How to diagnose and how to interpret microalbuminuria in the diabetic patient

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Introduction

The definition of microalbuminuria was introduced 10 years ago [1] and since then it has been widely accepted. In recently published guidelines for the prevention of diabetic renal failure [2] it was stressed that the term microalbuminuria refers to a persistent increase in the albumin excretion rate to values between 20 and 200 μg/min (30 and 300 mg/day). A persistent increase is documented when these values are transgressed in at least two of three consecutive sterile timed urine specimens performed within 6–12 weeks. The presence of microalbuminuria permits the diagnosis of incipient (early) nephropathy [3], since microalbuminuria is not a marker but the first sign of diabetic nephropathy.

How to obtain an adequate urine sample

The definition of microalbuminuria implies the use of 'timed urine specimens'. The most accurate method is urine collection either overnight (for approximately 8 h) or for 24 h [2]. However, this is impractical and inconvenient for many patients, since at least three urine collections should be performed. Therefore it is acceptable to perform short-term urine collections over one or several hours in the outpatient clinic or on the ward [3]. For correct evaluation only sterile urine specimens collected under standardized conditions should be used, and alternative causes of increased albumin excretion must be excluded [3]. In the diabetic patient who is tested for the first time for the presence of microalbuminuria, timed urine collections for evaluation of albumin excretion rate (UAER) should be preceded by appropriate screening procedures [2].

How to screen and measure urinary albumin

A reliable screening method is to measure albumin concentration or albumin/creatinine ratio in the first morning urine sample [2]. An albumin concentration below 20 mg/litre or an albumin/creatinine ratio below 2.5 mg/mmol for men and 3.5 mg/mmol for women should be considered normal. If normal values are found, timed urine collection is not needed and screening should be repeated each year.

When the albumin concentration is ≥ 20 mg/litre or the albumin/creatinine ratio ≥ 2.5 mg/mmol in men and ≥ 3.5 mg/mmol in women, the results must be confirmed in other urine samples. If a repeat value is within the normal range, no immediate action is needed, but the screening should be repeated in 1 year's time.

If the repeat value continues to be abnormal, timed urine collections are required to confirm the presence of microalbuminuria.

Different methods for measuring urinary albumin can be used: immunoturbidimetry, immunonephelometry, radio- or enzyme-immunoassays. Although immunoturbidimetry lacks the sensitivity to detect very low albumin concentrations and immunoassays have the highest sensitivity, all methods are considered equivalent when quality control is maintained [4].

When facilities for measurement of urinary albumin are not available locally, antibody-based semiquantitative tests for albumin concentration (Micral Test®, Boehringer Mannheim, Germany or Nycocard U-Albumin®, Nycomed Pharma AS, Oslo, Norway) may be used in the doctor's office or by the patients themselves as first-line screening. Abnormal values of these tests, indicating an albumin concentration exceeding 20 mg/litre should be confirmed, however, by quantitative assays.

Who should be screened for microalbuminuria?

Screening for microalbuminuria is recommended in all patients who have had insulin-dependent diabetes for more than 1 year and who are above the age of 12 years, and in all patients with non-insulin-dependent diabetes from the time of diagnosis. Screening should be repeated at least once a year [2].

It should be mentioned, however, that recently published recommendations in the USA are more liberal. They suggest annual microalbuminuria screens for patients with insulin-dependent diabetes mellitus who have had the disease for more than 5–10 years and/or have a family history of renal disease or hypertension [6].

What are the pitfalls which may confound correct evaluation of urinary albumin excretion?

Potential confounders of microalbuminuria have recently been extensively reviewed [5]. The most
important confounder is the inherent variability of urinary albumin excretion with an intradividual coefficient of variation averaging 30–50%. This makes it necessary to perform repeated test in order to arrive at the correct diagnosis of microalbuminuria. This is also true for follow-up examinations, where tests should be performed in a standardized fashion to eliminate confounding factors.

It is easy to exclude cardiac failure and established hypertension which may increase albumin excretion. Non-diabetic renal disease as the cause of increased albumin excretion is often more difficult to exclude. Non-diabetic renal disease should be considered (i) when microalbuminuria (albumin excretion rate exceeding 200 µg/min) is present in patients with a short duration of diabetes, especially in the absence of retinopathy, (ii) when albuminuria increases rapidly or when microalbuminuria appears suddenly, or (iii) when renal function deteriorates rapidly. In all these situations renal biopsy should be considered. When symptomatic urinary-tract infection is present, evaluation of albumin excretion must be postponed until the infection is effectively treated. Conversely microalbuminuric patients should be screened for urinary-tract infection. Several other factors may increase albumin excretion transiently in persons with diabetes: acute illness, stressful situations, heavy exercise, water diuresis, prolonged upright posture, menstruation and vaginal discharge. Poor metabolic control of diabetes increases urinary albumin excretion. Evaluation of albumin excretion should be postponed until patients are metabolically stabilized. It is recommended that albumin excretion rates for follow-up purposes are compared only when patients are at their usual level of metabolic control.

What are the criteria for diagnosing microalbuminuria?

Most investigators consider values of urinary albumin excretion rate (UAER) between 20 and 200 µg/min (or 30 and 300 mg/24 h) as indicators of increased albumin excretion. In some important studies a higher cut-off, namely UAER of 30–200 µg/min was used [7,8]. In other studies, based on evaluation of overnight albumin excretion (which is usually lower than daytime excretion rates), 15 µg/min was chosen as the lower limit [9]. The above lower limits of albumin excretion rate are arbitrary and clearly elevated when compared to the range of albumin excretion in the healthy population [6]. There are studies suggesting that excretion rates in upper range of normoalbuminuria are predictive of progression to diabetic renal disease. It has been suggested that a graded risk exists between albuminuria and diabetic nephropathy, i.e. the higher the level of urinary albumin excretion the higher the risk of renal involvement [6].

What are the implications of the diagnosis of microalbuminuria for patient management?

Correctly identified persistent microalbuminuria indicates diabetic nephropathy in its early (incipient) stage. It is necessary to diagnose incipient diabetic nephropathy in persons with IDDM or NIDDM in order to identify a subset of diabetic patients at risk of developing overt nephropathy, renal failure, and early cardiovascular morbidity and mortality [10]. More importantly this diagnosis permits introduction of effective intervention to postpone or perhaps even prevent progression of diabetic nephropathy [2]. In microalbuminuric patients (i) blood glucose control should be improved as much as possible, (ii) protein intake should be limited to approximately 0.8–1 g/kg bodyweight per day, and (iii) part of the protein of animal sources should be replaced by protein of vegetable sources, (iv) excess sodium intake should be avoided, (v) smoking should be vigorously discouraged, and (vi) blood pressure should be maintained in the low normal range [2]. There is growing consensus that antihypertensive treatment, especially with ACE inhibitors, should be given even to normotensive microalbuminuric IDDM patients and to younger NIDDM patients [5]. This opinion is based on the positive results of this approach in many trials. Individual adaptation of antihypertensive treatment is necessary, however. Concomitant cardiovascular disease may impact on the selection of antihypertensive drugs, particularly in patients with NIDDM [2]. In patients with microalbuminuria regular and frequent checkups are indispensable to assess glycaemic control, blood pressure levels, serum lipids, serum creatinine, and UAER as often as indicated by clinical conditions and treatment strategies. Regular screening for retinopathy, neuropathy, coronary, cerebrovascular, and peripheral artery disease is also necessary [2].

To conclude, screening for microalbuminuria should be a continuous process in all patients with diabetes. Early diagnosis of incipient diabetic nephropathy followed by appropriate treatment should be an essential part of diabetes care for all patients with IDDM and NIDDM.

References

The diabetic patient with ESRD: how to select the modality of renal replacement

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Introduction

The proportion of diabetics among patients requiring renal replacement therapy (RRT) continues to increase in most Western countries. Between 1984 and 1992, the fraction of new patients starting RRT whose end-stage renal disease (ESRD) was attributed to diabetic nephropathy increased from 11 to 17% in Europe [1], and 27 to 36% in the US [2]. As illustrated by a recent survey in the Neckar region, the vast majority of diabetics currently accepted for RRT are type II diabetics [3].

In each new diabetic patient with chronic renal failure, the question arises as how to select the most appropriate RRT modality. There is no uniform answer, especially in the difficult diabetic patient with multiple organ involvement. In this editorial, I will consider some of the elements to be taken into account. First, what is the expected survival in each of the RRT options? Though no randomized study provides a proper comparison between modalities, some insights can be found from registry data and single-centre studies.

Survival on RRT

The life expectancy of diabetics on RRT is clearly shorter than that of non-diabetics, whatever the treatment modality. As shown in Figure 1, the increased mortality of diabetics reported at the USRDS Registry is similar in haemodialysis (HD), peritoneal dialysis (PD), and renal transplantation both for patients aged 20–44 and for those aged 45–54, suggesting that the diabetic condition similarly affects survival in the three RRT modalities.

Encouragingly, the overall survival of diabetics on RRT is improving, as witnessed by the latest USRDS Report [2]. The first year mortality (adjusted for age, race and sex) in dialysis patients decreased from 46% in 1982 to 30% in 1992 [2]. Improvement was especially remarkable for renal transplantation: in 1992, first-year survival of diabetic recipients of a first cadaveric graft equalled that of non-diabetic controls [2]. Interestingly, the survival of diabetics on dialysis was similar whether the ESRD was due to diabetic nephropathy or to another primary nephropathy, suggesting that diabetes is the main determinant of survival whether or not it causes renal failure [4].

The main causes of death during RRT are similar in diabetics and non-diabetics and have not changed essentially over the past decade, with cardiovascular diseases accounting for about 60% of deaths [1].