

## Methodology of screening for albuminuria

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Albuminuria has been recognized as a marker of generalized vascular endothelial damage. Even low levels, called micro-albuminuria, independently predict poor cardiovascular and renal outcome in subjects with diabetes, hypertension, but also in non-diabetic, non-hypertensive individuals [1–4]. These complications consume a large proportion of health-care budgets. Recently, several nephrological societies, such as the ASN and ISN, proposed to initiate screening for albuminuria to identify subjects at high risk, who might benefit from preventive treatment [5,6]. Screening should be aimed at subjects with hypertension, diabetes and chronic kidney disease; however, mass screening of the general population has also been advocated.

Although it is recommended to start screening for albuminuria, there are questions that remain unanswered. For instance, should screening be based on assessment of albuminuria in 24 h urine samples, or are morning urine samples sufficiently reliable? Due to the diurnal rhythm in urinary albumin excretion, it has been assumed that 24 h albuminuria should be regarded as the gold standard. Albumin concentration or the albumin:creatinine ratio in spot urine samples may be less appropriate, because they vary in any given individual, depending on the point of time during the day that they are collected. The definitive answer, in the discussion as to which measure of urinary albumin excretion should be used in clinical practice, should be given by observational studies showing which of the three performs best in predicting cardiovascular and renal endpoints. One such study investigated this issue. Surprisingly, it showed that protein:creatinine ratio in

a spot sample is even more reliable than a 24 h urinary protein excretion in predicting decline in GFR and progression to end-stage renal failure, in subjects with non-diabetic renal disease [7]. Unfortunately, albuminuria was not measured. Given the paucity of data, measurement of 24 h urinary albumin excretion should remain the gold standard, at least in research areas, until other data come available.

Collecting a 24 h urine sample is time-consuming and inconvenient, and therefore not feasible for population screenings. Another possibility for organizing population screening is by pre-screening, based on albuminuria assessment in spot urine samples. Only subjects that score a value above a certain cut-off are then asked to collect 24 h urine samples for confirmation of the presence of micro-albuminuria. This practice may minimize the number of subjects that need to collect 24 h urines.

### Pre-screening followed by confirmation

Jafar *et al.* [8] tested this approach in subjects recruited from the general population in Pakistan. The results are published in this issue of the journal. They conclude that assessment of urinary albumin concentration, as well as the albumin:creatinine ratio in spot urine samples are acceptable pre-screening tests. In the general population, several studies have been devoted to the evaluation of urinary albumin concentration and the albumin:creatinine ratio *vs* timed urine collection procedures [9]. Most of these studies involved only small numbers of subjects. More importantly, nearly all of these studies are hampered by the fact that, unlike the procedure to be followed in mass-screening, they used a portion of a 24-h urine collection to measure urinary albumin concentration, the albumin:creatinine ratio and the same 24-h urine collection, for determination of the reference value of urinary albumin excretion. Thus, study variable and reference are inadmissibly interrelated. This way of analysing data addresses another question, whether a spot morning urine sample can *replace* a 24 h urine collection. It is expected that this flaw in study design

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will result in falsely high values for sensitivity and specificity, because it does not take into account day-to-day variability in albuminuria. In the study by Jafar *et al.* [8] subjects collected a spot urine sample and a 24 h urine on separate occasions. Therefore, this study is one of the first to really investigate the validity of albumin measurements from spot urine samples to identify, in the general population, subjects at risk for abnormal urinary albumin excretion in subsequent 24-hr urine collections. Furthermore, it included a sufficient number of subjects. For these reasons this study is to be appreciated.

The data obtained by Jafar *et al.* closely mimic the ones obtained in the only other available study on this topic, which was published by the PREVEND Study Group [10]. In the latter study, the diagnostic performance of urinary albumin concentration and the albumin:creatinine ratio to identify subjects with micro-albuminuria in subsequent 24 h urine samples were slightly higher than in the study by Jafar *et al.* (AUC of the ROC curves 0.92 and 0.93, respectively, *vs* 0.87 and 0.88 in the study by Jafar). These small differences may be due to the fact that a Caucasian population was studied by the PREVEND Study Group in comparison to Indo-Asians by Jafar, and also due to differences in laboratory techniques used. More likely, these differences can be explained by the fact that in the PREVEND Study, subjects collected a first morning void urine sample as pre-screening and two 24 h urine samples for confirmation, instead of a random urine sample and only one 24 h urine sample, as in the study by Jafar *et al.*

Of note, both studies found the diagnostic performance of assessment of the albumin concentration and the albumin:creatinine ratio satisfying and comparable [8,10]. From an economic perspective this is an important observation. Determination of creatinine in large numbers of spot morning urine samples obtained in mass screening will result in substantial costs, the exact amount of which will vary per laboratory. In order to keep costs involved in mass screening for micro-albuminuria as low as possible, it is therefore proposed that pre-screening should take place by measuring in a spot morning urine sample only urinary albumin concentration.

### **Lowering the present cut-off value for pre-screening?**

Jafar *et al.* [8] suggest that the cut-off value of urinary albumin concentration, indicating a high chance of micro-albuminuria, may be lowered. Traditionally, the cut-off value indicating micro-albuminuria has been a urinary albumin concentration of 20 mg/l [4,5]. This specific value was derived from studies performed in diabetic subjects, in which it was shown that a urinary albumin excretion of 30 mg/24-h corresponded with an urinary albumin concentration of approximately 20 mg/l [9]. However, when a spot morning urine

sample is used to predict which individuals have an abnormal urinary albumin excretion, in subsequent 24-h urine collections a lower value might be adopted. In the manuscripts of both the PREVEND Study Group and Jafar *et al.*, it is shown that using the traditional cut-off value of 20 mg/l to identify subjects 'at risk' for abnormal albuminuria, specificity appears high, whereas sensitivity is relatively low [8,10]. Consequently, the number of false-negative test results seems unacceptably high, whereas in order to meet the requirements for mass-screening, the number of false-negatives should be as low as possible. On the other hand, lowering the present-cut-off value is expected to result in increases in the percentage of false-positives. Since the 'penalty' for being false-positive is merely that 24-h urine collections have to be performed for confirmation, we think that a relatively large number of false-positive test results is acceptable. Based on these findings, we propose that in future, pre-screening for albuminuria take place using first morning void urine collections and applying a cut-off value of 10 or 15 mg/l for albumin concentration, both for mass-screening, as well as for case-finding in high risk populations.

### **Monitoring patients over time**

It has to be emphasized that the aforementioned considerations concern screening and do not apply to monitoring individuals over time. It might well be that for this latter purpose the urinary albumin concentration may be less useful due to dilution variations caused by changes in urinary volume, whereas the albumin:creatinine ratio, due to relatively parallel changes in urinary creatinine concentration, may be more helpful. Studies investigating the intra-patient coefficient of variation of various albuminuria measures will have to answer this question.

In a study using thawed urine samples stored for a prolonged period of time, Dyer *et al.* [11] found the inpatient coefficients of variation of 24 h urinary albumin excretion, and albumin concentration and albumin:creatinine ratio from a spot sample, to be nearly similar. In contrast, in a post-hoc analysis from a prospective study using fresh urine samples, we found the albumin:creatinine ratio to perform better [12]. We are currently performing a prospective study to investigate which urinary albumin measure can best be used to monitor patients over time.

### **Conclusion**

The studies by Jafar and the PREVEND Study Group together, performed in different populations with nearly similar results, imply strongly that mass-screening for micro-albuminuria, as proposed by these authors, is feasible and valid. Pre-screening can take place based on measuring albumin concentration

in spot urine samples, followed by confirmation by 24 h urine collections in which urinary albumin excretion is determined. Such a strategy will identify subjects at high risk for cardiovascular disease and renal function deterioration. These subjects should be investigated for presence of classical risk factors, such as hypertension, hypercholesterolaemia and diabetes, and for chronic kidney disease. If present, these risk factors should be treated. Such a screening programme may help to tackle the epidemic of end-stage renal disease, but at the same time to lower cardiovascular morbidity and mortality. Even in the absence of these risk factors micro-albuminuric subjects may benefit from medical interventions. The recent PREVEND IT study suggested that treatment with an ACE inhibitor of subjects with increased levels of albuminuria and (near) normal blood pressure and cholesterol is efficient in lowering cardiovascular morbidity and mortality [13]. Moreover, a pharmaco-economic analysis of this study indicates that such strategy is cost-effective [14,15]. However, these studies need confirmation before treatment of *isolated micro-albuminuria* can become clinical practice.

*Conflict of interest statement.* None declared.

(See related article by Jafar *et al.* Use of albumin creatinine ratio and urine albumin concentration as a screening test for albuminuria in an Indo-Asian population. *Nephrol Dial Transplant* 2007; 22: 2194–2200.)

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