MICROALBUMINURIA: DIAGNOSIS, SEMNIFICATION AND MANAGEMENT

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SUMMARY:
The entire world faces alarming increase in the number of people affected by diabetes, dangerous disease not only in number of cases currently available but also by the negative consequences deriving from it. In type 2 diabetes mellitus (DM), the principal death cause are represented by cardiovascular complications like: myocardial infarction, stroke, cardiac failure, renal failure. MA is an independent cardiovascular risk factor, both in general population and for the patients with high cardiovascular risk, with or without diabetes mellitus, an important marker for renal disease prognosis, both in diabetes mellitus and arterial hypertension.

The coexistence of hypertension (HTA) with MA places the patients in a category with higher renal and cardiovascular risk. MA is an independent risk factor also for proliferative retinopathy and for the appearance of hypertension. In the same time, MA is a strong predictor of increased cardiovascular morbidity and mortality.

The paper makes the pass through all aspects deriving from MA: methods of determination and interpretation of results, clinical significance, useful both in supporting a positive and differential diagnosis, but also as prognosis indicator and therapeutic evaluation.

Keywords: microalbuminuria, type 2 diabetes mellitus.

Rezumat: Intreaga lume se confrunta cu creșterea alarmantă a numărului persoanelor afectate de diabet zaharat, afecțiune periculoasă nu numai ca număr de cazuri existente la ora actuală, dar și prin consecințele negative care derivă din aceasta. Diabetul zaharat tip 2 este o boală în care, după cum s-a dovedit, cauza principală de deces este cea cardiovasculară: infarctul miocardic, accidentul vascular cerebral și insuficiența cardiacă, urmate apoi de insuficiență renală cronică.

Microalbuminuria (MA) este un factor de risc cardiovascular independent, atât în populația generală, cât și la pacienții cu risc cardiovascular înalt, cu sau fără diabet zaharat, marker important al prognosticului afecțiunii renale, atât la cei cu diabet zaharat, cât și la hipertensiivi.

Coexistența hipertensiunii arteriale cu MA plasează pacientul într-o categorie cu risc renal și cardiovascular crescut. Totodată, MA este un factor de risc independent pentru apariția retinopatiei proliferative, dar și a hipertensiunii arteriale. În același timp, MA este un predictor puternic al creșterii morbidității și mortalității cardiovasculare.

Lucrarea face o trecere prin toate aspectele ce derivă din microalbuminurie: metodele de determinare și de interpretare a rezultatelor obținute, semnificația clinică, utilă atât în susținerea diagnosticului pozitiv cât și a celui diferențial, dar și ca indicator prognostic și de evaluare terapeutică.

Cuvinte cheie: microalbuminurie, diabet zaharat, afecțiuni cardiovasculare, boală renală diabetică.

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**Introduction**

Albumin is a non-glycated protein with a 66000 GM, which is present in the blood, cerebrospinal liquid and urine. The urinary presence of albuminuria, in higher quantities than the physiological amount, but not at a high level, is called microalbuminuria (MA) and represents an abnormal growth of permeability for albumin, of the renal glomerular structure, which indicates morphological and functional renal changes, detectable by biological aims.

**Microalbuminuria determination**

Specific urinary strips can be used for the urinary detection and measure of albuminuria, however these aims are not sensitive enough to sustain a MA diagnosis, even when the protocol is strictly followed (2-3 time at 2-3 month). The diagnosis of MA from a 24-hour urine collection is the correct method. This is because the urinary albuminuria excretion has daily variations. In practice, it is inconvenient for the patient to collect all the 24 hours urine without interruptions. By this method, the value between 30-299 mg/daily sustains a MA diagnosis.

By collecting urinary samples in a short period (through the night), the values between 20-199 μg/min sustain the MA diagnosis. The pediatricians recommend it, because the method can exclude orthostatic proteinuria, which is frequent at teens. By collecting a urine sample spot, the values between 20-300 mg/l or μg/g sustain the MA diagnosis.

In practical terms, the most convenient method is to measure the albumin in the early morning urine sample. It is necessary to respect some conditions when collecting the sample:

- within 24 hours before the urine sample collection, the patient could not make an intensive effort; if the MA was diagnosed, the test will be repeated at 3-6 month.
- a false result may appear if the following conditions occur: fever, urinary infection, hematuria, congestive cardiac failure, severe or continue hypertension, period (4th-5th days). The lower limit of MA has been established at (30 mg/l), a value from which the risk regarding MA will be significant. For the urine samples collected through the night, the lower limit has been reduced currently at 15 mg/l.
- A valuable method is the albumin/creatinine ratio (ACR) determination from a urine sample spot, which is justified by the daily albumin variation in these spots. To reduce this effect, it is necessary to make urinary creatinine analysis, and after that, the albumin/creatinine ratio.

- The test is also inaccurate for persons with too much or too little muscle mass. This is due to the variation in creatinine levels produced by muscles.

The National Institute for Health and Clinical Excellence (NICE) guidance considers that an early morning urinary albumin/creatinine ratio (ACR) offers a greater sensitivity for the detection of the lower, but clinically significant, levels of proteinuria and recommends to make these tests before other methods for MA determination, already discussed, are being used.

The values for MA diagnosis are:

- for women: 3-30 mg/mmol or 30-300 mg/g
- for men: 2.5-20 mg/mmol or 25-300 mg/g

**The MA risk factors**

- Glomerular rate filtration (GRF) #60 ml/min/1.73 m²;
- Diabetes mellitus;
- Hypertension;
- Cardiovascular Disease;
- Structural renal tract disease;
- Multiple renal calculi;
- Prostatic hypertrophy;
- Multisystem diseases with potential kidney involvement, e.g. systemic lupus erythematosus;
- Family history of chronic kidney disease (CKD) stage 5 or hereditary kidney disease;
- On detection of hematuria,

**Microalbuminuria significance**

The definition of MA has represented a real progress in the estimation of different nephropathies, because it is proven that it has important diagnosis and evolutive significations from which we can mention the following:

- In the general population, the MA presence, even at levels under the diagnosis value of MA, is an independent risk factor for cardiovascular mortality and morbidity.
- A controversial diagnosis criterion of the metabolic syndrome, because of low prevalence at nondiabetics and the impossibility to establish a direct causal relation, between MA and insulinoresistence.
- Subclinical marker of cardiovascular disease. In association with other cardiovascular factors, it is a general endothelial dysfunction marker, with negative effects in arteriosclerosis processes. If MA is
present, other non-classical cardiovascular factors (inflammation, endothelial dysfunction) contribute to growth the cardio and cerebrovascular risk.\(^{21,22}\)

- An independent risk factor for cerebrovascular disease. In a general population study, at people with cerebrovascular disease (symptomatic or non-symptomatic), MA presence grows the ischemic stroke risk (an independent predictor), because of association between MA with carotid intima-media thickness growth, which represents an arteriosclerosis remodeling witness\(^{23-28}\). At the same time, the MRI investigation at hypertensive patients, shows advanced asymptomatic cerebral lesions if the MA was present, compared to patients without MA\(^ {24}\).

- In DM and hypertension, MA is an important prognosis marker of renal disease. The patient with hypertension and MA is a patient with renal and cardiovascular risk. At hypertensive patients with MA, the target organs lesions are more frequent and severe: an increase of left ventricular size, a higher hypertensive retinopathy prevalence, an increased thickness of carotid arterial walls, a reduced arterial vasodilatation capacity under amino acids and ACE perfusion, MA can be a nephrosclerosis marker\(^ {29,30,31,32}\). The MA prevalence is increased at hypertension patients with insufficient control under medication (40%) and it rises with the age, duration and severity of hypertension and it is lower (25%) under diuretics and betablockers\(^ {23,34}\). It is important to control both the MA and hypertensive value for the evaluation of the antihypertensive therapy\(^ {35}\).

- In intensive care units, the increase of MA, in the first 48 hours after being admitted is an indicator of respiratory deficiency risk, a multiple organ insufficiency or all causes of mortality\(^ {2}\).

- risk factor for trombembolism\(^ {18}\).

**Diabetes mellitus and MA**

The cumulative risk for diabetic nephropathy is 30-40%, after 40 years of evolution, higher at patients with diagnosis of type 1 DM in childhood. In the latest studies, the ND incidence was reduced, concomitant with an optimal glycemic control\(^ {36,37}\).

At type 1 DM patients, chronic renal disease is associated with the increase of morbidity and mortality risk, especially when proteinuria was diagnosed\(^ {37,38}\). There are five evolution degrees of diabetic nephropathy, three of them characterized by the MA presence, after 7-10 years from diagnosis\(^ {39,40}\). In this stage, glomerular morphological lesions are more severe (focal and segmental nodular sclerosis and minimal tubulo-interstitial modification), simple or medium hypertension, slow decline of GRF (but remain higher than 60 ml/min). Concomitantly, for patients with type 1 DM and MA, the proliferative retinopathy can be also seen\(^ {6} \). Cardiovascular disease represents the principal cause of mortality in this stage\(^ {39}\).

For an adult with type 1 DM (after 10-15 years of disease evolution), persistent MA is a high predictor for a nephropathy progression to the finale stages of chronic renal disease, but less predictive for teens with type 1 DM, in the first 10 years after diagnosis disease\(^ {41,42,43}\). Concomitantly, in type 1 DM, MA has a predictive value for the evolution to the proteinuric stage\(^ {6} \).

In type 1 DM the MA prevalence is variable, with limits between 4-21% however with a peak at the puberty period (about 14 years)\(^ {44,45}\). For safety, it is important to determine in every year the MA to all the children to type 1 DM, after the puberty or in the first five years after DM diagnosis\(^ {3}\).

In the same time, it is important to obtain urgently a good glycemic control, to prevent the evolution of MA to proteinuria. At puberty, the good glycemic control is not correlated with the albumin excretion rate (AER), this probably being due to a hormonal mechanism, like the growth of hormone secretion\(^ {46,47,48}\).

In type 1 DM, the glycemic control value and MA presence are the best prognosis indicators for the appearance of specific complications and for the general mortality, but in the matter of cardiovascular morbidity, the MA is a risk factor, independent from atherosclerosis\(^ {49}\).

In the same time, the MA is an independent risk factor for proliferative retinopathy\(^ {60}\) and the appearance of hypertension\(^ {51}\).

The epidemiological data shows that 70-100% of patients with type 1 DM and CKD will develop in their life diabetic retinopathy, but only 25-35% from the patients with diabetic retinopathy will be affected by CKD, in the same time\(^ {52,53}\). In case of differential diagnosis difficulties, the proliferative retinopathy existence, concomitant with a renal affection to a patient with type 1 DM, is an indicator for a diabetic cause of renal disease. The proteinuria without diabetic retinopathy is a rare condition, whereas, severe diabetic retinopathy without proteinuria is a frequent situation\(^ {54}\).

The EURODIAB study shows that although arterial hypertension was considered to be the link between diabetic retinopathy and CKD, the retinopathy prevalence is significantly correlated with arterial hypertension, both...
for albuminuria and normoalbuminuria patients. The AER is rising exponentially with the arterial hypertension values, only at the patients with retinopathy, but not at the patients without retinal affection. At the same blood pressure values, the patient with diabetic retinopathy and bad glycemic control have a significant increase of AER compared with the patients with good glycemic control. At the patients without diabetic retinopathy, the influence of glycemic control over the link between AER and does not apply.

At the diagnosis of type 2 DM, the MA prevalence is 20-40%, so it is recommended to screen for this, right from the first contact with the specialist. Because concomitant diseases could affect the kidney, such as arterial hypertension, cardiac failure, urinary infection, a discordance between relative increase of MA prevalence and lower renal morphological lesions, CKD characteristics, can exist.

MA is an independent cardiovascular risk factor, both in general population and for patients with high cardiovascular risk, with or without DM. In the same time, in Type 2 DM, which has the principal death cause a cardiovascular reason such as: myocardial infarction, stroke, cardiac failure, renal failure, MA is a powerful predictor of the increasing cardiovascular morbidity and mortality. More studies have attempted to determine the value limit of albuminuria, from which the mortality risk is increasing. Some studies have shown that in type 2 DM, from a value higher than 40 μg/min of AER, the MA is a predictive factor for mortality, but when the value is higher than 200 μg/min, the risk does not increase. Other studies have shown that this risk is rising when the AER is higher than 100 μg/min. Other prestigious sources sustain that, the limit value of MA as a mortality risk factor is different between type 1 and type 2 DM, because of different mechanisms for MA generation: between 10-100 μg/min for type 2 DM and 20-200 μg/min for type 1 DM.

Management

At the time of an MA diagnosis, an incipient stage of CKD, the primordial objective is to preserve the functional renal reserve that remains or to stop the progression of CKD to the end stages. Some means are available to meet this objective:

- To avoid nephrotoxic drugs or investigational methods which can increase the renal function decline: medication:
  - nephrotoxic medication: NSAID, Allopurinol, Furosemide;
  - medication that are contraindicated in advanced stages: Spironolactone, Metformin;
  - medication that require dose adjustment when the GRF is lower than 30-40 ml/min: Antibiotics, Digoxin;

As a result, when prescribing and dosing medication, we are required to follow the advice received from nephrologists, who will contraindicate or adjust the medication corresponding to the disease stage.

- contrast substances (for angio CT, necessary before vascular reconstruction- vascular by-pass) higher than 40 ml/min GRF are contraindicated and will be made only in emergency situations, however the procedure must follow the therapeutic protocol established by the nephrologist, to prevent renal function deterioration.

- to avoid urinary bladder catheterism, which can be complicated by urinary infection and then, to affect the renal functional reserve.

For the patients with MA, a role to prevent the progression to proteinuria is without any doubt the glycemic control improvement, evaluated by glycatedhemoglobin A1c, which must be under 7%, regardless of CKD. The antidiabetic medication will be prescribed with caution as follows: after GRF is lower than 40 ml/min, the sulphonylurea will be excluded (with an exception, glyquidon), glinidin (regaplinid), metformin and alpha-glycosidase inhibitors. The insulin therapy will be initiated. At patients with MA, the insulin could stabilize or reduce the AER (after 2 years with good glycemic control maintain). The insulin doses will be adjusted in such a way to prevent the postinsulinic hypoglycemia.

The diet adaptation has also a role in the reduction of the GRF decline. It is necessary to evaluate the nutritional status of patient, the presence of micro and macrovascular chronic diabetic complications, the CKD stage and secondary metabolic affection of this and the global cardiovascular risk.

The BMI will be monitored continuously, to avoid the reduction below 18.5 kg/m², and to prevent the general denutrition. In the same time, it is important to prevent the proteic denutrition, both somatic (muscle mass) and visceral (albumin), the predictive factor for cardiovascular mortality at the patients with chronic disease. Some methods can evaluate the proteic denutrition: SGA (subjective global assessment), muscle force created by the fist constriction, which can be quantified by using a special dynamometer.
The caloric intake will be normal or easy hypercaloric, in function of BMI (normo or overweight, obesity). The protein intake will be 0.7-0.8 g/kg/daily and will be based on proteins with great biological value, with reduced content of nonessential amino acids (AA), exception tyrosine and hystidin (the ideal food: egg whites, fish and chicken soft meat), or under 0.6 g/kg/daily up to 0.3 g/kg/daily, with essential AA supplement or ketoanalogs of those (Ketosteril).

The TA value control (optimal under 130/80 mm Hg) will be realized with double action medication, antihypertensive and renoprotection:

- ACE, is the first choice, from the MA stage (exception: older persons with type 2 DM and recent cardiovascular events, for whom angiotensinogen receptor blockers are recommended, for the reduction of TA values, AER and to prevent the CKD evolution). The creatinine value will be monitored in the first months, because its value can go up and the GRF can go down, which is a reversible phenomenon;
- Angiotensinogen receptor blockers;
- Calcium blockers (Verapamil, Diltiazem), which have antiproteinuric and additive effects.
- Betaadrenergical blockers, with reduced effectiveness, antiproteinuric and a GRF reduction action.

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