Determination of Microalbuminuria in Hypertensive Patients and in Patients with Coronary Artery Disease

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Summary

Background: The normal 24-hour albumin excretion rate is of 20 mg. A persistent rate of 30 to 300 mg/day is called microalbuminuria and is related to a higher prevalence of cardiovascular disease.

Objective: 1) To determine the prevalence of microalbuminuria in a group of hypertensive patients and in a group of patients with coronary artery disease; 2) To determine the relationship between the presence of microalbuminuria and hypertension, diabetes mellitus, dyslipidemia, smoking and obesity.

Methods: The presence of microalbuminuria in a group of hypertensive patients (73 individuals) and in a group of patients with coronary artery disease (39 individuals) was determined and compared with a control group (43 individuals). Microalbuminuria was defined as an albumin/creatinine ratio higher than 30 and lower than 300 in a spot morning urine sample. The chi-square test and the Fisher's exact test were used in the statistical analysis.

Results: Microalbuminuria was present in 9.5% of the hypertensive individuals and in 33% of the patients with coronary artery disease, and was absent in individuals of the control group. When the occurrence of microalbuminuria was analyzed according to the different clinical parameters, regardless of the group involved, a statistically significant correlation was found with age, diabetes and dyslipidemia.

Conclusion: 1) The prevalence of microalbuminuria in hypertensive individuals is high, and is even higher in patients with coronary artery disease; 2) There is a correlation of the presence of microalbuminuria with age, diabetes and dyslipidemia. (Arq Bras Cardiol 2008; 90(2):99-103)

Key words: Albuminuria/complications; hypertension; coronary disease.

Introduction

The normal 24-hour albumin excretion rate is of 20 mg. A persistent rate of 30 to 300 mg/day is called microalbuminuria.

Twenty-four-hour urine collection is the standard method for the detection of microalbuminuria, although it can also be detected with the collection of the first morning void[1-2].

The volume effect can be avoided using the calculation of the albumin/creatinine ratio in a urine sample[3].

The three major limitations for the determination of microalbuminuria are: 1) Strenuous exercise, which may lead to a transient increase in albumin excretion[4]; 2) Alteration during the day in the relation between the collection of a spot urine sample and the 24-hour collection: there is a better correlation if the samples are obtained in the middle of the morning[5]; 3) The accuracy of the albumin/creatinine ratio decreases if creatinine excretion is very different from the estimated value, as occurs in men with high muscle mass or in cachectic individuals[6].

Preliminary studies demonstrated that microalbuminuria represented the earliest clinical manifestation of diabetic nephropathy, and its determination is now recommended for the initial assessment and follow-up of diabetic patients.

Further studies demonstrated an association between microalbuminuria and cardiovascular disease in both diabetic and non-diabetic patients.

The HOPE study showed that the presence of microalbuminuria was associated with an increased relative risk of primary endpoints (myocardial infarction, stroke or cardiovascular death). The risk of an adverse cardiovascular event increased progressively with the increase in the levels of microalbuminuria[7].

Further analysis of the LIFE study on hypertensive patients with electrocardiographic evidence of left ventricular hypertrophy showed that for every increase of 10 times in the albumin/creatinine ratio, the risk of infarction or stroke increased by 57%, and the risk of cardiovascular death by

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98% for non-diabetic patients. Increases in diabetic patients were of 39% and 47%, respectively[8].

An analysis of the PREVEND study showed an increase in the relative risk of cardiovascular mortality of 1.35 for every two-fold increase in the value of albuminuria[9].

In elderly individuals, the combination of microalbuminuria and hyperinsulinemia, a reflex of insulin resistance, is associated with increased risk of coronary events and mortality[10].

Even very low levels of microalbuminuria may be associated with increased cardiovascular risk, as was demonstrated in the "Copenhagen City Heart Study". Patients with albuminuria greater than 6.9 mg/day had a relative risk of death of 1.9, and risk of coronary artery disease of 2.0[11].

The mechanism explaining the association between microalbuminuria and cardiovascular disease remains unknown. Microalbuminuria in non-diabetic individuals seems to be a sign from the kidneys that the vasculature, mainly the endothelium, is not functioning properly. This fact may be confirmed by the following evidences: 1) Vasodilation in response to some stimuli is reduced in normal elderly individuals with microalbuminuria when compared with those without albuminuria[12]. 2) Among non-diabetic hypertensive individuals, those with microalbuminuria show higher levels of von Willebrand factor than those without microalbuminuria. Since von Willebrand factor has been associated with occlusive thrombosis, elevations of this factor may contribute to an increase in cardiovascular disease[13].

Among non-diabetic hypertensive individuals, microalbuminuria is associated with higher pressure levels, higher cholesterol levels, and lower HDL levels[14].

The objectives of this study are: 1) To determine the prevalence of microalbuminuria in a group of hypertensive patients and in a group of patients with coronary artery disease; 2) To determine the relationship of the presence of microalbuminuria with hypertension, diabetes mellitus, dyslipidemia, smoking and obesity.

Materials and methods

Patients

Inclusion criteria - hypertensive patients with coronary artery disease treated at *Hospital Universitário Walter Cantídio*. Healthy employees of the same hospital comprised the control group.

Individuals with three or more blood pressure measurements equal to or higher than 140/90 mmHg or those with previous diagnosis of hypertension who were receiving antihypertensive drugs were considered hypertensive. Individuals with at least two fasting plasma glucose levels higher than 125 mg/dL or those being treated for diabetes with oral hypoglycemic agents and/or insulin were considered diabetic. Patients with cholesterol levels higher than 200 mg/dL or triglyceride levels higher than 150 mg/dL or who were receiving lipid-lowering drugs were considered dyslipidemic. Individuals who had smoked any amount of cigarettes in the past year were considered smokers.

Patients with angiographically confirmed severe lesion (stenosis > 70%) in at least one coronary artery were include in the group of coronary artery disease.

Exclusion criteria - patients with creatinine levels higher than 2 mg/dL were excluded from the study.

Methods

After weight and height were measured, the body mass index (BMI) was calculated using the formula: BMI = Weight/height^2. Individuals with a BMI equal to or higher than 25 were considered overweight, and those with a BMI equal to or higher than 30 were considered obese.

Waist circumference was measured and considered increased when higher than 80 cm for women or higher than 90 cm for men.

An albumin/creatinine ratio higher than 30 in a spot morning urine sample was considered microalbuminuria.

Statistical analysis

The comparison of the H (hypertension) group and CAD (coronary artery disease) group with the control group regarding the different clinical parameters was performed using the chi-square test and the Fisher's exact test.

In order to determine whether the incidence of MA (microalbuminuria) among CAD patients was different from that among H patients and individuals of the control group, the analysis of proportions with a sample proportion test (binomial) was used.

To measure the presumed importance of microalbuminuria, BMI, waist circumference, smoking, dyslipidemia, diabetes mellitus and hypertension as determinant factors of coronary artery disease, the three original groups (CAD, H and control) were clustered so as to serve as a basis for a multivariate logistic analysis. In order to make that possible, the patients of each group received the auxiliary variables necessary to mark their original enrollment. Considering coronary artery disease as a dependent variable and all the other variables previously mentioned as independent variables, we started to seek the most appropriate model. We started from a model including all independent variables and used conventional techniques to include and eliminate variables.

P values < 0.05 were considered statistically significant.

Results

The group of hypertensive patients was comprised of 73 individuals, 23% of whom were males; the group of coronary patients included 39 individuals (43% males), and the control group was comprised of 43 individuals (9% males).

When the group of hypertensive patients was compared to the control group, we observed that the hypertensive individuals were older, more obese, had a higher proportion of diabetic and dyslipidemic individuals, and of individuals with microalbuminuria. When the group of patients with coronary artery disease was compared to the control group, we observed that coronary patients were more frequently males, were older, and had a higher proportion of diabetic and dyslipidemic individuals and of individuals with

microalbuminuria. Microalbuminuria was present in 9.5% of the hypertensive individuals, and in 33% of the patients with coronary artery disease, and was absent in individuals of the control group (Table 1 and Figure 1). Also as regards microalbuminuria, a statistically significant difference was found when the CAD group was compared to the control group ($p<0.001$), when the H group was compared to the control group ($p< 0.001$), and when the CAD group was compared to the H group ($p<0.001$).

When the occurrence of microalbuminuria was analyzed according to the different clinical parameters, regardless of the group considered, a statistically significant correlation was found with age, diabetes and dyslipidemia (Table 2). When we analyzed microalbuminuria in relation to the individuals' weight, we found that microalbuminuria was absent in all the 37 obese individuals, but was present in 13 of the 67 overweight individuals (19.4%), and in 7 of the 39 individuals with normal weight (17.9%). When obese individuals were grouped with overweight individuals, we found a prevalence of only 13%, which is lower than that of individuals with normal weight.

When the importance of microalbuminuria, BMI, waist circumference, smoking, dyslipidemia, diabetes mellitus, and hypertension was tested as determinant factors of the

Table 1 - Comparison of H and CAD groups with the control group according to the different clinical parameters

	H n (%)	CAD n (%)	Control Group n (%)
Male/Female (male proport.)	17 / 56 (23%)	17 / 22 (43%)#	4 / 39 (9%)
DM	14 (19.1%)#	20 (51.2%)#	1 (2.3%)
Dyslipidemia	40 (54.7%)#	30 (76.9%)#	5 (11.6%)
Smoking	7 (9.5%)	2 (5.1%)	7 (16.2%)
Increased waist circumference	69 (94.5%)*	31 (79.4%)	35 (81.3%)
Obesity	27 (36.9%)#	6 (15.3%)	4 (9.3%)
Overweight	33 (45.2%)	17 (43.5%)	17 (39.5%)
Age > 55 years	38 (52%)#	30 (76%)#	
Microalbuminuria	7 (9.5%)*	13 (33.3%)#	0 (0%)
Total	73	39	43

*H – group with hypertension, CAD – group with coronary artery disease; * p < 0.05; # p < 0.01.*

Table 2 - Relationship between the occurrence of microalbuminuria and the different clinical variables

Variables	Microalbuminuria -	Microalbuminuria +	P
Gender			
Female	102 (87.2%)	15 (12.8%)	1.000
Male	33 (86.8%)	5 (13.2%)	
Age			
18 to 55 years	81 (95%)	4 (5%)	
56 to 83 years	54 (77%)	16 (23%)	0.001
BMI			
16.7 to 24.9	44 (86.2%)	7 (13.8%)	
25 to 42.5	91 (87.5%)	13 (12.5%)	0.831
Waist Circ.			
normal	15 (75%)	5 (25%)	
increased	120 (88.9%)	15 (11.1%)	0.143
Diabetes			
absent	109 (91.5%)	10 (8.5%)	
present	25 (71.4%)	10 (28.6%)	0.004
Dyslipidemia			
absent	70 (94.5%)	4 (5.5%)	
present	60 (80%)	15 (20%)	0.008
Smoking			
absent	120 (86%)	19 (14%)	
present	15 (93%)	1 (7%)	0.696

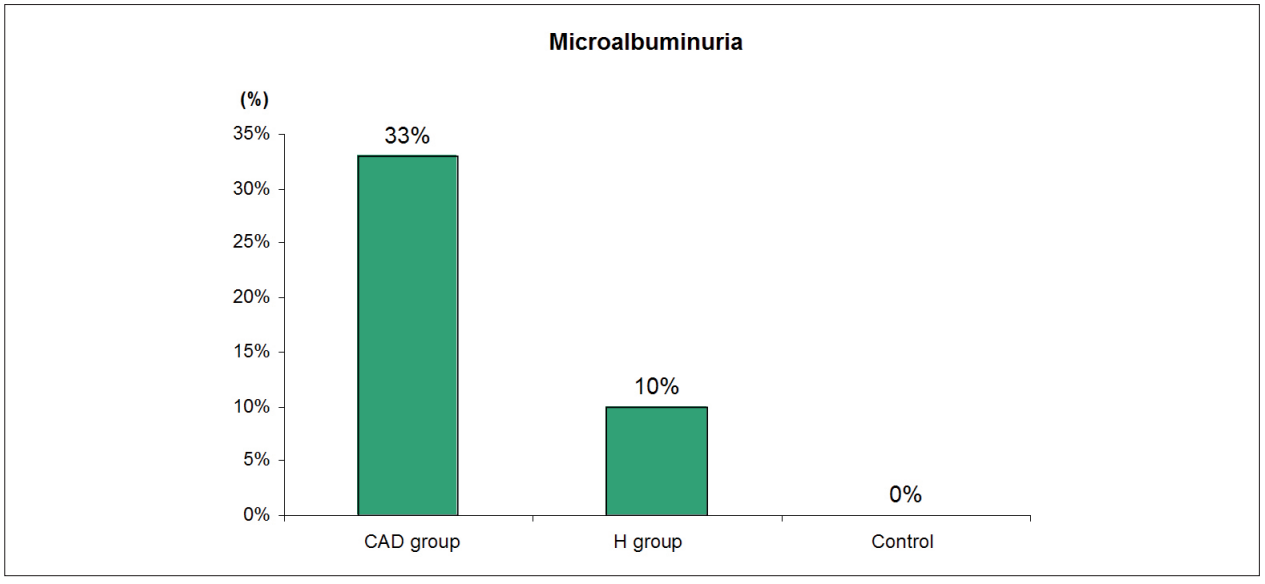

***Figure 1** - Incidence of microalbuminuria in the three groups.*

occurrence of coronary artery disease, we observed that diabetes mellitus, dyslipidemia, and microalbuminuria were determinant factors. Patients with microalbuminuria have a 4.5-fold higher chance of having coronary artery disease when compared to those without microalbuminuria. Diabetic patients and patients with dyslipidemia have a 4.3 and 4.1-fold higher chance, respectively.

Discussion

Microalbuminuria is known to be a risk factor for cardiovascular disease; however, it is not known whether this association results from an effect of microalbuminuria in the development of subclinical atherosclerosis or whether microalbuminuria destabilizes subclinical atherosclerosis, thus leading to clinical events. Cao et al[15] evaluated a population of 3312 participants in the "Cardiovascular Health Study" as regards MA. The participants were divided into three groups: individuals without diabetes or hypertension (33%), individuals with hypertension (52%), and diabetic individuals with or without hypertension (15%). For each one of the three groups, the relative risk of cardiovascular disease in the presence of MA increased by 1.7 to 1.8 times. However, MA was not associated with risk of subclinical atherosclerosis in the absence of hypertension or DM, which makes us believe that the mechanism of association of MA with cardiovascular disease involves destabilization of the vascular system, thus leading to clinically overt disease[15].

According to Cirillo, the main correlate with microalbuminuria is blood pressure, whether systolic or diastolic. The relationship between blood pressure and microalbuminuria is continuous and gradual because the prevalence of microalbuminuria increases with the severity of hypertension. For hypercholesterolemia, smoking and diabetes, data are less incisive, but they point to a positive independent association with microalbuminuria[16].

The prevalence of microalbuminuria in hypertensive individuals in our study was 9.5%, a value slightly lower than that found by other authors[17].

The prevalence of microalbuminuria among our obese or overweight patients was of only 13%, thus lower than that of the patients with normal weight (17.9%). Valensi et al[18] found prevalences of up to 12% of microalbuminuria among obese individuals. When hypertension was associated with obesity, the prevalence reached up to 19%[18]. In another study with obese or overweight individuals, central fat distribution implied an 18-fold higher risk of microalbuminuria in relation to lean individual, whereas among obese individuals with peripheral fat distribution, the risk was 4-fold higher[19]. A Brazilian study demonstrated a trend to borderline levels of nocturnal microalbuminuria, which was higher in normotensive obese females with central fat distribution[20].

A high prevalence of microalbuminuria was found among our patients with coronary artery disease (33%). Since the past decade, the association between microalbuminuria and coronary artery disease has been demonstrated, when Tuttle et al[21] studied 308 patients undergoing coronary angiography, previously determining the albumin/creatinine ratio in a spot morning urine sample. Urinary albumin excretion (UAE) in patients with CAD was significantly higher than in patients without CAD. Albumin excretion increased progressively with the severity of CAD. In patients without DM, a relationship between UAE and CAD was observed, but it was more significant in diabetic patients. In multiple regression analysis, the relative risk for severe CAD was 2.2 for MA (Am. J. Kidney Disease)[21].

The relationship between MA and CAD seems to be influenced by ethnicity. Tillin et al[22] studied a population from the city of London comprised of 1460 Europeans, 946 Asians, and 559 African-Caribbean and observed an association of MA with prevalence and mortality of CAD only for Asian males and European females. It should be noted that, in this study, the diagnostic criterion for CAD is highly debatable, because it includes only the clinical history and electrocardiographic changes[22]. MA is present not only in overt ischemia, but also in silent ischemia[23].

Also in relation to CAD, MA was studied in non-diabetic patients with a previous history of myocardial infarction and was found in 11% of these patients. UAE was also associated with increased thickness of the intima-media complex in the brachial and carotid arteries[24].

As regards peripheral arterial disease (PAD), a relationship between MA and this disease was also observed. Spanish researchers studied 141 patients with acute coronary syndrome and divided them into two groups according to the presence or absence of PAD, and observed that MA was significantly higher in the PAD group[25]. In the following year, Turkish researchers studied a population of 65 patients with PAD undergoing coronary angiography and observed that UAE was significantly higher in the group with CAD than in the group without CAD. We should point out that the authors used excessively encompassing diagnostic criteria for the diagnosis of CAD, such as the presence of coronary stenosis equal to or higher than 25%[26].

In conclusion: 1) The prevalence of microalbuminuria in hypertensive individuals is high, and is even higher in patients with coronary artery disease; 2) There is a correlation between the presence of microalbuminuria and age, diabetes and dyslipidemias; 3) Microalbuminuria is a strong predictor of the occurrence of coronary artery disease.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any graduation program.

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