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Cystatin C, CRP, Log TG/HDLc and Metabolic Syndrome are Associated with Microalbuminuria in Hypertension

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Abstract

Background: In patients with systemic hypertension, microalbuminuria is a marker of endothelial damage and is associated with an increased risk for cardiovascular disease.

Objective: To determine the factors that may lead to the occurrence of microalbuminuria in hypertensive patients with serum creatinine lower than 1.5 mg/dL.

Methods: This cross-sectional study included 133 Brazilians with essential hypertension followed up at a hypertension outpatient clinic. Those with serum creatinine higher than 1.5 mg/dL, as well as those with diabetes mellitus, were excluded. Systolic and diastolic blood pressures were measured, and body mass index (BMI) and GFR estimated by using the CKD-EPI formula were calculated. The serum levels of the following were assessed: CysC, creatinine, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, C-reactive protein (CRP) and fasting glucose. Microalbuminuria was determined in 24-hour urine. Hypertensive patients were classified according to the presence of one or more criteria for metabolic syndrome.

Results: In a multiple regression analysis, the serum levels of CysC and CRP, the atherogenic index log TG/HDLc and the presence of three or more criteria for metabolic syndrome were positively correlated with microalbuminuria (r^2: 0.277, $p < 0.05$).

Conclusion: CysC, CRP, log TG/HDLc, and the presence of three or more criteria for metabolic syndrome, regardless of serum creatinine, were associated with microalbuminuria, an early marker of kidney damage and cardiovascular risk in patients with essential hypertension. (Arq Bras Cardiol. 2014; 102(1):54-59)

Keywords: Metabolic Syndrome X; Hypertension; Albuminuria; Kidney Diseases.

Introduction

Stratification of cardiovascular risk and early detection of end-organ damage are essential to guide the treatment of hypertensive individuals. Renal involvement in hypertensive disease is an independent and untraditional risk factor for adverse cardiovascular events, and its presence may result in higher morbidity and mortality.

Increased levels of microalbuminuria are an early indicator of renal injury. In diabetics, microalbuminuria is used in the screening of early diabetic nephropathy; however, in hypertensive subjects, its use is not routine in clinical practice, although it is recommended by some guidelines[1]. Microalbuminuria predicts proteinuria and cardiovascular mortality, but the collection procedure can be complicated for some patients. Range values of microalbuminuria can also be influenced by external factors such as diet, posture, and acute illness[2].

Cystatin C has been suggested as a simple and early marker of renal damage. It is a 13 kD basic protein, member of the cystatin superfamily of endogenous cysteine proteinase inhibitors, produced by all nucleated cells at a constant rate[3]. Previous research has suggested that CysC is an alternative to creatinine to estimate glomerular filtration rate, especially to detect early-stage renal dysfunction[4-7]. Recent reports suggest that CysC can predict the risk of death and cardiovascular events independently of renal function[8-10].

CRP is a classical cardiovascular risk factor and is associated with microalbuminuria in hypertensive subjects. This suggests the involvement of inflammation and endothelial dysfunction in vascular and kidney damage[11,12].

The atherogenic index of plasma (logarithm of the ratio of triglycerides to HDL cholesterol - Log TG/HDLc)

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ratio is highly associated with phenotype B of LDL cholesterol, elevated apoprotein B and small dense LDL particles. It is also associated with the occurrence of cardiovascular events[13,14]. It could be a useful index for identifying hypertensive subjects at risk for dyslipidemia and metabolic syndrome.

This is a cross-sectional survey of Brazilian essential hypertensive subjects with serum creatinine lower than 1.5 mg/dL. This study aims at evaluating the possible correlations of serum CysC, creatinine, CRP, log TG/HDLc, BMI, and the presence of three or more criteria of metabolic syndrome with microalbuminuria, an early marker of renal damage and risk factor for hypertensive subjects.

Methods

Adult patients with essential hypertension participated in this study. They were recruited at the hypertension ambulatory of the University of Brasilia Hospital from May 2008 to September 2009. Patients included in the study presented with Stage 1 or 2 hypertension and were referred to a hypertension clinic to confirm the diagnosis. After confirmation, all hypertensive subjects were treated according to the V Brazilian guidelines[15]. Patients with diabetes mellitus, smokers, with secondary hypertension, and with creatinine ≥ 1.5 mg/dL were excluded from the study. Of the162 individuals invited to participate in the study, 16 subjects were excluded because they showed serum creatinine higher than 1.5 mg/dL. Seven of them had fasting glycemia higher than 100 mg/dL and were also excluded. Six individuals did not return for clinical examination and did not complete the clinical investigation. Therefore, one hundred and thirty-three patients, fifty-six male, were included in this study. The patients were interviewed and clinically examined. Blood pressure was measured in the sitting position using a mercury sphygmomanometer according to the V Brazilian Guidelines[15]. Weight (kg) and height (m) were measured with an automated scale (Filizola®) and waist circumference (cm) was obtained with measuring tape. Body Mass Index (BMI) was calculated. Body surface (m^2) was calculated according to the DuBois and DuBois method[16]. Subjects were classified according the presence or absence of three or more criteria of metabolic syndrome as defined by Brazilian recommendations[17].

Individual blood samples were collected in the morning after an overnight fasting period of at least 12 hours. Measurements of creatinine, glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, and triglyceride were done using an automatic analyzer (Architect c 800). CysC was measured using a BN II Nephelometer (Dade Behring Inc.) by a particle-enhanced immunonephelometric assay (N latex Cystatin C). CRP was measured by means of a high-sensitivity assay.

Microalbuminuria was determined through immunoturbidimetry (Malb Urin-Pack Bayer®). Log TG/HDL) was calculated[18]. Elevated serum glucose was defined as fasting glucose ≥ 100 mg/dL and high HDL-C when serum concentration was > 40 mg/dL in men and > 50 mg/dL in women.

Hypertriglyceridemia was characterized as serum TG concentration ≥ 150 mg/dL[17].

To estimate GFR the CKD-EPI equation was used[19]. The study protocol was approved by the University Ethics Committee, and all patients gave their written informed consent to participate. The study followed the Declaration of Helsinky.

Statistical Analysis

Values are expressed in medians (interquartile range). The relationship between urinary albumin excretion (microalbuminuria) and clinical and laboratory variables (age, gender, BMI, CRP, CysC, logTG/HDLc, presence or absence of three or more criteria of metabolic syndrome, and creatinine) was studied. Most variables did not follow a Gaussian distribution, and a nonparametric test of Spearman rank correlation coefficient (r_s) was used. Multiple linear regression analysis was used to evaluate which clinical and laboratory variables had an independent effect on microalbuminuria. Log microalbuminuria was the dependent outcome, and age, gender, BMI, CRP, CysC, log TG/HDLc, Metabolic Syndrome, EPI-CKD and creatinine were included as either continuous or dichotomous data. Residuals were normally distributed when the dependent outcome - urinary albumin concentration - was $\log_e$ transformed. Inflation was used to verify multicollinearity among variables. EPI-CKD presented multicollinearity with age and CysC and was excluded from the model. Manual backward elimination was performed, and variables that were not significant ($p \geq 0.05$) were excluded from the analysis.

The software SAS (version 9.2) was used for statistical analysis. Values of $p < 0.05$ were considered statistically significant.

Results

The demographic and laboratory characteristics of the hypertensive subjects studied are presented in Table 1.

According to the classification of hypertension, 18 patients had stage 2 and 115 had stage 1 hypertension. Ninety patients had high blood triglycerides (> 150 mg / dL) and 83 subjects had low HDLc (<40 mg/dL for men or < 50 mg/dL for women). Fifty subjects presented three or more criteria for metabolic syndrome. Thirty-one hypertensive subjects had microalbuminuria higher than 30 mg/day (23.3%). Values of systolic and diastolic blood pressure were not associated with microalbuminúria ($p>0.05$), but microalbuminuria was positively correlated with CRP ($r_s=0.293$, $p=0.0008$), LogTG/HDLc ($r_s = 0.343$, $p = 0.0001$), and CysC (rs = 0.191 e $p = 0.036$), but not with creatinine ($r_s = 0.141$, $p = 0.11$), age ($r_s = 0.172$, $p = 0.052$) or BMI ($r_s = 0.037$, $p = 0.671$). (Table 2)

The dependent variable microalbuminuria may be predicted by the combination of the following predictor variables: CysC, CRP, log TG/HDLc, and three or more components of metabolic syndrome after adjustment for gender and age (Table 3).

Table 1 - Demographic and Biochemical Data of Hypertensive Subjects (n = 133)

Variables	Median (interquartile range)
Age (years)	53 (59.25 – 45.75)
Gender (M / F)	56/77
BMI (kg/m^2)	28.08 (31.83 – 25.77)
Waist circumference (cm)	96.50 (102.00 – 88.50)
SBP (mmHg)	140 (150 - 130)
DBP (mmHg)	90 (97 - 80)
Cystatin c (mg/L)	0.89 (1.20 – 0.75)
Creatinine (mg/dL)	0.80 (1.00 – 0.70)
CKD-EPI (ml/min/1,73m^2)	88.00(102.25 – 73.75)
TC (mg/dL)	209.00 (234.00 – 186.00)
TG (mg/dL)	178.00 (251.25 – 135.00)
HDLc(mg/dL)	42.00(48.00-36.00)
Malb(mg/24h)	8.60(32.45-4.00)
Metabolic Syndrome (Absence/Presence)	83/50
CRP (mg/dL)	0.39(0.70-0.30)

BMI: Body Mass Index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration - Estimated Glomerular Filtration Rate-MDRD; TC: Total Cholesterol; TG: Triglycerides; HDLc: High Density Lipoprotein Cholesterol; Malb: Microalbuminuria; CRP: C-Reactive Protein.

Discussion

Hypertension has high prevalence worldwide, affecting about one billion people. It is believed that identification and treatment of risk factors associated with cardiovascular diseases and early detection of end-organ damage directly affect the prognosis[20]. Kidney injury can be detected by decreased GFR and/or proteinuria. Previous studies show that CysC is capable of detecting mild and moderate kidney damage[4-7], and research has been conducted to evaluate whether CysC can also be considered a cardiovascular risk factor independently of renal function[8-10].

We conducted a cross-sectional study of 133 essential hypertensive patients to evaluate whether CRP, log TG / HDLc, the criteria for metabolic syndrome, and CysC are correlated with microalbuminuria, an early expression of kidney damage. As the mechanism of kidney damage differs among patients with hypertension and diabetes, only patients with essential hypertension but without diabetes mellitus were studied. Patients with serum creatinine equal to or higher than 1.5 mg/dL were excluded from the study since our objective was to evaluate early kidney damage.

All patients included in the study presented creatinine within reference limits (below 1.5 mg/dL), but sixteen patients (12.0%) had CKD-EPI < 60ml/min/1.73m^2 and forty- three patients (36.7%) presented CysC higher than 0.95mg/L. This shows that measurement of serum creatinine alone was not efficient to detect all cases of renal dysfunction.

Table 2 - Association of microalbuminuria with clinical and laboratory variables in hypertensive subjects using Spearman Rank Correlation Analysis

Variables	Spearman Coefficient (r_s)	p value
Age	-0.172	0.052
Creatinine	0.141	0.110
BMI	0.037	0.671
Cystatin C	0.191	0.036
CRP	0.293	0.0008
Log TG/HDLc	0.343	0.0001

BMI: Body Mass Index; CRP: C-reactive Protein; Log TG/HDL: Logaritm of the relation Triglycerides/High Density cholesterol.

Table 3 - Multiple regression analysis of the association of microalbuminuria with cystatin C, CRP, log TG/HDLc, Metabolic Syndrome, gender, and age in hypertensive subjects

Variables	Non-standardized Coefficients*		Standardized Coefficients*		
	B	Std Error	Beta	T	p value
(Constant)	1.130	0.900		1.26	0.210
Cystatin C	0.656	0.309	0.176	2.12	0.036
CRP	0.511	0.246	0.175	2.07	0.040
Log TG/HDLc	0.985	0.473	0.173	2.08	0.039
Female	-0.183	0.249	-0.060	-0.74	0.463
Age	-0.011	0.014	-0.070	-0.84	0.405
Presence MS	1.056	0.252	0.341	4.19	< 0.001

** Dependent variable: log microalbuminuria Statistic F = 7.22, p < 0.001 and R Square = 0.277; CRP: C-Reactive Protein; Log TG/HDL: Logarithm of the relation Triglycerides/High Density cholesterol; MS: Metabolic Syndrome.*

In subjects with hypertension but without cardiovascular complications, prevalence of moderate-to-severe renal dysfunction is strongly influenced by the method used to estimate glomerular filtration rate[21]. Research studies suggest that CysC is better than creatinine to diagnose mild and moderate chronic kidney injury[4-7,22,23]. In addition, previous meta-analysis have suggested that CysC has greater correlation with GFR than creatinine[24]. Furthermore, CysC may predict adverse cardiovascular events independently of its role as a marker of renal function.

Microalbuminuria has been considered a marker of endothelial damage and is associated with higher prevalence of diabetes, hypertension, metabolic syndrome, renal dysfunction, and with an increased risk for cardiovascular diseases[25-27]. In the present study there was a positive correlation between CRP, CysC, log TG/HDLc, and three or more components of metabolic syndrome with microalbuminuria even after adjustment for sex and age. There was no association between creatinine and microalbuminuria. These results indicate that CRP, CysC, log TG/HDLc and the presence of components of metabolic syndrome partially explain microalbuminuria and are related to kidney damage in patients with essential hypertension with serum creatinine lower than 1.5 mg/dL. Previous relevant population studies including a large sample have shown that central obesity is an independent risk factor for albuminuria and should be considered in the context of metabolic or insulin resistance syndrome[28-30]. We analyzed the ratio logTG/HDL, which is highly associated with phenotype B of LDL cholesterol, elevated apoprotein B, small dense LDL particles, and cardiovascular events[13,14,31]. The expression logTG/HDL is called "plasma's atherogenic index" by many authors and is associated with hyperinsulinemia and metabolic syndrome. The index was correlated with microalbuminuria. Considering the association observed between the components of metabolic syndrome and microalbuminuria, the two are complementary because both point to the influence of metabolic syndrome on the onset of microalbuminuria in hypertensive patients without diabetes mellitus. Levels of insulin were not measured, but 50 subjects in our sample of hypertensive individuals met at least 3 criteria for metabolic syndrome, except for hyperglycemia, even though abnormal fasting glucose is one of the MS criteria.

High triglycerides and low HDLc have been associated with metabolic syndrome, and hyperinsulinemia may contribute to dyslipidemia by increasing the synthesis of VLDL by the liver [32], resulting in increased concentrations of triglycerides. Low concentrations of HDL may indicate an increased rate of apoAI catabolism seen in subjects with high levels of insulin[33]. Therefore, microalbuminuria has been associated with metabolic syndrome, and the mechanisms that might associate hyperinsulinemia with higher urinary albumin excretion are increased pressure in glomerular capillary, enhanced permeability of the filtration barrier due to advanced glycosylation end products, and endothelial dysfunction[34].

On the other hand, our results showed that CysC was highly associated with microalbuminuria.

Cystatin C has been previously described as being associated with urinary protein excretion, left ventricular mass index, and intimae media thickness. It might become a sensitive marker of early renal dysfunction[5,35].

Cystatin C should be a predictor of microalbuminuria in the early stages of hypertension and, thus, predict cardiovascular events beyond its use as a marker of renal function[36]. In addition, CysC showed a positive correlation with the number of metabolic syndrome criteria in patients with dyslipidemia, regardless of creatinine levels and Modification of Diet in Renal Disease (MDRD)[37]. Moreover, Vigil et al[38] showed that CysC was associated with metabolic syndrome in a hypertensive population and concluded that measurement of CysC concentration in hypertensive patients may be useful for evaluating their cardiovascular risk profile.

In the present study, microalbuminuria was also positively correlated with CRP. CRP is a marker of systemic low-grade inflammation and is frequently high in the general and essential hypertension population. It may also predict cardiovascular risk[11,12,39,40].

Conclusion

We noticed that the independent variables CRP, CysC, log TG/HDLc, and the number of metabolic syndrome criteria, but not creatinine, are correlated with microalbuminuria in patients with essential hypertension. Therefore, CysC, together with the more traditional risk markers, seems to detect early kidney damage better than creatinine and appears to be a marker of cardiovascular risk and early renal dysfunction in Brazilian patients with essential hypertension. The limitations of this study are its design (cross-sectional), sample size (small) and the inclusion of only one hospital outpatient clinic. However, the results of this study indicate that CysC is an early marker of renal dysfunction in hypertensive individuals due to the presence of microalbuminuria. Nevertheless, routine measurement of CysC in hypertensive individuals is still rare due to its high cost. Therefore, further prospective research studies are necessary to better evaluate the association between CysC and cardiovascular events in this highly miscegenated population.

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Author contributions

Conception and design of the research: Moura RSSS, Vasconcelos DF, Moura FJD, Rosa TT, Veiga JPR; Acquisition of data: Moura RSSS; Analysis and interpretation of the data: Moura RSSS, Vasconcelos DF, Freitas E, Moura FJD, Rosa TT, Veiga JPR; Statistical analysis: Freitas E; Writing of the manuscript: Moura RSSS, Vasconcelos DF, Moura FJD, Rosa TT, Veiga JPR; Critical revision of the manuscript for intellectual content: Moura RSSS, Vasconcelos DF, Freitas E, Moura FJD, Rosa TT, Veiga JPR.

Potential Conflict of Interest

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

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Study Association

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