuria or increased urinary albumin excretion (UAE) rate).

B. Prognosis

Microalbuminuria has prognostic significance. In 80% of people with type 1 diabetes and microalbuminuria, urinary albumin excretion increases at a rate of 10 – 20% per year, with development of clinical proteinuria (> 300 mg albumin/day) in 10 –15 years. After development of clinical grade proteinuria, most (> 80 %) patients go on to develop decreased glomerular filtration rate and, given enough time, end-stage renal disease. In type 2 diabetes, 20 – 40 % of patients with microalbuminuria progress to overt nephropathy, but by 20 years after overt nephropathy only ~ 20 % develop end-stage renal disease. In addition, patients with diabetes (type 1 and type 2) and microalbumuria are at increased risk for cardiovascular disease.

C. Monitoring

The roles of routine urinalysis and albumin measurements are less clear in patients with a diagnosis of microalbuminuria. Some have advocated urine protein testing to monitor treatment, which may include improved glycemic control, more assiduous control of hypertension, dietary protein restriction and therapy with angiotensin inhibitors (231). Therapy (e.g., with angiotensin-converting enzyme inhibitors) has been shown to slow the rate of increase of urinary albumin excretion rate or to prevent it in short-term studies, and intensive glycemic control is associated with delayed progression of urinary albumin excretion (for a recent study, see (232). Patients who were prescribed angiotensin converting enzyme inhibitors are not being tested as frequently as others (233). This finding points to an ambiguity in current guidelines as recommendations for renal screening in patients on angiotensin converting enzyme inhibitors are not clearly defined.

2. Rationale

Recommendation: Annual microalbumin testing of patients without clinical proteinuria should begin in pubertal or postpubertal individuals five years after diagnosis of type 1 diabetes and at the time of diagnosis of type 2 diabetes. The role of testing is unclear in patients under treatment with angiotensin-converting enzyme inhibitors and in those with short life expectancy.

Level of evidence: E

Early detection of microalbuminuria allows early intervention with a goal of delaying the onset of overt diabetic nephropathy. As stated earlier, microalbuminuria is a marker of increased risk of cardiovascular morbidity and mortality in both type 1 and type 2 diabetes. Thus, it is a signal for more intensive efforts to reduce cardiovascular risk factors.

Microalbuminuria rarely occurs with short duration of type 1 diabetes or before puberty. Thus testing is less urgent in these situations. Although the difficulty in precisely dating the onset of type 2 diabetes warrants initiation of annual testing early after diagnosis of diabetes, older patients (age > 75 years or life expectancy < 20 years) may never be at risk for clinically significant nephropathy in view of a projected life-span that is too brief for renal dysfunction to develop. In such patients, the role of treating microalbuminuria is far from clear, and the need to screen for it is, thus, uncertain at best.

3. Analytical Considerations

A. Analytical

> **Recommendation:** The analytical CV of methods to measure microalbuminuria should be <15%.
>
> Level of evidence: E

Analytical goals can be related to the degree of biological variation, with less precision required for analytes that vary widely in subjects to be tested. The within-person variation of albumin excretion is large in people without diabetes and even higher in patients with diabetes. Howey et al (234) studied day-to-day variation, over 3-4 weeks, of the 24-hour albumin excretion, the concentration of albumin and the albumin:creatinine ratio. The latter two were measured in the 24-hour urine sample and also in (a) the first morning void and (b) random untimed urine. In healthy volunteers, the lowest within-person CVs were found for the concentration of albumin in the first morning void (36 %) and for the albumin:creatinine ratio in that sample (31 %). They recommended use of the urine albumin concentration in the first morning void rather than 24-hour urinary excretion of albumin which had a higher within-person CV.

To keep analytical CV less than half the biological CV, Howey (234) proposed an analytical goal of 18 % CV. Alternatively, if the albumin:creatinine ratio is to be used, one may calculate the need for somewhat lower imprecision (that is, a better precision) to accommodate the lower biological CV for the ratio and the imprecision contributed by the creatinine measurement). Assuming a CV of 5 % for the measurement of creatinine, we calculate a goal of 14.7% for the analytical CV for albumin when it is used to estimate the albumin:creatinine ratio. A goal of 15% appears reasonable to accommodate use of the measured albumin concentration for calculation of either timed excretion rate or the albumin:creatinine ratio.

In subjects with diabetes, the within-person variation (CV) was 61% for albumin concentration in the first morning void and 39 % for the albumin:creatinine ratio. Thus the goals above appear more than adequate for use in subjects with diabetes.

B. Premeasurement

> **Recommendation:** Acceptable samples to test for increased urinary albumin excretion are timed (e.g., 12 or 24 hour) collections for measurement of albumin concentration and timed or untimed samples for measurement of the albumin:creatinine ratio. For screening, an untimed sample for albumin measurement (without creatinine) may be considered if a concentration cutoff is used that allows high sensitivity for detection of an increased albumin excretion rate.
>
> Level of evidence: E

Collection of 24-hour samples has advantages (e.g., possibility to measure creatinine clearance), but the albumin:creatinine ratio appears to be an acceptable alternative. The ratio has a within-person, biological variation similar to that of the excretion rate, and correlates well with timed excretion as well as with albumin concentration in a first morning void of urine (234). A first-morning void sample is somewhat preferable for the ratio as the ratio in a first morning sample had a lower within-person variation than did the ratio in a random sample of urine during the day (234). Although the ratio appears entirely acceptable for screening, limited data are available for its use in monitoring the response to therapy, and 12- or 24-hour collections may be preferable.

Albumin is stable in untreated urine stored at 4˚ C or 20˚ C for at least a week (235). Neither centrifugation nor filtration appears necessary before storage at – 20˚ C or – 80˚ C (236). Whether centrifuged, filtered or not treated, albumin concentration decreased by 0.27 % per day at – 20˚ C, but showed no decrease over 160 days at – 80˚ C (236).

The urinary albumin excretion rate reportedly has no marked diurnal variation in diabetes, but it does in essential hypertension (237).

C. Measurement: Detection limit, imprecision

Commercially available quantitative methods for microalbuminuria have documented detection limits of ~ 20 ug/L or less. Within-run imprecision and day-to-day (total) imprecision are well within the analytical goal of ~ 15 %, and often much less. A recent study showed that most methods, but not all, agree well with each other and support a reference interval of 2 – 20 μg albumin/mg creatinine (238) .

> **Recommendation:** Semiquantitative or qualitative screening tests for microalbuminuria should be positive in >95% of patients with microalbuminuria to be useful for screening. Positive results must be confirmed by analysis in an accredited laboratory.
>
> Level of evidence: E

Qualitative (or semiquantitative) tests for microalbuminuria have been proposed for use as screening tests for microalbuminuria. To be useful, screening tests must have high detection rates for abnormal samples, i.e., a high clinical sensitivity. Although many studies have assessed the ability of reagent strips ("dipstick" methods) for microalbumin to detect increased albumin concentrations in urine, the important question is whether the method can detect microalbuminuria, that is, increased albumin excretion rate or its surrogate, increased albumin:creatinine ratio. We can find no published study in which the sensitivity for detection of an increased albumin excretion rate reached 95 %.

In a large study (239), the sensitivity for detection of an albumin excretion rate > 30 mg/24 hours was 91 % when the test was performed by a single laboratory technician, 86 % when performed by nurses, and 66 % when performed by general practitioners. In two more recent studies (240, 241), the sensitivities were 67 % - 86 %. False-positive results also appear to be common, with false positive rates as high as 15 % (239). Thus it appears that at least some of the tests, especially as used in practice, have the wrong characteristics for use in screening because of low sensitivity (high false negative rates), and positive results must be confirmed by a laboratory method.

The available "dipstick" methods for microalbumin do not appear to lend themselves to viable screening strategies either in the physician's office or for home testing. Usual screening tests (e.g., for phenylketonuria) have low false negative rates, and, thus, only positive results require confirmation by a quantitative method. When a screening test has diagnostic low sensitivity, negative results also must be confirmed, a completely untenable approach. With semiquantitative tests, it may be possible (or, indeed, necessary) to use a cutoff below 20 mg/L to ensure detection of samples with albumin > 20 mg/L as measured by laboratory methods.

We recommend evaluation of chemical strip methods by testing of samples with albumin concentrations in the range of 20 – 50 mg/L as it is insufficient to show that the methods can detect albumin at higher concentrations.

Further studies are needed before the "dipstick" tests for microalbuminuria can be recommended as replacements for the quantitative tests. The use of the qualitative tests at the point of care is reasonable only when it can be shown to avoid quantitative testing in a sizeable proportion of the patients and to ensure detection of those patients who have early renal disease.

4. Interpretation

A. Nonanalytical sources of variation

Transient increases of urinary albumin excretion have been reported with short-term hyperglycemia, exercise, urinary tract infections, marked hypertension, heart failure and acute febrile illness (231).

B. Frequency of measurement

The ADA recommends annual measurement for microalbumin in patients with negative ("dipstick") results for overt proteinuria. After the documentation of a diagnosis of microalbuminuria (i.e., with results as defined above on 2 of 3 tests performed within a period of 3 – 6 months), repeated testing is reasonable to determine whether a chosen therapy is effective. It may also be useful in determining the rate of progression of disease and thus support planning for care of end-stage renal disease. Although the ADA recommendations suggest that such testing is not generally needed before puberty, testing may be considered on an individual basis if it appears appropriate because of early onset of diabetes, poor control or family history of diabetic nephropathy. A recent study indicates that the duration of diabetes prior to puberty is an important risk factor in this age group and thus can be used to support such testing in individual patients (232).