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Microalbuminuria in systolic and diastolic chronic heart failure patients

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Abstract

Background: *Microalbuminuria is considered a major risk factor predisposing to cardiovascular morbidity and mortality. Microalbuminuria levels in patients with or without diabetes have been associated with a higher risk of chronic heart failure (HF). However, there are limited data regarding prevalence of microalbuminuria in chronic heart failure and its prognostic value. The aim of this study was to assess the occurence of microalbuminuria in chronic heart failure patients as well as its association with clinical, echocardiographic, and body composition markers.*

Methods: *In a cross-sectional study, we included 72 chronic heart failure patients (NYHA I–III) on standard HF therapy. All patients had an echocardiogram and body composition by vector bioelectric impedance analysis (measured by Body Stat Quad Scan).*

Results: *The studied population consisted of 64% men at mean age of 62.6 ± 15.1 years. Patients were divided into systolic and diastolic HF groups. Microalbuminuria was observed in 40% of diastolic and 24% systolic HF patients ($p = 0.04$). Microalbuminuria was present in more patients with volume overload (80* vs. *21.9%, $p = 0.002$), with a worse phase angle and lower serum albumin (4.7* vs. *5.9° and 3.5* vs. *4.0 mg/dl, $p = 0.02$) and higher pulmonary arterial pressure compared with patients without microalbuminuria in systolic HF patients. There was no significant association between frequency of microalbuminuria and ejection fraction. In the diastolic HF group, the presence of microalbuminuria was not associated with any known risk factor.*

Conclusions: *Microalbuminuria was more frequent in diastolic than systolic HF patients. In systolic HF patients microalbuminuria was associated with factors known to be markers of worse prognosis.* (Cardiol J 2008; 15: 143–149)

Key words: microalbuminuria, systolic and diastolic heart failure, body composition markers

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Introduction

Microalbuminuria has been recognized as a risk factor for cardiovascular disease (CVD) [1, 2], especially in coronary heart disease (CHD) [3–5], and it occurs most often in hypertensive and diabetic patients. Moreover, microalbuminuria has been proposed as a useful parameter in patients at high risk of developing heart failure (HF) [6]. In patients with diabetes mellitus older than 50 years, 4% with albuminuria > 20 mg/L developed HF [7]. In addition, the HOPE study showed that the rate of developing HF significantly increased in the presence of microalbuminuria (1.82) [8]. In spite of this information, its role in the development of HF has not yet been established [9–14].

Microalbuminuria is not only associated with high risk for CVD diseases: a cross-sectional study of 94 stable chronic heart failure patients found that 32% of them had microalbuminuria and no significant reduction of glomerular filtration rate [15]. It has also been associated with elevated levels of several inflammatory factors in the presence or absence of hypertension or diabetes. The association of inflammatory factors with microalbuminuria also was present regardless of the presence or absence of CVD [16].

Since microalbuminuria has been associated with several HF risk factors, the aim of this study was to asses the prevalence of microalbuminuria in systolic and diastolic chronic heart failure patients in relation to clinical, echocardiographic and body composition markers.

Methods

We carried out a cross-sectional study that included 72 patients with chronic heart failure (CHF). Among them, 42 had systolic HF and 30 had diastolic HF. They were consecutively included from January 2004 to April 2006. They were stable outpatients in New York Heart Association (NYHA) functional classes I–III, attending the Heart Failure Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán (INCMNSZ). Patients were recruited if they were ≥ 18 years old, with confirmed heart failure diagnosis (defined as systolic and/or diastolic dysfunction by an echocardiogram; and if showing signs and symptoms of heart failure). Subjects were excluded if they had proteinuria and end-stage renal disease, non-controlled disthyroidism, hepatic failure, valvular disease, chronic obstructive pulmonary disease, pericardial constriction, restrictive miocardiopathies, unstable ischemic heart disease (unstable angina and/or acute myocardial infarction), recent myocardial revascularization procedures (percutaneous transluminal coronary artery angioplasty and/or aortic-coronary bypass grafting in the last three months) or life threatening arrhythmias.

All patients were on standard HF therapy (diuretics, ACE inhibitors, angiotensin II antagonists, aldosterone receptor blockers, digitalis and beta-adreno-receptor blockers). No patients were undergoing insulin treatment. Diabetic patients were on oral hypoglicemiant drugs

Systolic ventricular dysfunction was diagnosed when the left ventricle ejection fraction (LVEF) was ≤ 45% and/or shortening fraction was ≤ 28%, and severe left ventricle wall movement abnormalities or dilatation of the left ventricle (end diastolic left ventricular diameter ≥ 55 mm) were present. Diastolic dysfunction was diagnosed when the LVEF was > 45%, and shortening fraction ≥ 28%, without severe segmental left ventricle wall movement abnormalities but there was an abnormal left ventricular filling and relaxation patterns (in cases without atrial fibrillation in which of them was not possible to get Doppler inflow mitral pattern) and evidence of left ventricular hypertrophy ((posterior wall + interventricular septum thickness)/2 ≥ 1.3 cm), posterior wall thickness ≥ 1.2 cm, and/or left atrial dilatation ≥ 4.5 cm were present. Diastolic and/or systolic dysfunction was diagnosed when one or more of the above points were observed in the echocardiogram [17, 18].

The study was approved by the local bioethical committee and all patients gave their informed consent.

Body composition evaluation

Anthropometry. Weight and height were measured in accordance to the reference manual of anthropometric standardization [19]: all subjects wore light clothing and were barefoot. Body mass index (BMI) was calculated by dividing total body weight [kg] by the squared height (in square metres).

Bioelectrical impedance analysis. Whole-body bioelectrical impedance was measured by using tetrapolar and multiple frequency equipment BodyStat QuadScan 4000 (BODYSTAT LTD; Isle of Man, British Isles). All measurements were made by the same investigator following the method reported in the literature [20]. The standard 50 kHz frequency was selected to obtain total body water (TBW), extra cellular water (ECW), resistance (R), reactance (Xc) and phase angle for all patients. The resistance and

reactance values were normalized by the height (H) of the subjects, thus expressing both R/H and Xc/H in Ohm/m and were plotted in the RXc graph (abscise R/H, ordinate Xc/H) [21].

Biochemical analysis

Twenty-four-hour urine samples were collected in standardized conditions for albumin quantification. The urinary albumin concentration was measured by ELISA technique, and urinary albumin excretion was calculated as urinary albumin concentration multiplied by diuresis. Serum creatinine was measured using standard techniques. Serum creatinine, age, weight and gender were used to calculate glomerular filtration rate using the Cockcroft--Gault equation (GFRc) [22].

Microalbuminuria was defined as 20 to 200 μg/min albumin excreted by urine per minute (15 to 150 μg/min in urine samples collected at night) [23].

Statistical analysis

Continuous variables are given as mean ± standard deviation (SD), and categorical variables are presented as absolute and relative frequency. Comparisons among groups were made with Pearson's χ^2 for categorical variables and unpaired t-test for continuous variables. A p value < 0.05 was considered statistically significant. Analyses were performed using a commercially available package (SPSS for Windows, version 10.0 1999 Chicago SPSS Inc.).

Results

Seventy-two patients with CHF were included, 64.3% were men, 63.9% had hypertension and 52.8% had diabetes mellitus type 2. Microalbuminuria was present in 30.6% of all patients, and in systolic HF patients the prevalence was significantly lower compared with diastolic HF patients (23.8 *vs*. 40%, respectively; p = 0.04).

Among systolic and diastolic HF patients, we did not find statistically significant differences in NYHA functional class. Nevertheless, those with diastolic HF had higher BMI (32.4 ± 8.6 *vs*. 24.9 ± ± 5.7; p 0.001), volume overload [body impendance vector analysis (BIVA) 75.0% *vs*. 80%; p = 0.013)] and oedema (58.3 *vs*. 30%; p = 0.001), and less albumin serum level (3.4 ± 0.1 *vs*. 3.5 ± 0.2; p = = 0.025) compared with systolic HF patients.

Table 1 shows the comparison between patients with and without microalbuminuria in systolic HF, and we can observed that those with microalbuminuria had a higher prevalence of type 2 diabetes and more volume overload, as well as increased frequency of high systolic pulmonary artery pressure, than patients without microalbuminuria. These patients also had lower phase angle and albumin levels, even after adjustments for diabetes presence. No significant association was found with NYHA functional classification or ejection fraction.

In the diastolic heart failure group, microalbuminuria was not associated with any variable (Table 2).

Fewer patients with systolic heart failure and microalbuminuria were receiving angiotensin receptor blockers than those without microalbuminuria; on the contrary, those with diastolic HF and microalbuminuria did not show such an apparent benefit that could elicit a sort of paradoxical effect of angiotensin receptor blockers (ARBs) (Table 3).

Table 4 shows the multivariate analysis, where only volume overload by BIVA was independently associated with the presence of microalbuminuria after adjustments for ejection fraction and diabetes.

Discussion

The main finding of this study was the relation between volume overload by BIVA and the presence of microalbuminuria in patients with systolic dysfunction, but not in those with diastolic dysfunction.

In our population, microalbuminuria was found in 30.6%; however, in those with diastolic heart failure it was 40.6%, even though most of them were receiving treatment with angiotensin-converting enzyme inhibitors (ACEI) or ARBs that, according to available information, reduce microalbuminuria [24]. Nevertheless, significantly fewer patients with systolic HF and microalbuminuria were receiving ARBs than those with diastolic HF and microalbuminuria, so the latter did not show such an apparent benefit derived from therapy. Such a finding could be related to a sort of paradoxical effect of ARBs.

The prevalence of microalbuminuria in hypertensive and diabetic patients (10–15% and 15–20%, respectively) is increased compared with the general population (6–8%) [25, 26]. However, in heart failure patients it was not recorded until the study of Van de Wal, who found it in one third of his patients. Such a prevalence is higher than in diabetic and hypertensive patients [15, 27, 28].

Several pathophysiological mechanisms have been involved. Microalbuminuria has traditionally been thought of as an expression of renal damage because of increased glomerular blood flow and increased hydraulic pressure that leads to hyperfiltration and excretion of protein [29]. However, in our cases we did not find significant differences

Table 1. Characteristics of patients with systolic dysfunction according to the presence or absence of microalbuminuria.

	Microalbuminuria (n = 10)	No microalbuminuria (n = 32)
Males	70.0% (7)	62.5% (20)
Age (years)	67.7 ± 15.23	62.16 ± 15.09
Body mass index [kg/m^2]	24.9 ± 5.7	26.9 ± 4.2
Weight [kg]	63.6 ± 20.1	66.8 ± 15.5
Height [cm]	160.3 ± 13.2	154.5 ± 16.0
Extra cellular water (%)	24.6 ± 0.8	23.6 ± 0.4
Patients with volume overload BIVA	80.0% (8)	21.9% (7)*
Phase angle (°)	4.7 ± 0.4	5.9 ± 0.2*
Albumin [g/dL]	3.5 ± 0.2	4.0 ± 0.7*
Total cholesterol [mg/dL]	157.0 ± 21.1	183.2 ± 7.7
LDL cholesterol [mg/dL]	92.0 ± 11.3	104.7 ± 24.8
HDL cholesterol [mg/dL]	41.5 ± 19.1	37.1 ± 6.5
Triacylglycerol [mg/dL]	112.5 ± 20.5	234.6 ± 157.6
Sodium [mmol/dL]	135.6 ± 2.8	137.9 ± 2.7
Glucose [mg/dL]	200.4 ± 109	110.1 ± 38
Serum creatinine [mg/dL]	1.18 ± 0.23	1.04 ± 0.29
GFRc [mL/min]	52.0 ± 17.85	72.0 ± 29.9
LVSF (%)	16.8 ± 3.8	24.9 ± 8.8
LVEF (%)	30.0 ± 9.6	40.0 ± 14.7
LVEDd [mm]	54.1 ± 10.7	52.1 ± 9.7
LVESd [mm]	43.3 ± 10.4	39.3 ± 11.5
IVS [mm]	11.3 ± 3.3	10.2 ± 1.9
PW [mm]	10.8 ± 3.0	9.3 ± 1.4
LAD [mm]	43.3 ± 8.1	44.5 ± 7.9
Ao D [mm]	33.2 ± 2.6	31.4 ± 6.2
RVDd [mm]	34.0 ± 9.7	9.3 ± 1.4
IVRTI (seg)	65.9 ± 16.8	115.9 ± 9.0*
PAP [mm Hg]	79.9 ± 5.5	49.0 ± 2.25*
NYHA I	60.0% (6)	68.7% (22)
NYHA II	30.0% (3)	25% (8)
NYHA III	10.0% (1)	6.3% (2)
Oedema	30.0% (3)	12.5% (4)
Ischemic etiology	70.0% (7)	65.6% (21)
Dyslipidemia	80.0% (8)	90.6% (29)
Hypertension	50.0% (5)	53.1% (17)
Diabetes mellitus	90.0% (9)	40.6% (13)*

BIVA — body impedance vector analysis; LVSF — left ventricular shortening fraction, LVEF — left ventricular ejection fraction; LVEDd — left ventricular end diastolic diameter; LVESd — left ventricular end systolic diameter; IVS — interventricular septum, PW — posterior wall; LAD — left atrium diameter; Ao D — aorta diameter; RVDd — right ventricular diastolic diameter; IVRTI — isovolumetric relaxation time index; PAP — pulmonary artery pressure; GFRc — glomerular filtration rate. Values are expressed as mean ± standard deviation or percentage when corresponding; *$p < 0.05$ compared to microalbuminuria

among patients with microalbuminuria in creatinine serum levels and glomerular filtration rates (GFRc), with respect to those without it.

Microalbuminuria has also been considered as a manifestation of generalized endothelial dysfunction, which results in leakage of albumin through the endothelium and glomerular basement membrane, probably in the context of the severe abnormality of endothelial function observed in HF. These conditions explain its higher prevalence in HF patients [15, 30, 31].

Other studies have demonstrated increased urinary albumin excretion, attributed in some way to cardiac systolic dysfunction, as a reflection of extensive endothelial and vascular changes [32, 33]. Van de Wal et al. [15], however, rejected this

Table 2. Characteristics of patients with diastolic dysfunction according to the presence or absence of microalbuminuria.

	Microalbuminuria (n = 12)	No microalbuminuria (n = 18)
Males	50.0% (6)	38.9% (7)
Age (years)	61.8 ± 15.4	64.9 ± 18.8
Body mass index [kg/m^2]	32.4 ± 8.6	32.3 ± 8.3
Weight [kg]	82.8 ± 25.4	77.6 ± 22.7
Height (cm)	159.6 ± 12.4	154.9 ± 9.1
Extra cellular water (%)	22.5 ± 1.5	22.3 ± 3.7
Patients with volume overload BIVA	75.0% (9)	55.6% (10)
Phase angle (°)	5.7 ± 1.9	5.04 ± 1.1
Albumin [g/dL]	3.4 ± 0.1	3.8 ± 0.2
Total cholesterol [mg/dL]	163.8 ± 25.0	185.9 ± 36.0
LDL cholesterol [mg/dL]	92.1 ± 13.0	130.5 ± 10.6
HDL cholesterol [mg/dL]	34.0 ± 10.1	41.7 ± 6.6
Triacylglycerol [mg/dL]	158.4 ± 20.5	131.3 ± 46.2
Sodium [mmol/dL]	138.8 ± 2.1	136.9 ± 3.6
Glucose [mg/dL]	136.6 ± 35.7	117.1 ± 55.0
Serum creatinine [mg/dL]	1.07 ± 0.33	0.99 ± 0.29
GFRc [mL/min]	66.09 ± 17.33	78.75 ± 31.8
LVSF (%)	36.0 ± 12.7	36.2 ± 7.9
LVEF (%)	54.5 ± 16.0	58.5 ± 8.8
LVEDd [mm]	48.9 ± 8.7	44.8 ± 6.8
LVESd [mm]	31.4 ± 11.7	28.4 ± 6.8
IVS [mm]	14.4 ± 1.6	13.4 ± 2.6
PW [mm]	12.3 ± 1.3	11.9 ± 2.1
LAD [mm]	44.3 ± 6.6	45.9 ± 4.6
Ao D [mm]	31.4 ± 3.7	29.2 ± 3.0
RVDd [mm]	27.0 ± 0.6	58.5 ± 0.6
IVRTI [seg]	97.5 ± 10.4	109.4 ± 21.0
PAP [mm Hg]	59.7 ± 18.1	56.6 ± 19.0
NYHA I	33.3% (4)	66.7% (12)
NYHA II	58.3% (7)	16.7% (3)
NYHA III	8.3% (1)	16.7% (3)
Oedema	58.3% (7)	50.0% (9)
Ischemic etiology	41.7% (5)	33.3% (6)
Dyslipidemia	58.3% (7)	100% (18)*
Hypertension	83.3% (10)	77.8% (14)
Diabetes mellitus	75.0% (9)	38.9% (7)

BIVA — body impedance vector analysis; LVSF — left ventricular shortening fraction; LVEF — left ventricular ejection fraction; LVEDd — left ventricular end diastolic diameter; LVESd — left ventricular end systolic diameter; IVS — interventricular septum; PW — posterior wall; LAD — left atrium diameter; Ao D — aorta diameter; RVDd — right ventricular diastolic diameter; IVRTI — isovolumetric relaxation time index; PAP — pulmonary artery pressure; GFRc — glomerular filtration rate. Values are expressed as mean ± standard deviation or percentage when corresponding; *$p < 0.05$ compared to microalbuminuria

explanation because their patients had no differences in left ventricular ejection fractions or in other markers of systolic function.

In our cases, the prevalence of microalbuminuria has also shown differences regarding the type of HF; it was more frequent in those with diastolic HF. This finding is in agreement with Van de Wal et al. [15] because in those cases with diastolic dysfunction and preserved systolic function, microalbuminuria was present, although this group received ACEI or ARB. However, in those patients with systolic heart failure, microalbuminuria was associated with more volume overload and lesser phase angle in the electrical bioimpedance study as an expression of increased total extracellular water, as well as severe pulmonary

Table 3. Medication in patients with systolic and diastolic dysfunction according to the presence or absence of microalbuminuria.

Drug	Microalbuminuria	No microalbuminuria
Systolic heart failure patients	**(n = 10)**	**(n = 32)**
Beta-adrenoreceptor antagonist	90.0% (9)	90.6% (29)
ACE inhibitor	90.0% (9)	65.6% (21)
Angiotensin receptor blockers	10.0% (1)	53.1% (17)*
Thiazide diuretics	50.0% (5)	53.1% (17)
Loop diuretics	40.0% (4)	12.5% (4)
Digitalis	50.0% (5)	53.1% (17)
Oral nitrate	10.0% (1)	34.4% (11)
Aldosterone receptor antagonist	70.0% (7)	43.8% (14)
Diastolic heart failure patients	**(n = 12)**	**(n = 18)**
Beta-adrenoreceptor antagonist	66.7% (8)	55.6% (10)
ACE inhibitor	8.3% (1)	16.7% (3)
Angiotensin receptor blockers	100% (12)	72.2% (13)*
Thiazide diuretic	75.0% (9)	72.2% (13)
Loop diuretic	16.7% (2)	5.6% (1)
Digitalis	25.0% (3)	5.6% (1)
Oral nitrate	25.0% (3)	27.8% (5)
Aldosterone receptor antagonist	83.3% (10)	44.4% (8)

*$p < 0.05$ compared to microalbuminuria

Table 4. Logistic regression model for microalbuminuria in heart-failure patients.

Variable	β	Odds ratio	P value (Wald test)	95% CI
Diabetes (yes/no)	0.77	2.16	0.20	0.67–6.9
Ejection fraction (%)	–0.015	0.98	0.39	0.95–1.02
Volume overload by BIVA (yes/no)	1.45	4.28	0.02	1.28–14.37
Constant	–1.37			

BIVA — body impedance vector analysis; CI — confidence interval

hypertension compared with patients without albuminuria, even if all these patients also received ACEI. Therefore, it is possible that in these patients, the renin angiotensine system could be more active [15].

In another way, the fact that systolic HF patients were associated with worse parameters of BIVA, higher PAP and lower BMI, allows us to speculate whether these characteristics indicate the early stages of cardiac cachexia , which, in other papers, have been found to be related to elevated levels of TNF-α [34]. However, in our cases it was not investigated.

Nonetheless, diastolic and systolic HF patients have no differences in NYHA functional class. However, in systolic HF microalbuminuria presence could be an easily available parameter of more severe cardiovascular damage and advanced stage of cardiac dysfunction.

Limitations of the study

Being an observational study, no determination of neurohormonal or NT-proBNP concentration was performed. In addition, we could not infer the prognostic impact of microalbuminuria, as is suggested by its association with other bad prognosis factors. TNF-α levels were not determined and their potential roll in the cardiovascular damage and microalbuminuria presence remain unknown.

Conclusions

In summary, microalbuminuria was more frequent in diastolic than systolic HF patients. In systolic HF patients, microalbuminuria was associated with factors known to be markers of worse prognosis. More information is necessary before drawing any conclusions regarding the presence

of microalbuminuria as a prognostic risk marker, considering that in our cases it was associated with higher levels of pulmonary pressure, lesser serum albumin and more volume overload — all of them, known markers for worse prognosis.

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