Available online at www.sciencedirect.com
ScienceDirect
Diabetes & Metabolism 33 (2007) 303–309
Diabetes & Metabolism
http://france.elsevier.com/direct/diabet

Guidelines and recommendations

Microalbuminuria and urinary albumin excretion: French clinical practice guidelines

J.-M. Halimi[a,*], S. Hadjadj[b], V. Aboyans[c], F.-A. Allaert[d,o], J.-Y. Artigou[e], M. Beaufils[f], G. Berrut[g], J.-P. Fauvel[h], H. Gin[i], A. Nitenberg[j], J.-C. Renversez[k], E. Rusch[l], P. Valensi[m], D. Cordonnier[n]

[a] *Service de néphrologie–immunologie clinique, CHU de Tours, 37044 Tours cedex, France*
[b] *Service d'endocrinologie diabétologie, Inserm ERM 324, CHU de Poitiers, BP 577, 86021 Poitiers cedex, France*
[c] *Service de chirurgie thoracique et cardiovasculaire et angiologie, hôpital Dupuytren, CHU de Limoges, France*
[d] *DIM CHRU de Dijon, France*
[e] *Service de cardiologie, hôpital Avicenne, 93009 Bobigny cedex, France*
[f] *Service de médecine interne, hôpital Tenon, 75020 Paris, France*
[g] *Service de gérontologie clinique, CHU de Angers, 49933 Angers cedex 09, France*
[h] *Département de néphrologie–hypertension, hôpital E.-Herriot, Hospices civils de Lyon, France*
[i] *Service de diabétologie, université de Bordeaux, 33604 Pessac, France*
[j] *Service d'explorations fonctionnelles, CHU de Jean-Verdier, université Paris-XIII, 93140 Bondy, France*
[k] *Département de biologie intégrée, 4e étage, hôpital A.-Michallon, CHU de Grenoble, 38043 Grenoble, France*
[l] *Service d'informatique médicale, CHU de Tours, 37044 Tours cedex, France*
[m] *Service d'endocrinologie diabétologie nutrition, hôpital Jean-Verdier, APHP, université Paris-Nord, CRNH–IdF, Bondy, France*
[n] *Service de néphrologie, CHU de Grenoble, BP 217, 38043 Grenoble cedex, France*
[o] *Département épidémiologie McGill, université Montréal, Canada*

Received 13 June 2007; accepted 27 June 2007
Available online 16 August 2007

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.

* Corresponding author.
E-mail address: halimi@med.univ-tours.fr (J.-M. Halimi).

1262-3636/$ - see front matter
doi:10.1016/j.diabet.2007.06.001

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.

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 minuté. 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/mol (chez la femme) créatinine urinaire ; 3) échantillon urinaire minuté : 20–200 μg/min. La place du dosage semi-quantitatif (bandelettes) n'est pas clairement définie. La microalbuminurie est considérée comme un reflet 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 (créatininémie 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.

Keywords: Albuminuria; Cardiovascular risk; Diabetes mellitus; Renal failure; Hypertension

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

reading panel (members of a reading panel will be put on the website of the sponsor professional organizations including the French Nephrology Society (www.soc-nephrologie.org)) which proposed changes to the working panel. The working panel finalized the final version of these Clinical Practice Guidelines and the case statement.

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, immunonephelemetry, 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 microalbuminuric 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 microalbuminuric 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 I 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 excreton, 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).

Table 1
Risk factors used to evaluate global cardiovascular risk in hypertensive patients according to the HAS (*in* Recommandations pour la Pratique Clinique HTA 2005, www.has.fr)

Age (> 50 years in men and > 60 years in women)
Smoking (current or cessation for less than 3 years)
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 (< *45 years*)
Treated or untreated diabetes
Dyslipidaemia (LDL-cholesterol ≥ 1.60 g/l (4.1 mmol/l); HDL-cholesterol ≤ 0.40 g/l (1 mmol/l).

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.

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);
- Methodological representative: Olivier Chassany;

A.2. Industrial support

Support from the following partners must be acknowledged:

- Bayer Diagnostic;
- Bristol-Myers-Squibb;
- Chiesi S.A.;
- Medtronic;
- Novonordisk;
- Sanofi aventis;

These laboratories provided financial support (meetings…), but they had no access to the texts. The authors had no contact with these laboratories regarding the writing of the present guidelines.

A.3. Logistics and secretarial services

Société LOb Conseils, Cachan.

References

[1] ADA (American Diabetes Association). Diabetic nephropathy. Diab Care 2004;27(suppl 1):S79–83.
[2] Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo Jr. JL, et al. Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. Hypertension 2003;42:1206–52.
[3] European Society of Hypertension-European Society of Cardiology Guidelines Committee. 2003 European Society of Hypertension-European Society of Cardiology guidelines for the management of arterial hypertension. J Hypertens 2003;21:1011–53.
[4] Sarnak M, Levey AS, Schoolwerth AC, Coresh J, Culleton B, Hamm LL, et al. Kidney disease as a risk factor for development of cardiovascular disease: A statement from the American Heart Association Councils on Kidney in Cardiovascular disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Hypertension 2003; 42:1050–65.
[5] Fioretto P, Stehouwer CD, Mauer M, et al. Heterogeneous nature of microalbuminuria in NIDDM: studies of endothelial function and renal structure. Diabetologia 1998;41:233–6.
[6] Allen KV, Walker JD. Microalbuminuria and mortality in long-duration type 1 diabetes. Diabetes Care 2003;26:2389–91.
[7] Gerstein HC, Mann JF, Yi Q, Zinman B, Dinneen SF, Hoogwerf B, et al., HOPE Study Investigators. Albuminuria and risk of cardiovascular events, death, and heart failure in diabetic and nondiabetic individuals. JAMA 2001;286:421–6.
[8] Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. N Engl J Med 1984;311:89–93.
[9] Mogensen CE, Hansen KW, Nielsen S, Pedersen MM, Rehling M, Schmitz A. Monitoring diabetic nephropathy: glomerular filtration rate and abnormal albuminuria in diabetic renal disease-reproducibility, progression, and efficacy of antihypertensive intervention. Am J Kidney Dis 1993;22:174–87.
[10] Perkins BA, Ficociello LH, Ostrander BE, Silva KH, Weinberg J, Warram JH, et al. Microalbuminuria and the risk of progressive renal function decline in type 1 diabetes. J Am Soc Nephrol 2007;18:1353–61.
[11] Rossing P, Hougaard P, Borch-Johnsen K, Parving HH. Predictors of mortality in insulin dependent diabetes: 10 year observational follow up study. BMJ 1996;313:779–84.

[12] Vittinghus E, Mogensen CE. Graded exercise and protein excretion in diabetic man and the effect of insulin treatment. Kidney Int 1982;21: 725–9.
[13] Agewall S, Persson B, Samuelsson O, Ljungman S, Herlitz H, Fagerberg B. Microalbuminuria in treated hypertensive men at high risk of coronary disease. The Risk Factor Intervention Study Group. J Hypertens 1993;11: 461–9.
[14] Araki SI, Haneda M, Koya D, Hidaka H, Sugimoto T, Isono M, et al. Reduction in microalbuminuria as an integrated indicator for renal and cardiovascular risk reduction in patients with type 2 diabetes mellitus. Diabetes 2007;56:1727–30.
[15] Asselbergs FW, Diercks GF, Hillege HL, van Boven AJ, Janssen WM, Voors AA, et al. Prevention of Renal and Vascular Endstage Disease Intervention Trial. (PREVEND IT) Investigators. Effects of fosinopril and pravastatin on cardiovascular events in subjects with microalbuminuria. Circulation 2004;110:2809–16.
[16] Bigazzi R, Bianchi S, Baldari D, Campese VM. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. J Hypertens 1998;6:1325–33.
[17] Borch-Johnsen K, Feldt-Rasmussen B, Strandgaard S, Schroll M, Jensen JS. Urinary albumin excretion: an independent predictor of ischemic heart disease. Arterioscler Thromb Vasc Biol 1999;19:1992–7.
[18] Branstma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT. Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. Diabetes Care 2005;28:2525–30.
[19] Brosius FC, Hostetter TH, Kelepouris E, Mitsnefes MM, Moe SM, Moore MA, et al. Detection of chronic kidney disease in patients with or at increased risk of cardiovascular disease: a science advisory from the AHA Kidney and Cardiovascular disease council; the councils of HBP research; council on cardiovascular disease in the Young; council on epidemiology and prevention; quality of care and outcomes research interdisciplinary working group. Circulation 2006;114:1083–7.
[20] Damsgaard EM, Froland A, Jorgensen OC, Mogensen CE. Microalbuminuria as predictor of increased mortality in elderly people. BMJ 1990; 300:297–300.
[21] de Boer IH, Sibley SD, Kestenbaum B, Sampson JN, Young B, Cleary PA, et al. Central obesity, incident microalbuminuria and change in creatinine clearance in the epidemiology of diabetes interventions and complications study. J Am Soc Nephrol 2007;18:235–43.
[22] Hillege HL, Janssen WM, Bak AA, Diercks GF, Grobbee DE, Crijns HJ, et al., Prevend Study Group. Microalbuminuria is common, also in a nondiabetic, nonhypertensive population, and an independent indicator of cardiovascular risk factors and cardiovascular morbidity. J Intern Med 2001;249:519–26.
[23] Hoy WE, Wang Z, VanBuynder P, Baker PR, McDonald SM, Mathews JD. The natural history of renal disease in Australian Aborigines. Part 2. Albuminuria predicts natural death and renal failure. Kidney Int 2001;60:249–56.
[24] Ibsen H, Olsen MH, Wachtell K, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Reduction in albuminuria to reduction in cardiovascular events in hypertensive patients: Losartan intervention fot endpoint reduction in hypertension study. Hypertension 2005;45:198–202.
[25] Ibsen H, Wachtell K, Olsen MH, Borch-Johnsen K, Lindholm LH, Mogensen CE, et al. Does albuminuria predict cardiovascular outcome on treatment with losartan versus atenolol in hypertension with left ventricular hypertrophy? A LIFE substudy. J Hypertens 2004;22:1805–11.
[26] Klausen KP, Scharling H, Jensen JS. Very low level of microalbuminuria is associated with increased risk of death in subjects with cardiovascular or cerebrovascular disease. J Intern Med 2006;260:231–7.
[27] Mann JF, et al. Albuminuria as a predictor of cardiovascular and renal outcomes in people with known artherosclerotic cardiovascular disease. Kidney Int suppl 2004;92:S59–62.
[28] Bigazzi R, Bianchi S, Baldari D, Campese VM. Microalbuminuria predicts cardiovascular events and renal insufficiency in patients with essential hypertension. J Hypertens 1998;16:1325–13333.
[29] Verhave JC, Gansevoort RT, Hillege HL, Bakker SJ, De Zeeuw D, de Jong PE, PREVEND Study Group. An elevated urinary albumin excretion predicts de novo development of renal function impairment in the general population. Kidney Int Suppl 2004(92):S18–21.
[30] Wada M, Nagasawa H, Kurita K, Koyama S, Arakawa S, Kawanami T, et al. Microalbuminuria is a risk factor for cerebral small vessel disease in community-based elderly subjects. J Neurol Sci 2007;255:27–34.
[31] Yudkin JS, Forrest RD, Jackson CA. Microalbuminuria as predictor of vascular disease in non-diabetic subjects. Islington Diabetes Survey. Lancet 1988;2:530–3.
[32] Wang TJ, Evans JC, Meigs JB, Rifai N, Fox CS, D'Agostino RB, et al. Low-grade albuminuria and the risks of hypertension and blood pressure progression. Circulation 2005;111:1370–6.
[33] Branstma AH, Bakker SJ, Hillege HL, de Zeeuw D, de Jong PE, Gansevoort RT. Urinary albumin excretion and its relation with C-reactive protein and the metabolic syndrome in the prediction of type 2 diabetes. Diabetes Care 2005;28:2525–30.
[34] Wang Z, Hoy WE. Albuminuria as a marker of the risk of developing type 2 diabetes in non-diabetic Aboriginal Australians. Int J Epidemiol 2006;35:1331–5.
[35] Halimi JM, Buchler M, Al-Najjar A, Laouad I, Marlière JF, Chatelet V, et al. Urinary albumin excretion and the risk of graft loss and death in proteinuric and non-proteinuric renal transplant recipients. Am J Transplant 2007;7:618–25.
[36] Pedersen LM, Milman N. Microalbuminuria in patients with lung cancer. Eur J Cancer 1998;34:76–80.
[37] Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabets mellitus and microalbuminuria : the steno type 2 randomized study. Lancet 1999; 353:617–22.
[38] Marre M, Lievre M, Chatellier G, Mann JF, Passa P, Menard J, DIABHYCAR Study Investigators. Effects of low dose ramipril on cardiovascular and renal outcomes in patients with type 2 diabetes and raised excretion of urinary albumin: randomised, double blind, placebo controlled trial (the DIABHYCAR study). BMJ 2004;328:495–501.
[39] Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. Irbesartan in Patients with Type 2 Diabetes and Microalbuminuria Study Group. The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 Diabetes. N Engl J Med 2001; 345:870–8.
[40] Ruggenenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, et al., Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators. Preventing microalbuminuria in type 2 diabetes. N Engl J Med 2004;351:1941–51.