Microalbuminuria and urinary albumin excretion: French clinical practice guidelines

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Abstract

Urinary albumin excretion (UAE) may be assayed on a morning urinary sample or a 24 h-urine sample. Values defining microalbuminuria are: 1) 24-h urine sample: 30–300 mg/24 h; 2) morning urine sample: 20–200 mg/ml or 30–300 mg/g creatinine or 2.5–25 mg/mmol creatinine (men) or 3.5–35 mg/mmol (women); 3) timed urine sample: 20–200 μg/min. The optimal use of semi-quantitative urine test-strip is not clearly defined. It is generally believed that microalbuminuria reflects a generalized impairment of the endothelium; however, no definite proof has been obtained in humans.

In diabetic subjects. – Microalbuminuria is a marker of increased risk of cardiovascular (CV) and renal morbidity and mortality in type 1 and type 2 diabetic subjects. The increase in UAE during follow-up is associated with greater CV and renal risks in type 1 and type 2 diabetic subjects; its decrease during follow-up is associated with lower risks.

In non-diabetic subjects. – Microalbuminuria is a marker of increased risk for diabetes mellitus, deterioration of renal function, CV morbidity and all-cause mortality. It is a marker of increased risk for the development of hypertension in normotensive subjects, and is associated with unfavorable outcome in patients with cancer and lymphoma. Persistence of elevated UAE during follow-up is associated with poor outcome in some hypertensive subjects. Measurement of UAE may be recommended in hypertensive medium-risk subjects with 1 or 2 CV risk factors in whom CV risk remains difficult to assess, and in those with refractory hypertension: microalbuminuria indicates a high CV risk and must lead to strict control of arterial pressure. Studies focused on microalbuminuria in non-diabetic non-hypertensive subjects are limited; most of them suggest that microalbuminuria predicts CV complications and deleterious outcome. Subjects with a history of CV or cerebrovascular disease have an even greater CV risk if microalbuminuria is present than if it is not; however, in all cases, therapeutic intervention must be aggressive regardless of whether microalbuminuria is present or not. It is not recommended to measure UAE in non-diabetic non-hypertensive subjects in the absence of history of renal disease. Monitoring of renal function (UAE, serum creatinine and estimation of GFR) is recommended annually in all subjects with microalbuminuria.
Management. – In patients with microalbuminuria, weight reduction, sodium restriction (< 6 g per day), smoking cessation, strict glucose control in diabetic subjects, strict arterial pressure control are necessary; in diabetic subjects: use of maximal doses of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) are recommended; ACEI/ARB and thiazides have synergistic actions on arterial pressure and reduction of UAE; in non-diabetic subjects, any of the five classes of anti-hypertensive medications (ACEI, ARB, thiazides, calcium channel blockers or beta-blockers) can be used. © 2007 Elsevier Masson SAS. All rights reserved.

Résumé

Microalbuminurie et excrétion urinaire d’albumine : recommandations françaises

Le dosage de l’excrétion urinaire d’albumine (EUA) peut se faire sur un échantillon urinaire sur les premières urines du matin, sur les urines de 24 heures ou sur prélèvement urinaire minuit. Les valeurs définissant la microalbuminurie sont : 1) urines de 24 heures : 30–300 mg/24 h ; 2) échantillon urinaire : 20–200 mg/ml ou 30–300 mg/g créatinine urinaire ou 2,5–25 mg/mol (chez l’homme) ou 3,5–35 mg/mmol (chez la femme) créatinine urinaire ; 3) échantillon urinaire minuité : 20–200 μg/min. La place du dosage semi-quantitatif (bandelettes) n’est pas clairement définie. La microalbuminurie est considérée comme un réflet d’une atteinte généralisée de l’endothélium, mais ce n’est pas démontré.

Chez le sujet diabétique. – La microalbuminurie est un marqueur indépendant de risque cardiovasculaire (CV), rénal et de mortalité totale chez les diabétiques de type 1 et 2. L’augmentation de l’EUA au cours du temps est un marqueur de risque CV et rénal chez le diabétique de type 1 ; sa régression est associée à une régression de ces risques.

Chez le sujet non diabétique. – La microalbuminurie est un marqueur indépendant de risque CV, de risque de diabète, d’altération de la fonction rénale et de mortalité totale. Elle est un marqueur de risque de développer une hypertension artérielle chez le sujet normotendu et un marqueur de risque d’évolution défavorable ou de décès au cours de cancers et de lymphomes. L’élévation ou la persistance d’une EUA élevée au cours du temps est associée à un pronostic péjoratif chez certains hypertendus. La mesure d’EUA peut être recommandée chez certains hypertendus ayant 1 ou 2 facteurs de risque CV associés dont le risque CV semble mal évalué ou ayant une hypertension réfractaire : la microalbuminurie indique ici un risque CV élevé et incite à assurer un contrôle tensionnel strict. Il y a peu d’études chez les sujets non hypertendus et non diabétiques ; elles suggèrent globalement que la microalbuminurie est un facteur de comorbidité et de mauvais pronostic comme chez les sujets hypertendus ou diabétiques. En prévention secondaire, la microalbuminurie est un marqueur de risque indépendant, mais n’a pas de retombées thérapeutiques spécifiques. Il n’est pas recommandé de rechercher systématiquement une microalbuminurie chez le sujet non hypertendu, non diabétique, sans antécédent de maladie rénale. Il est recommandé d’effectuer une surveillance de la fonction rénale annuelle (créatinémie et estimation du débit de filtration glomérulaire) chez les sujets microalbuminuriques.

Thérapeutique. – Chez tout patient ayant une microalbuminurie : réduction pondérale et de l’apport sodé excessif (< 6 gr/jour), arrêt du tabagisme, amélioration du contrôle glycémique, contrôle tensionnel strict ; chez le diabétique, prescription d’un inhibiteur de l’enzyme de conversion (IEC) (diabète de type 1) ou d’un antagoniste des récepteurs de l’angiotensine 2 (ARA2) (diabète de type 2) à dose suffisante en première intention. Les diurétiques thiazidiques ont un effet synergique avec les bloqueurs du système rénine angiotensine sur la réduction de l’EUA ; chez le non diabétique, les cinq grandes classes d’antihypertenseurs (IEC, ARA2, diurétiques, antagonistes calciques, bêtabloquants) sont utilisables en première intention.

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Mots clés : Insuffisance rénale ; Diabète ; Albuminurie ; Risque cardiovasculaire ; Hypertension

1. Introduction

Cardiovascular disease is the leading cause of death in industrialized countries. In parallel, the widespread use of serum creatinine levels to assess renal function has increased awareness of the high incidence of renal failure in the general population and in particular in very elderly subjects (> 75 years) and in subjects at risk of cardiovascular disease.

Estimation of cardiovascular and renal risk is therefore a major public health concern. This estimation is based on the detection of predictive markers during initial workups for diseases such as hypertension and diabetes mellitus. Risk assessment is the basis for detection, monitoring and management of patients with cardiovascular and renal disease, and should include measurement of urinary albumin excretion.

In the present guidelines regarding urinary albumin excretion (and microalbuminuria) use, it is probably necessary to separate diabetic patients in whom most of the studies were carried out and for whom formal national and international guidelines exist, and non-diabetic subjects (in particular hypertensive patients) for whom optimal strategy for microalbuminuria testing is less defined.

2. Purpose of the present guidelines

Following the discussions of the Steering Committee (composition in the appendix) and approval by the Working Panel, the primary objective of the present guidelines is to answer the following two questions:

● what are the diagnostic, prognostic and therapeutic benefits expected from the detection and monitoring of microalbuminuria for each category of subjects at risk of cardiovascular and renal disease?
● Is microalbuminuria testing among the general public useful in terms of cost-efficiency in particular for prevention?

A first version of the Clinical Practice Guidelines (“short version”) and the case statement (“long version”), intended to be placed on the website of the sponsoring professional organizations were sent for a second reading to members of a
3. Measurement of urinary albumin excretion and definition of microalbuminuria

Microalbuminuria is an elevation of urinary albumin excretion above physiological levels (and not a special form of albumin). It is therefore considered to be pathological. There is variability in the measurement of urinary albumin excretion due, among other reasons, to the sampling conditions: physical exercise, fever, heart failure in particular, which may considerably modify the results, though there is also intra-individual variability.

Urinary albumin excretion must be measured with validated quantitative assay methods. These methods are immunoturbidimetry, immunonephelometry, RIA and ELISA. HPLC (High-Performance Liquid Chromatography) has been introduced very recently; its optimal use is not defined (Expert consensus).

Urinary albumin excretion may be assayed on a single urine sample and preferably a first morning urine sample: its variability may be reduced by expressing the results as a urinary albumin/creatinine ratio. It may also be assayed on the 24-h urine or a timed urine sample.

The role of semi-quantitative test-strips has not yet been clearly defined. These semi-quantitative assays may be used as a method for screening target populations (e.g., occupational medicine) but they remain expensive.

By convention, values defining microalbuminuria in type I diabetic subjects have been extrapolated to other fields (hypertension etc.) (Expert consensus):

- 24-h urine sample: 30–300 mg/24 h;
- morning urine sample: 20–200 mg/ml or 30–300 mg/g urinary creatinine or 2.5–25 mg/mmol urinary creatinine in man or 3.5–35 mg/mmol urinary creatinine in women;
- timed urine sample: 20–200 μg/min.

Different attitudes may be proposed depending on whether measurement is made in a research or clinical setting (expert consensus) [1–4].

3.1. Clinical setting

The use of a first morning urine sample is sufficient for practical reasons. The test must be repeated during the following weeks when the first microalbuminuria test is positive. If the results of the two tests disagree, a third microalbuminuria test is required. It is not necessary to repeat the assay if a first microalbuminuria test is negative. During follow-up, it is recommended to carry out the microalbuminuria test under the same conditions (sampling conditions, assay method, laboratory).

3.2. Research

It is recommended to assay microalbuminuria on three urine samples collected over a short time interval (expert consensus).

4. Urinary albumin excretion or microalbuminuria?

There is probably a continuous (though nonlinear) relationship between urinary albumin excretion and cardiovascular and renal risk and the risk of diabetes, although no particular threshold has yet been defined. Microalbuminuria (rather than urinary albumin excretion used as a continuous parameter) has been initially identified as a cardiovascular and renal risk marker. However, it should be pointed out that there is a dose-dependent relationship between urinary albumin excretion and associated risks (cardiovascular risk, renal risk and the risk of developing diabetes) with no clearly defined lower (normoalbuminuria) or upper threshold (macroalbuminuria or proteinuria, this latter parameter is usually about one third higher as it includes other proteins).

5. Physiopathology, pathology and epidemiological data

5.1. Physiopathological data (diabetic and non-diabetic subjects)

The level of urinary albumin excretion is modulated by arterial pressure levels. Microalbuminuria is considered to be a marker of end-organ damage in hypertension (expert consensus). A relationship has also been found between microalbuminuria and many cardiovascular and metabolic risk markers. In this respect, microalbuminuria may be a global risk marker (expert consensus).

Most authors agree that microalbuminuria reflects a generalized endothelium-dysfunction, although this hypothesis has not been directly confirmed (expert consensus).

5.2. Anatomical data

In diabetic subjects, microalbuminuria is often associated with the existence of renal lesions [5] (grade C). Renal histology in microalbuminuric non-diabetic subjects has not been documented.

5.3. Epidemiology in diabetic subjects

Microalbuminuria is an independent renal and cardiovascular risk marker (and a risk marker of all-cause mortality) during type I and type 2 diabetes [6–12] (Grade B).

The increase during time in urinary albumin excretion is a cardiovascular and renal risk marker in type 1 diabetics and, conversely, its regression is associated with an improvement in cardiovascular and renal prognosis (grade B).

5.4. Epidemiology in non-diabetic subjects

Many concordant studies indicate that microalbuminuria is an independent cardiovascular risk marker and a marker of all-cause mortality in the general population, in elderly subjects...
and in hypertensive patients (grade B). In patients with cardiovascular disease (myocardial infarction, stroke, abdominal aortic aneurysm), the presence of microalbuminuria is associated with a more severe cardiovascular prognosis and to a greater risk of cardiovascular complications or death. The change in urinary albumin excretion with time is also associated with cardiovascular risk: persistence of an elevated urinary albumin excretion or an increase during follow-up is associated with a worse prognosis, at least in hypertensive patients with left ventricular hypertrophy (Grade B) [13–31].

Microalbuminuria is a risk marker of development of hypertension in normotensive subjects (Grade C) [32]. Microalbuminuria is an independent risk marker of development of type 2 diabetes mellitus (Grade C) [18,33,34].

In microalbumuric subjects (compared to subjects with normal urinary albumin excretion), glomerular filtration rate falls more rapidly with time in hypertensive subjects (grade C), there is a greater risk of developing renal failure than in the general population (grade C) and the risk of graft loss is higher in renal allograft recipients (expert consensus) [35].

Microalbuminuria is a marker of an unfavorable outcome or death in many non-cardiovascular diseases (bacterial meningitis, acute pancreatitis, cancer, lymphoma, acute respiratory distress syndrome, etc) (expert consensus) [36].

6. Microalbuminuria testing and management

It is recommended not to conduct a microalbuminuria test in subjects with a positive urinary strip test for proteinuria (quantitative assay of proteinuria is sufficient), in the presence of urinary infection or macroscopic hematuria (Expert consensus) which may bias the result.

6.1. Diabetic subjects

6.1.1. Microalbuminuria testing

All national and international recommendations indicate that microalbuminuria should be tested annually in diabetic subjects [1–4,19]. The existence of microalbuminuria constitutes:

A cardiovascular risk marker in type 1 and type 2 diabetics (Grade B).

A renal risk marker in type 1 diabetics (especially during the first twenty years of the disease) and in type 2 diabetics (Grade B).

6.1.2. Therapeutic management in diabetic subjects

In microalbumuric diabetic subjects, the reduction in urinary albumin excretion is a therapeutic goal (grade A). Optimal therapeutic management which reduces urinary albumin excretion includes [37–40]:

- a strict control of blood pressure by lifestyle measures (reduction in body weight and sodium restriction (< 6 g of salt per day; cf food composition table: high-salt foods (www.afssa.fr)) (grade B), improvement in glycaemic control (grade B) and pharmacological interventions. Blockade of the renin angiotensin aldosterone system: preferably an angiotensin-converting enzyme inhibitor (ACEI) in type 1 diabetes mellitus and an angiotensin 2 receptor blocker in type 2 diabetes (ARB)) at a sufficient dose as first-line treatments (grade A). Thiazide diuretics have a synergistic effect with ACEI and ARB on the reduction in urinary albumin excretion (Grade B);

- smoking cessation (expert consensus).

6.1.3. Effect of the reduction of urinary albumin excretion on cardiovascular risk in diabetic subjects

The reduction in urinary albumin excretion induced by the use of a high dose ACEI compared with placebo was associated with a reduction in the incidence of cardiovascular events (Grade A) whereas such a result was not observed when the same ACEI was used at low dose (Grade A).

The use of high doses of ARB more effectively prevents progression to the overt nephropathy stage (proteinuria) than lower doses (Grade A). The reduction in urinary albumin excretion is associated with a reduction in the risk of renal function impairment and the subsequent risk of end-stage chronic renal failure (Grade B).

The reduction in urinary albumin excretion is associated with cardiovascular protection at least in diabetic patients with a high risk of cardiovascular disease (grade B).

6.1.4. Renal surveillance in diabetic subjects

It is recommended to yearly monitor renal function (urinary albumin excretion, serum creatinine levels and estimation of glomerular filtration rate) in all diabetic subjects, and in particular those with microalbuminuria.

6.2. Non-diabetic subjects

Non-diabetics will be discussed mainly in the context of hypertension as there are few data in other clinical settings.

6.2.1. Microalbuminuria testing in hypertensive patients: cardiovascular risk assessment

According to hypertension clinical practice Guidelines of the French Health Agency (Recommandations pour la Pratique Clinique HTA 2005, www.has.fr), microalbuminuria testing may be performed in some, but not all non-diabetic hypertensive subjects. Microalbuminuria testing is not relevant in the following cases:

- in hypertensive patients with a high risk of cardiovascular disease: cardiovascular risk is already known to be high and management would not therefore be modified by the presence of microalbuminuria, for example in hypertensive patients with 3 cardiovascular risk factors (Table 1) or in hypertensive subjects with history of cardiovascular disease (myocardial infarction, angina, stroke, peripheral artery disease);

- in hypertensive patients with a low cardiovascular risk (with no associated cardiovascular risk factors for example), it has not been shown that the presence of microalbuminuria alone in hypertensive subjects with controlled blood pressure indicates a high cardiovascular risk.
The microalbuminuria test is probably more relevant in medium-risk hypertensives. Microalbuminuria testing is recommended for primary prevention in some hypertensive with one or two associated risk factors:

- with a cardiovascular risk that seems to be poorly evaluated at the end of the initial examination (Table 1);
- or with refractory hypertension.

The detection of microalbuminuria in this case indicates a high cardiovascular risk and should lead to a change in therapeutic management: rapid decision (< 1 month) for antihypertensive medication and strict control of blood pressure in patients receiving antihypertensive treatment (Recommandations pour la Pratique Clinique HTA 2005, www.has.fr).

6.2.2. Management of non-diabetic hypertensives with microalbuminuria

It is based on:

- strict control of blood pressure by lifestyle measures (reduction in body weight and sodium restriction (< 6 g of salt per day; cf. food composition table high-sodium foods (www.afssa.fr)) (grade B), and pharmacological measures: the five main classes of antihypertensive agents (ACEI, ARB, diuretics, calcium antagonists, beta-blockers) may be used as first line treatments (expert consensus). Unlike in diabetic subjects, it has not been shown that microalbuminuria constitutes a preferential indication for the use of an ACEI or an ARB in non-diabetic hypertensive subjects;
- smoking cessation (expert consensus).

6.2.3. Effect of the reduction of urinary albumin excretion on cardiovascular risk

Management based on the use of an ARB has been shown to induce a more marked reduction of urinary albumin excretion and more effective cardiovascular protection than management based on the use of a beta-blocker in hypertensives with left ventricular hypertrophy (grade B).

6.2.4. Renal surveillance in non-diabetic subjects

Renal function should be monitored yearly (urinary albumin excretion, blood creatinine levels and estimation of glomerular filtration rate) in all microalbuminuric hypertensive subjects (expert consensus). Assay of urinary albumin excretion after a few months of treatment is recommended in patients with initial microalbuminuria (expert consensus).

6.3. Urinary albumin excretion in non-diabetic non-hypertensive subjects

Urinary albumin excretion in non-diabetic non-hypertensive subjects.

6.3.1. Elderly

There are few studies in very elderly subjects (> 75 years) on the prognostic value of microalbuminuria; these studies suggest that microalbuminuria is associated with comorbid conditions and a poor prognosis in this population. Studies including less elderly subjects (50–75 years) indicate that this parameter constitutes an independent marker of cardiovascular and/or renal risk (expert consensus).

It is not recommended to systematically test for microalbuminuria in non-diabetic non-hypertensive elderly subjects with no history of renal disease (expert consensus).

6.3.2. Obese subjects

The prevalence of microalbuminuria is higher in overweight or obese subjects (Expert consensus). Microalbuminuria has the same cardiovascular prognostic value in this population (expert consensus). It is not recommended to systematically test for microalbuminuria in non-diabetic non-hypertensive obese subjects with no history of renal disease (expert consensus).

6.3.3. Subjects with dyslipidemia

There is insufficient evidence suggesting that microalbuminuria testing should be proposed in subjects who only have dyslipidaemia as a cardiovascular risk factor (expert consensus).

6.3.4. Secondary prevention of cardiovascular risk and renal risk

Microalbuminuria is an independent risk marker in patients who have already had a history of cardiovascular condition or a stroke. However, the presence of microalbuminuria does not modify therapeutic management of such patients: aggressive management of cardiovascular risk must be proposed including reduction in blood pressure, lifestyle measures, smoking cessation and use of a statin and aspirin in most cases (expert consensus).

Patients at high risk for cardiovascular disease are also considered to be at risk for renal disease (expert consensus). Renal function should be monitored yearly (urinary albumin excretion, serum creatinine levels and estimation of glomerular filtration rate) in all subjects in whom microalbuminuria has been detected and confirmed (expert consensus).

6.3.5. Pharmacoeconomic analysis

Few pharmacoeconomic studies have been carried out to investigate the cost-efficacy of microalbuminuria testing as a screening strategy (for renal or cardiovascular risk) in diabetic subjects and even fewer in non-diabetic subjects.

Table 1

<table>
<thead>
<tr>
<th>Risk factors used to evaluate global cardiovascular risk in hypertensive patients according to the HAS (in Recommandations pour la Pratique Clinique HTA 2005, <a href="http://www.has.fr">www.has.fr</a>)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt; 50 years in men and &gt; 60 years in women)</td>
</tr>
<tr>
<td>Smoking (current or cessation for less than 3 years)</td>
</tr>
<tr>
<td>Family history of an early cardiovascular accident (myocardial infarction or sudden death before the age of 55 years in the father or a 1st degree male relative, myocardial infarction or sudden death before the age of 65 years in the mother or a 1st degree female relative; early stroke (&lt; 45 years)</td>
</tr>
<tr>
<td>Treated or untreated diabetes</td>
</tr>
<tr>
<td>Dyslipidaemia (LDL-cholesterol ≥ 1.60 g/l (4.1 mmol/l); HDL-cholesterol ≤ 0.40 g/l (1 mmol/l))</td>
</tr>
</tbody>
</table>
6.3.6. Perspectives

It is possible that the threshold of urinary albumin excretion constituting a cardiovascular risk is much lower than that defining microalbuminuria. It is also possible that the relationship between cardiovascular events (and the risk of death from all causes) and urinary albumin excretion is continuous, without any individual threshold. In the future, the term of high or abnormal urinary excretion may replace the concept of microalbuminuria.

6.4. Research protocols and need for new data

There remain many fields in which new knowledge must be obtained in order to better identify the conditions under which microalbuminuria testing is essential. These mainly concern:

- optimal long-term management of microalbuminuric subjects (for example: ACEI vs. ARB, addition of a diuretic or antialdosterone…);
- medicoeconomic evaluation studies on screening for microalbuminuria in diabetic and non-diabetic subjects;
- the relationship between microalbuminuria and the development of renal insufficiency;
- the relation between regression of microalbuminuria during treatment and improvement in prognosis (cardiac risk, renal risk and the risk of developing diabetes);
- the prognostic value of microalbuminuria as a cardiovascular and renal risk marker in the elderly and very elderly, in dyslipidaemic or overweight patients, in patients with metabolic syndrome or in secondary prevention (infarction, stroke, peripheral artery disease…), and in subjects with isolated microalbuminuria (i.e. without other clinical or paraclinical abnormalities).

7. Bibliography

All the references used will be indicated in the full text (long version: "Microalbuminuria and urinary albumin excretion: clinical practice Guidelines – case statement") which will be put on the website of the sponsor professional organizations including the French Nephrology Society (www.soc-nephrologie.org).

Appendix A. Acknowledgements

A.1. Organization Committee

Sponsoring Professional Organization: Société de Néphrologie.

Co-Sponsor Professional Organization:

- Association Française d’Étude et de Recherche sur l’Obésité (AFERO);
- Association de Langue Française pour l’Étude du Diabète et des Maladies Métaboliques (ALFEDIAM);
- Société Française d’Angiologie (SFA);
- Société Française de Cardiologie (SFC);
- Société Française d’Hypertension Artérielle (SFHTA);
- Société Française de Gériatrie et Gérontologie (SFGG);
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References


