Assessment of microalbuminuria in hypertensive patients with established coronary artery disease

Evaluarea microalbuminuriei la pacienți hipertensivi cu boală coronariană instalată

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Abstract

Objectives. Cardiovascular risk assessment is continuously improving due to a better understanding of the atherosclerotic pathomechanism by investigating new risk factors. Microalbuminuria is known as a predictor of renal, as well as cardiovascular morbidity and mortality in patients with hypertension. The aim of this study was to determine the clinical relevance of microalbuminuria and its relationship with traditional cardiovascular risk factors in hypertensive high-risk patients with established coronary artery disease. Methods. We have collected clinical and laboratory data from 94 hypertensive patients (currently treated or newly diagnosed) with known coronary artery disease (angiographically documented) admitted in the Institute of Cardiovascular Diseases. From January 2012 to April 2013 they were screened for microalbuminuria. For the diagnosis of microalbuminuria, a first-morning urine sample was analyzed by immunoturbidimetry (MAU range: 20-200 mg/l, the microalbuminuric group). Patients with urinary albumin excretion >200 mg/l were excluded. Patients with values <20 mg/l were considered the normoalbuminuric group. Results. A large percentage (53.2%) of the study group was found with microalbuminuria. Patients with microalbuminuria were older, mostly male, with a longer duration of hypertension, and with a higher prevalence of left ventricular hypertrophy (LVH). None of the traditional cardiovascular risk factors – age, male gender, obesity, smoking, diabetes mellitus, dyslipidemia - indicated a statistical significance in relation with MAU. Although left ventricular ejection fraction (LVEF) didn't influence the level of microalbuminuria, a strong correlation was achieved with the presence of LVH (p=0.005) and duration of hypertension (p=0.046). Conclusion. Hypertensive high-risk patients should be routinely screened for microalbuminuria and when confirmed they may need a more aggressive medical therapy to lower the cardiovascular risk.

Keywords: microalbuminuria; hypertension; coronary artery disease.

Rezumat

Obiective. Evaluarea riscului cardiovascular este îmbunătățită continuu datorită unei mai bune înțelegeri a patomecanismului aterosclerotic prin investigarea de noi factori de risc. Microalbuminuria este

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recunoscută ca predictor de morbiditate şi mortalitate renală, dar şi cardiovasculară la pacienţii hipertensivi. Scopul acestui studiu a fost de a determina relevanţa clinică a microalbuminuriei şi relaţia sa cu factorii de risc cardiovascular tradiţionali la pacienţii hipertensivi cu risc foarte înalt şi boală coronariană stabilă. Metode. Am colectat datele clinice şi de laborator de la 94 de pacienţi hipertensivi (aflaţi sub tratament sau nou diagnosticaţi) cu boală coronariană cunoscută (documentată angiografic) internaţi în Institutul de Boli Cardiovasculare în perioada ianuarie 2012 – aprilie 2013. Pentru diagnosticul de microalbuminurie s-a analizat o probă din prima urină de dimineaţă prin imunturbidimetrie (valori de referinţă 20-200 mg/l, grupul microalbuminuric). Pacienţii cu excreţie urinară de albumină >200 mg/l au fost excluşi. Pacienţii cu valori <20 mg/l au fost consideraţi grupul normoalbuminuric. Rezultate. Un procent înalt (53.2%) din populaţia de studiu a fost găsit cu microalbuminurie. Pacienţii cu microalbuminurie au fost mai în vârstă, majoritatea bărbaţi, cu o durată mai lungă a hipertensiunii şi cu o prevalenţă mai înaltă a hipertrofiei ventriculare stângi. Nici unul dintre factorii de risc cardiovascular tradiţionali – vârsta, sexul masculin, obezitatea, fumatul, diabetul zaharat, dislipidemia – nu a atins semnificaţia statistică în relaţie cu microalbuminuria. Deşi fracţia de ejecţie a ventriculului stâng nu a influenţat nivelul microalbuminuriei, o corelaţie strânsă s-a obţinut cu prezenţa hipertrofiei ventriculare stângi (p=0.005) şi cu durata hipertensiunii (p=0.046). Concluzii. Pacienţii hipertensivi cu risc înalt ar trebui testaţi de rutină pentru microalbuminurie şi când aceasta este confirmată, ar putea necesita o terapie medicală mai agresivă pentru scăderea riscului cardiovascular.

***Cuvinte cheie** Microalbuminurie; hipertensiune arterială; boală coronariană ischemică.*

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Introduction

Microalbuminuria, an abnormal increase in the rate of urinary excretion of albumin, is recognized as an early manifestation of diabetic kidney disease and as a marker of endothelial dysfunction and atherosclerotic disease. In addition, a large number of studies suggest that microalbuminuria (MAU) is a powerful independent predictor of microvascular lesions, cardiovascular disease (1), cardiovascular mortality, and kidney disease, including end-stage renal failure. Albuminuria is an early marker of diabetic nephropathy, and previous reports described the association between albuminuria and risk of adverse cardiovascular and kidney events (2, 3). Both the presence of microalbuminuria and its extent became valuable instruments for risk stratification of hypertensive patients (4), since large trials showed conclusive evidence that early determination and treatment of microalbuminuria, as well as blood pressure control, can delay the onset and the complications of cardiovascular disease (5, 6).

In hypertensive subjects, MAU has often been related to an excess of atherosclerotic cardiovascular disease (7, 8), and to an increased level of atherosclerotic risk markers (9). The relationship between MAU and the development of vascular disease is strengthened by its presence in acute ischemic heart disease (10), congestive heart failure (11), stroke (12), peripheral arterial disease, and carotid atherosclerosis (13). Thus, MAU might serve as a 'diagnostic window' for the whole vasculature, acting as an indicator of generalized endothelial injury (4, 14).

In the present study we aimed to investigate the clinical relevance of MAU in high-risk hypertensive patients with established coronary heart disease, and to underline the significant correlations with traditional cardiovascular risk factors.

Methods

Patients

94 patients with arterial hypertension (currently treated or newly diagnosed) and of known coronary artery disease (angiographically documented), admitted in the Institute of Cardiovascular Diseases from January 2012 to April 2013, were screened for microalbumin-

uria. MAU was measured in all patients except for those with fever (> 38ºC), renal disease (eGFR <60 ml/min/1.73 m², Cockroft-Gault formula), urinary tract infection or having practiced extensive physical effort 24 h before the measurement. All patients gave written informed consent for participating in the study. The study was in accordance with the ethical principles of the Declaration of Helsinki and was approved by the local ethics committee.

Study design and procedures

Collected baseline data of the patients included medical history, demographics, biometric data, urine and blood collections, and laboratory analysis. For the diagnosis of microalbuminuria, a first-morning urine sample was analyzed by immunoturbidimetry (MAU range: 20-200 mg/l, the microalbuminuric group). Patients with urinary albumin excretion >200 mg/l were excluded. Patients with values <20 mg/l were considered the normoalbuminuric group.

Hypertension was defined as systolic blood pressure >140 mm Hg, diastolic blood pressure > 90 mm Hg, and/or use of antihypertensive drugs. Dyslipidemia was defined as cholesterol > 180 mg/dl and/or HDL < 40 mg/dl in male patients and < 50 mg/dl in female patients and/or LDL > 160 mg/dl and/or triglycerides > 150 mg/dl and/or use of lipid-lowering treatment. Obesity was defined as BMI >= 30 kg/m². Diabetes was defined as fasting plasma glucose levels > 126 mg/dl and/or use of antidiabetic therapy.

Left ventricular hypertrophy (LVH) and left ventricular ejection fraction (LVEF) were assessed echocardiographically by a single investigator. LVH was defined as posterior wall thickness or/and interventricular septum thickness > 12 mm (M-Mode measurement). Left ventricular ejection fraction (LVEF) was determined using the Sympson method.

Statistical methods

Results are presented as mean ± SD for continuous variables and as percentages of the total number of patients for categorical variables. Correlation analysis was conducted using Pearson (r) or Spearman (ρ) tests. The data were also logarithmically transformed to achieve normal distribution, whenever possible. We performed univariate analysis using a *t*-test for normally distributed continuous variables and Mann-Whitney test if variables were not normally distributed. Comparisons of categorical variables were analyzed by the Chi-square test. A P value ≤ 0.05 was considered significant. Statistical analysis was performed with SPSS 21.0 (SPSS Inc., Chicago, IL, USA).

Results

Clinical and biological characteristics of the study population are presented in *Table 1*. Laboratory results from urine showed that an important percentage (53.2%) of our study group represented by high-risk hypertensives had evidence of MAU. Patients with microalbuminuria were older, mostly male, with a longer duration of hypertension, and with a higher prevalence of left ventricular hypertrophy. An important proportion was dyslipidemic (80%).

A correlation analysis was performed to assess the relationship of microalbuminuria with traditional risk factors: male gender (p=0.48), age (p=0.07), smoking (p=0.139), diabetes mellitus (p=0.75), dyslipidemia (p=0.406), obesity (p=0.837). None of them showed a statistical significance. Microalbuminuria and serum levels of glucose and lipids didn't show any correlation (ρ = -0.002 and 0.041, respectively). Microalbuminuria was not influenced by eGFR (p=0.249). LVEF values didn't reach a statistical significance in relationship with microalbuminuria (p=0.824). However, a strong correlation was achieved with the presence of left ventricular hypertrophy (p=0.005, *Figure 1*) and duration of hypertension (p=0.046).

Discussion

First of all, this study shows a high prevalence of microalbuminuria among patients with coronary artery disease, supporting the ex-

Table 1. Clinical and biological characteristics of the study population

	Normoalbuminuric group n = 44	Microalbuminuric group n=50	p-value
Age, y	60 (50-72)	62.5 (55-75)	0.29
Male, %	54.50%	60%	0.67
Smokers, %	56.80%	46%	0.31
Hypertension, y	5 (2-9)	6 (3-10.25)	0.26
Dyslipidemia, %	77.30%	80%	0.8
Diabetes mellitus, %	52.30%	44%	0.53
Obesity, %	36.40%	46%	0.4
LVH, %	50%	66%	0.144
EF (%)	45 (35-50)	45 (40-50)	0.676
Laboratory data			
Glucose (mg/dl)	117 (105-180)	108 (100.25-173)	0.179
HDL-C (mg/dl)	50 (32-59)	48 (38.75-54)	0.964
LDL-C (mg/dl)	113 (95-164)	119 (93-139)	0.578
Cholesterol (mg/dl)	185 (159-221)	193 (163.5-215.25)	0.894
Triglycerides (mg/l)	154 (108-200)	118(73-212.25)	0.1
eGFR (ml/min/1.73m2)	89.6 (64.3-117.97)	84.65 (68.64-99.75)	0.74
Microalbuminuria (mg/l)	10.12 (6.21-15.77)	48.65 (30.62-87.06)	
Log microalbuminuria	1 (0.78-1.19)	1.68 (1.48-1.93)	

tent of the generalized state of inflammation and endothelial dysfunction. Previous studies report a prevalence of microalbuminuria in patients with hypertension and diabetes of 10% to 15% and 15% to 20%, respectively, which is higher than the prevalence in individuals from the general population in whom values of 6% to 8% have been described (15, 16).

The increased cardiovascular risk of hypertensive patients, together with a higher mortality rate in the general population, are closely related to the comorbidities and risk factors that accompany this pathology. In the I-SEARCH study, both microalbuminuria itself and its value increased significantly with the number of associated morbid conditions, suggesting that endothelial dysfunction and the addition of pathological disorders go well together (17).

Copenhagen City Heart study revealed a strong correlation between microalbuminuria and the metabolic syndrome (18), showing that MAU is associated with increased risk of death and cardiovascular disease to a similar extent as the metabolic syndrome, irrespective of its concomitant presence. Our study population has a high prevalence of the components of metabolic syndrome, however we did not assess its influence separately.

Our findings are in line with data from the I-SEARCH study, where patients with left ventricular hypertrophy presented, in 68% of the cases, microalbuminuria (17). LVH, as a sign of target organ damage, is a strong and independent predictor of both cardiovascular events and all-cause mortality in patients with hypertension (19). Therefore, patients diagnosed with left ventricular hypertrophy (electro-
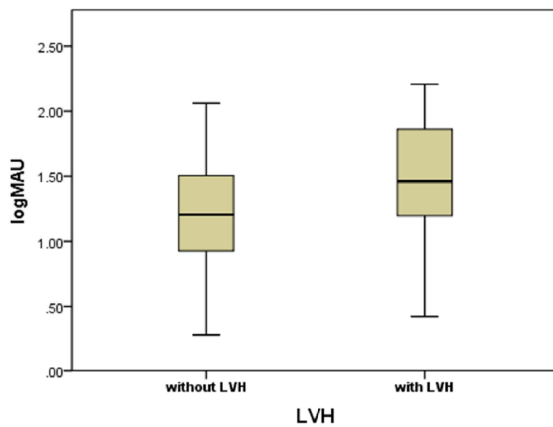
Figure 1. Relationship between the level of microalbuminuria (logMAU) and the presence of left ventricular hypertrophy (LVH)

cardiographically or echocardiographically) should be thoroughly investigated, keeping in mind the likelihood of a coronary disease.

Data from the HOPE study suggested that any level of microalbuminuria predicts coronary heart disease in individuals with or without diabetes (20), and furthermore MAU is a strong determinant of coronary artery disease and death independently of age, sex, hypertension, diabetes mellitus, renal function, and lipids (21). It has been proven that the majority of cardiovascular events don't necessarily occur in patients with high blood pressure, therefore it is important to detect and to treat hypertension as early as possible (22).

MAU reflects widespread vascular damage and is associated with the presence of an unfavorable risk score and target organ damage. However, the pathophysiological link between MAU and coronary artery disease is not yet elucidated. Accumulative evidence suggests that the pathological changes causing MAU and the pathological changes leading to premature atherosclerosis are the same. Decreased density of heparan sulphate in the endothelial cells of vessels leads to decreased binding of lipoprotein lipase, which results into decreased clearance of very low density lipoproteins and leads to hyperlipidemia. Similar to endothelial dys-

function, the initial stage of atherosclerosis with low grade inflammation is common between MAU and cardiovascular disease (23, 24).

Microalbuminuria may imply a vulnerability for atherosclerosis due to its association with inflammatory and prothrombotic changes involved in endothelial dysfunction (25-29). There is conflicting evidence that MAU reflects a systemic transvascular leakage of albumin, which may be associated with leakage of lipoproteins and other macromolecules (30, 31). Thus, defective endothelial permeability allows lipid influx into the vessel wall causing atherosclerotic changes (32). Regarding the microvascular damage, Ebinç et al. (33) demonstrated that levels of vascular endothelial growth factor (VEGF) are higher in hypertensive patients in the presence of microalbuminuria. VEGF is the most important regulator of pathological and physiological angiogenesis and it additionally leads to increased vascular permeability, therefore it may also increase glomerular permeability and lead to MAU in hypertension.

Hypertensive patients with high urinary albumin excretion might be candidates to atherosclerotic diseases. Therefore the European guidelines underline the importance of assessing microalbuminuria as a routine measurement in every hypertensive patient (34). Nevertheless, in 2010, a joint task force of the American College of Cardiology and AHA (35) issued guidance on which novel risk factors or biomarkers, in addition to classical risk factors, might be currently considered in CHD risk prediction. The task force categorized microalbuminuria assessment as reasonable in adults with hypertension or diabetes. Thanks to its relatively low cost and wide applicability, more widespread use of this test in the diagnostic workup will help detect subsets of patients at greater risk for whom additional preventive and therapeutic treatment is advisable (36).

Limitations of the study

First, the study population is small and it doesn't allow us to make predictions on a

large-size effect. However, this preliminary data marks an important result that needs further evaluation. Second, we used a single morning spot urine sample to assess microalbuminuria, instead of timed urine collections, which would have been preferable. However, single analysis is an established, easy, and valid screening tool in a controlled group. Its results can point towards certain medication to start with and it also brings data about the risk profile.

Third, LVH was interpreted by using only two dimensions of the wall thickness, and not the left ventricular mass index. The concordance between wall thickness and a left ventricular mass index is only 60% (37). In addition, wall thickness tends to underestimate LVH in women and overestimate it in men. However, echocardiography, if available, should be the test of choice to assess for LVH, being much more sensitive than electrocardiography (38).

Last, there is no sustainable data about prior antihypertensive medication. It would have been of interest the assessement of ACEI/ARB medication, given the fact that an analysis of the ONTARGET trial have provided evidence for slowing the progression of renal disease demonstrated by level of microalbuminuria in at-risk patients, including those with diabetes, being treated with telmisartan or ramipril (39, 40). In addition, ROADMAP trial showed that pharmacological blockade of angiotensin II receptors by olmesartan is effective in reducing the risk of new-onset albuminuria in type 2 diabetic patients (41).

Conclusions

MAU is very common in high-risk hypertensive patients, however it is often under-diagnosed and awareness of its importance as a marker of cardiovascular risk is still poor. Given its feature as a strong, early and independent marker of cardiovascular morbidity and mortality, our study highlights the importance of evaluating the presence of microalbuminuria and the need for a more aggressive medical therapy for the hypertensive patients.

Conflict of interest: None declared.

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