

Screening, Monitoring, and Treatment of Albuminuria: Public Health Perspectives

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Microalbuminuria is an early sign of progressive cardiovascular and renal disease in individuals with and without diabetes. Despite compelling data, at present only a minority of patients with diabetes and rarely individuals without diabetes are screened for albuminuria in a systematic way. All of the criteria to implement systematic albuminuria screening are fulfilled in diabetes, and most are nearly fulfilled for microalbuminuria screening in individuals without diabetes. Because of the growing evidence that treatment of microalbuminuria in individuals without diabetes may offer a cost-effective benefit to prevent cardiovascular disease, nephrologists and other health care providers should pay more attention to the early detection and subsequent treatment of individuals with microalbuminuria.

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Microalbuminuria is an early sign of progressive cardiovascular and renal disease. We discuss whether screening for albuminuria is warranted and, if so, how screening and subsequent monitoring could be carried out.

The criteria that a screening program should fulfill have been described by Wilson and Jungner (1) and are given in Table 1. As more data are available on the impact of elevated albuminuria on renal and cardiovascular prognosis in individuals with diabetes than in individuals without diabetes, we discuss separately the evidence that is available for the need for albuminuria testing in these two groups.

Screening for Albuminuria to Prevent Chronic Kidney Disease and Cardiovascular Disease

Albuminuria screening first may be used as a tool to detect individuals with undiagnosed chronic kidney disease (CKD). Elevated albuminuria (30 to 300 mg/d albumin is the definition of microalbuminuria) is an early predictor of progressive renal function loss in type 1 (2,3) and type 2 diabetes (4,5). At the time that microalbuminuria becomes manifest, GFR typically is normal or elevated or only modestly impaired (stage 1 or 2 CKD). Increased urinary albumin excretion (UAE) also may indicate a worse renal prognosis in individuals without diabetes. In a Japanese study, >100,000 individuals were tested for dipstick proteinuria. After a period of >17 yr, the likelihood of being on dialysis increased according to the degree of dipstick protein-

uria at baseline (6). A similar finding was reported from the Prevention of Renal and Vascular End Stage Disease (PREVEND) study: After a 4.2-yr follow-up, the number of individuals who *de novo* had developed stage 3 or worse CKD was related to baseline albuminuria (7) (Figure 1). By screening for elevated albuminuria, one of course will not only detect individuals with microalbuminuria but also individuals with macroalbuminuria (>300 mg/d), who most likely are already in stage 3 or 4 CKD.

The benefits of screening for albuminuria in the short term are to detect individuals who are at risk for cardiovascular disease in individuals with diabetes (8) and individuals without diabetes (9,10). We should keep this in mind in view of the pros and cons for screening for albuminuria in the general population. Especially in individuals without diabetes, the short-term benefits will be to prevent cardiovascular events; only in the long term might it be found to prevent ESRD.

Does Screening for Albuminuria Help Detect Individuals at Risk for CKD and CVD in an Early Phase?

The time course of albuminuria in relation to progressive renal function loss has been well described. When microalbuminuria becomes manifest, the phase of glomerular hyperfiltration is shifting to that of progressive renal function loss. This has been shown in type 1 (11) and type 2 diabetes (5). This loss of GFR ultimately leads to ESRD. Evidence is accumulating that the same holds true for individuals who do not have diabetes and have microalbuminuria (12,13). It is a great benefit that we may detect individuals who are at risk for progressive disease in an early phase, because it is widely known that CKD typically becomes symptomatic only in stages 4 and 5 CKD. In that

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Table 1. The Wilson-Jungner criteria

	Individuals with Diabetes	General Population
1. The disease for which the screening test could be used is an important health problem.	Yes	Yes
2. The natural course of the disease should be well described.	Yes	Yes
3. The disease should be detectable in an early phase.	Yes	Yes
4. Treatment in an early phase should offer benefit.	Yes	Probably
5. A suitable test should be available to indicate the early phase of the disease.	Yes	Yes
6. The test should be acceptable, and there should be a well-defined cutoff.	Yes	Yes
7. The interval at which it should be tested should be well known.	Yes	Not yet
8. The extra workload needed in case of a positive test should be possible and acceptable.	Yes	Yes
9. The risk of screening, both somatic and psychiatric, should outweigh the benefits.	Yes	Yes
10. Screening and subsequent treatment in case of positive tests should be cost-effective.	Yes	Probably

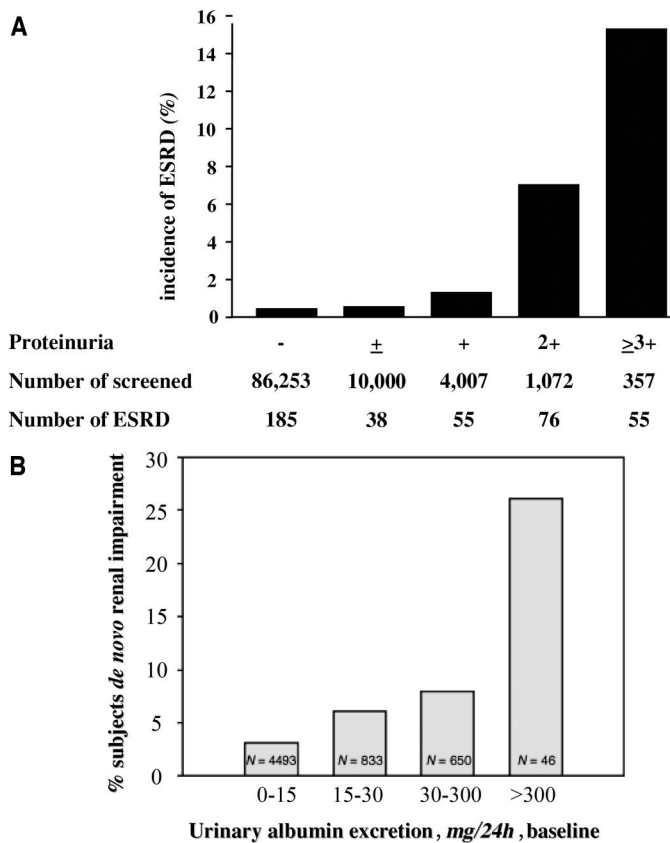


Figure 1. The incidence of new ESRD after 17 yr of follow-up (A) and of new stage 3 chronic kidney disease after 4.2 yr of follow-up (B) according to dipstick proteinuria (A) or albuminuria (B) in a community-based screening in Japan (A) or the Netherlands (B) (references [6] and [7], respectively).

respect, it is noteworthy that most patients with CKD are not aware of having diseased kidneys (14). Patients with earlier stages of CKD need increased attention because they are at

increased risk for cardiovascular disease. Because nephrologists presently are focusing predominantly on renal replacement therapy programs for patients with ESRD, the International Society of Nephrology issued a call to action to pay attention to patients with earlier CKD. Remuzzi and Weening (15) drew the parallel with an iceberg. What we are looking for presently is only the tip of what we should look for in the future.

Is Lowering of Albuminuria, Started at an Early Phase, Associated with Better Renal and Cardiovascular Outcomes?

The trials in individuals with macroalbuminuria (16–19) showed that lowering of albuminuria by either an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocker (ARB) was associated with a better renal (20) and cardiovascular (21) outcome. Moreover, it has been shown that the renoprotective and cardioprotective effects were related to the extent to which albuminuria was lowered. These trials all were performed in patients with stage 3 or 4 CKD. Recently, however, a few trials have been carried out in individuals with earlier stages of renal disease. The Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria (IRMA) study in patients with type 2 diabetes and microalbuminuria (GFR > 90 ml/min) showed that treatment with an ARB effectively prevented progression from micro- to macroalbuminuria (22). The Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) showed that an ARB even effectively prevented progression from normo- to microalbuminuria, again in type 2 diabetes (23). There are few data to show that lowering of albuminuria in individuals with still normal GFR results in a better cardiovascular outcome. Gaede *et al.* (24) recently showed that an intervention that aimed to correct multiple risk factors in type 2 diabetes and microalbuminuria reduced the risk for cardiovascular and microvascular events by approximately 50%. In the Prevention of Renal and Vascular Endstage Disease Inter-

vention Trial (PREVEND IT), who did not have diabetes but had UAE of 15 to 300 mg/d and a normal GFR were treated for 4 yr with fosinopril and/or pravastatin. There was a trend for fewer cardiovascular events in the fosinopril-treated group, in which albuminuria was lowered by 30% persistently during the 4-yr period. Pravastatin, in contrast, did not lower albuminuria and had no effect on cardiovascular events (25). The group with the higher baseline albuminuria (50 to 300 mg/d) showed the most benefit from fosinopril for preventing cardiovascular events.

Is the Screening Test Acceptable and Reliable?

The albuminuria screening debate is hampered by differences in laboratory methods used, urine samples studied, and definitions of microalbuminuria, which lead to different conclusions. The best approach depends on the number of individuals to be screened and the way the screening will be organized.

Which Laboratory Method Should We Use?

Traditionally, the dipstick test was used to detect protein in the urine. The test is semiquantitative, however, and insensitive to detect reliably albumin concentrations in ranges <300 mg/d albumin. At present, various antibody-based methods are used to measure lower levels of urinary albumin. These include RIA, nephelometry, immunoturbidimetry, and ELISA. It is beyond the scope of this review to evaluate these different techniques in detail. Recently, an HPLC method was developed by which not only immunoreactive but also immunounreactive albumin is measured (26). Using this method, more patients are found to have an albumin excretion in the microalbuminuric range (27). Whether patients who are detected as having microalbuminuria by HPLC are equally at risk for progressive renal and cardiovascular disease as those who are detected by the traditional antibody-based methods has yet to be determined. Whichever method is chosen, it is preferable to measure albumin in fresh samples (28).

These methods all require laboratory facilities. Antibody-based dipstick tests for microalbuminuria also are available (29,30). Although only semiquantitative, these tests have the advantage that they can be used easily by the general practitioner or the patient at home. A recent study in hypertensive patients found a sensitivity of 88%, a specificity of 80%, a positive predictive value of 69%, and a negative predictive value of 92% (30). The development of point-of-care testing systems may provide in the near future a quantitative urine albumin value within seconds.

Which Sample Should We Collect?

For the diagnosis of microalbuminuria, a 24-h urine collection is the gold standard. Because of the effort involved, it is not the method of choice for screening. The second best is a timed overnight urine collection. Again, because this requires collection of urine over a given time period, this may be acceptable for screening specific patient groups such as patients with diabetes or hypertension, but it is less feasible for population screening. The next best is a first-morning urine sample. This

has the advantage over a spot-urine sample because it is always performed at the same time of the day, and it is least influenced by hydration status and physical activity of the patient, reducing the variability that is caused by these factors. This may be a good choice for population screening if the patient is asked to mail a urine sample, as was done in the PREVEND study (31). In clinical practice, however, a spot-urine sample is collected when the patient visits either the general practitioner or the health care office, where the screening takes place. Some of the variability in timing of collection can be overcome by correcting urinary albumin concentration for urinary creatinine concentration.

Taking these considerations together, the best approach is to use a spot-urine sample (either the first-morning void or at the time of the visit to the medical office) as a prescreening. The patients whose urine is found positive then either should deliver two more samples to confirm whether the first value indeed was abnormal or, preferably, should collect two 24-h urine samples. This latter approach was tested in the PREVEND study. After using just one first-morning urine sample for measurement of urinary albumin concentration, patients with a urinary albumin concentration above a certain cutoff were invited for two 24-h urine collections. It was suggested that a cutoff value of 10 mg albumin/L could be used for mass screening to identify individuals who are more likely to have a UAE >30 mg/24 h (32).

How Should We Express Albuminuria, and Which Definition Should be Used for Abnormally Elevated Albuminuria?

Preferably, the excretion of albumin per unit of time should be used: UAE per 24 h or per minute (in case of timed overnight collections). For untimed samples, the albumin-to-creatinine ratio is advocated most (33). Because it corrects albumin for creatinine concentration, it may be more reliable than just a urinary albumin concentration. The albumin-to-creatinine ratio, however, introduces the need to use different definitions for an abnormal value for men and women (Table 2). Moreover, creatinine excretion in the urine depends not only on gender but also on age and race (34,35). This may explain why urinary albumin concentration from a spot sample performs equally well for the definition of microalbuminuria as albumin-to-creatinine ratio (32). In case a specific individual is followed over time with serial urine samples, the albumin-to-creatinine ratio may offer an advantage over albumin concentration alone.

The definitions for microalbuminuria and macroalbuminuria are given in Table 2. Because the relation between albuminuria and an increased cardiovascular (or renal) risk is continuous, it is difficult to conclude what is a normal level. In general, it is desirable to define specific cutoff values that could be used in clinical guidelines. The lower cutoff value may change over the years, as has been seen for BP and cholesterol values in the past decades. In fact, cutoff levels are defined depending the cost-effectiveness of screening for albuminuria and treatment to lower albuminuria in an attempt to prevent cardiovascular disease and CKD. If it is found to be cost-effective to lower

Table 2. Classification of abnormal urinary albumin excretion

	24-H Urine Albumin (mg/24 h)	Overnight Urine Albumin (μ g/min)	Albumin (mg/L)	Spot Urine		
				Albumin/Creatinine Ratio		
				Gender	mg/mmol	mg/g
Normal	<15	<10	<10	M	<1.25	<10
				F	<1.75	<15
High normal	15 to <30	10 to <20	10 to <20	M	1.25 to <2.5	10 to <20
				F	1.75 to <3.5	15 to <30
Microalbuminuria	30 to <300	20 to <200	20 to <200	M	2.5 to <25	20 to <200
				F	3.5 to <35	30 to <300
Macroalbuminuria	>300	>200	>200	M	>25	>200
				F	>35	>300

albuminuria from levels >15 mg/L, then it is wise to set the definition of abnormal albuminuria at that level. It may be appropriate to use a lower albuminuria cutoff in case of concomitant morbidities, such as diabetes.

What Extra Work Should Be Done When an Individual Is Found to Be Positive?

When someone is found to be positive for microalbuminuria, one first should confirm the positive test by repeated testing. It has been argued that two of the three tests need to be positive. After confirmation, one should look for a potential cause underlying the albuminuria, especially in case of macroalbuminuria. One should ascertain whether there is any classical renal disease, such as glomerulonephritis or interstitial nephritis. If medical history for such a disease is negative, then a urinary sediment and measurement of renal function may be sufficient. In addition, cardiovascular risk factors (BP, cholesterol, and glucose) should be screened.

Is Screening to Detect Microalbuminuria Followed by Appropriate Treatment of Positive Individuals Cost-Effective?

In diabetes, it has been shown that ACE inhibitor or ARB treatment is cost-effective (36) for preventing ESRD. Moreover, it has been shown that, in the long term, cost-effectiveness is even more favorable when treatment is started earlier (37). The evidence for individuals without diabetes is limited. Boulware *et al.* (38) showed that screening for dipstick proteinuria by primary care providers followed by treatment of those who were positive was not cost-effective in terms of preventing ESRD. This is not surprising, because it generally takes many years before a who does not have diabetes but has dipstick-positive proteinuria will reach ESRD. There are alternatives to the Boulware approach, however (39). First, the use of a dipstick would require screening of many individuals to find the few who were positive, whereas screening for microalbuminuria would detect more positive individuals; the prevalence of microalbuminuria is approximately 30 times higher than that of macroalbuminuria (31). Although the costs of an albuminuria measurement are higher than those of a dipstick test, the higher

yield of the test will outweigh that difference. Second, screening *via* the general practitioner is labor-intensive, whereas the delivery of a urine sample to a central laboratory facility will be cheaper. Third, although it takes many years for an individual with microalbuminuria to develop stage 5 CKD, cardiovascular events may be manifest already within a few years. We therefore studied the cost-effectiveness of screening for albuminuria and subsequent treatment of individuals with an elevated UAE with an ACE inhibitor. This approach was cost-effective to prevent cardiovascular events (40).

How Can a Screening Program for Albuminuria Be Organized?

Taking the evidence together, we can conclude that screening for albuminuria and treatment of those who are found to be positive is well accepted in individuals with diabetes. Indeed, annual screening for albuminuria in individuals with diabetes is recommended in the guidelines of the American Diabetes Association (41). At present, it seems too early to recommend such an approach for the general population: More studies to examine the beneficial effect of albuminuria lowering are needed. It seems sensible to screen individuals who are at higher risk for cardiovascular disease and CKD. Besides individuals with diabetes, attention should focus on individuals with hypertension (42), hyperlipidemia, and obesity and those who smoke. However, a focused approach will overlook many individuals with an elevated UAE. First, many individuals are not aware that they have diabetes, hypertension, or hyperlipidemia. Indeed, in the PREVENT study, two thirds of those screened were found to have previously undiagnosed hypertension and/or diabetes (43). Second, it has been shown that UAE gradually increases with increasing plasma glucose level or systolic or diastolic BP even within the normal ranges (44). This suggests that individuals with higher but still normal levels of plasma glucose and systolic or diastolic BP are at risk for having microalbuminuria. They will not be detected when the screening is limited only to those with manifest diabetes and/or hypertension. It is of interest that the presence of microalbuminuria may even precede manifest diabetes (45,46) and hypertension (47,48). Microalbuminuria may be considered

one of the earliest manifestations of the insulin resistance syndrome. Indeed, it has been shown that the prevalence of microalbuminuria increases according to the number of components of the metabolic syndrome present (49). The aforementioned data raise doubt whether we should limit our screening strategies to those with known risk factors or preferably should screen the general population.

The composition of the population and the type of health care delivery system will dictate the optimal design of the screening program. The components to consider include who will do the testing (*e.g.*, physician, nurse, technician), where the screening will take place (*e.g.*, clinic, health fair), and how it will be financially supported.

How Should a Patient with Microalbuminuria Be Monitored in the Long Term?

Screening for albuminuria in individuals with diabetes has been advocated to be performed once every year. In case of a positive test, it is advocated to repeat testing twice within 3 to 6 mo. If two of the three tests are positive, then treatment to lower albuminuria should be started (41). Thus far, no hard data are available for the optimal time interval for albuminuria testing in individuals with hypertension or in other groups. As progression of albuminuria may be slower in individuals without diabetes than in individuals with diabetes, it seems acceptable to perform albuminuria testing in individuals with hypertension or other risk categories every 3 yr.

Both in type 1 diabetes (50) and in the general population (51), progression and regression of albuminuria can be observed. After 4.2 yr, UAE had regressed in 9.8% individuals in the general population, whereas progression was found in 11.4%. Progression and regression of albuminuria were most prevalent in the group of individuals with a UAE of 15 to 30 mg/d (21.3 and 47.4%, respectively). This suggests that especially in individual with a borderline elevation in UAE, repeated testing every 3 to 5 yr is indicated.

Lowering of BP with agents that interfere with the renin-angiotensin-aldosterone system, such as ACE inhibitors or ARB is most effective for lowering UAE. It has been shown in patients with manifest renal disease (*i.e.*, those with overt proteinuria of >300 mg/d) that the extent to which proteinuria is lowered during treatment predicts the prevention of both CKD and progressive cardiovascular disease (20,21). It is highly likely but not proved that the same will hold true for individuals with microalbuminuria. Thus far, however, we cannot define a certain cutoff level below which albuminuria should be lowered; we suggest use of the same cutoff as for the definition of microalbuminuria: <30 mg/d.

Conclusion

There is compelling evidence that screening for albuminuria should be carried out in individuals with diabetes. Evidence is accumulating that it also should be implemented in individuals with hypertension and in individuals with increased cardiovascular and renal risk. Further studies are needed to confirm that systematic screening for albuminuria also is cost-effective in the general population. The short-term benefits for prevention of

cardiovascular disease may outweigh those of the long-term prevention of ESRD.

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