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Left Ventricular Hypertrophy and Microalbuminuria in Patients With Essential Hypertension

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Introduction. Microalbuminuria and left ventricular hypertrophy (LVH) have both been shown to predict increased cardiovascular morbidity and mortality, especially in diabetic patients. The present study investigated the relationship between microalbuminuria and LVH in patients with essential hypertension.

Materials and Methods. After a primary workup to rule out secondary hypertension, 110 essential hypertensive patients with LVH (mean age, 62.97 ± 11.02 years) and 10 essential hypertensive patients without LVH (mean age, 65.13 ± 10.15 years) were enrolled in this case-control study. Spot urine sample was collected for the assessment of microalbuminuria and creatinine concentrations in the two groups. Smoking status, blood pressure, and serum levels of total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and creatinine were evaluated.

Results. Patients with LVH had significantly higher microalbuminuria level compared with those without LVH (mean urine albumin-creatinine ratio, 54.4 ± 39.48 µg/mg versus 33.56 ± 21.73 µg/mg; $P < .001$). Multivariable regression analysis showed that the patients with a higher urine albumin-creatinine ratio were more likely to have LVH (OR, 1.028; 95% CI, 1.015 to 1.041; $P < .001$). Other significant predictive factors for LVH in the model were diastolic blood pressure, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and serum creatinine.

Conclusions. Left ventricular hypertrophy is associated with microalbuminuria in patients with essential hypertension. These data are strengthening the role of microalbuminuria as an indicator of high cardiovascular risk.

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INTRODUCTION

Microalbuminuria is often found in essential hypertension and represents a sign of renal and cardiovascular damage.[1] Defined as elevated urinary albumin excretion below the level of proteinuria,[2,3] microalbuminuria is a relatively common condition in patients with primary hypertension and has proved to be an excellent predictor of cardiovascular morbidity and mortality in several prospective studies.[4-6] It has been proposed that microalbuminuria is a reflection of early kidney dysfunction and a marker of asymptomatic preclinical disease which precedes and predicts the occurrence of major morbid events.[7]

Increased left ventricular mass or left ventricular hypertrophy (LVH) is a frequent complication of hypertension. This condition is another manifestation of preclinical disease and has long been known as a powerful independent risk factor for all of the cardiovascular complications

of hypertension and also has been associated with increased morbidity and mortality.[8-14] Similarly, urine albumin levels are predictive for cardiovascular events in hypertensive patients.[10]

The present study aimed to investigate the relationship between microalbuminuria and LVH in patients with essential hypertension.

MATERIALS AND METHODS

Study Population

This case-control study was performed on patients with essential hypertension who were referred to Razi Hospital in Rasht, north of Iran, from February 2009 to March 2010. To rule out secondary hypertension, a clinical workup including clinical history, physical examination, and laboratory evaluation was performed. Based on echocardiographic findings, 110 essential hypertensive patients with LVH and 110 age- and sex-matched essential hypertensive patients without LVH were enrolled in this study. Demographic information including age, sex, smoking habits, and a family history of hypertension was recorded for all of the participants.

Inclusion Criteria

Participants had a systolic blood pressure (SBP) of 140 mm Hg and higher, a diastolic blood pressure (DBP) of 90 mm Hg and higher, or both measured at the clinic on 3 visits at 1-week intervals. Only those with echocardiographic recordings of a good quality were included. All participants provided informed consent for enrollment.

Exclusion criteria were previous treatment for hypertension (70%) or withdrawal from antihypertensive drugs at least 4 weeks before the study and clinical or laboratory evidence of heart failure, coronary heart disease, previous stroke, valvular defects, secondary causes of hypertension, and important concomitant diseases. Therefore patients with the following were excluded: a neoplastic, inflammatory, hepatic, or kidney disease (including a history of proteinuria, hematuria, serum creatinine greater than 1.3 mg/dL in men and 1.2 mg/dL in women, and a positive urine culture); a positive history or clinical signs of ischemic heart disease; diabetes mellitus; severe obesity (defined as a body mass index greater than 30 kg/m^2); febrile condition; anemia; disabling diseases such as dementia; and inability to cooperate.

Blood pressure was measured by auscultation with a mercury sphygmomanometer in the right arm of the patients in the sitting position, with an appropriate-sized cuff and the arm positioned at the heart level. Three measurements were made, each separated from the next by at least 5 minutes. The 1st and 5th Korotkoff sounds were used to determine SBP and DBP, respectively. The average of the three determinations for SBP and DBP was used in the analysis. Hypertension was defined as an SBP of 140 mm Hg and higher or a DBP of 90 mm Hg and higher.

The first morning spot urine samples were used for determination of microalbuminuria and creatinine concentrations and the measurements were repeated after 1 month if the albumin-creatinine ratio (ACR) was greater than 30 µg/mg to 1000 µg /mg. Microalbuminuria was defined as an ACR more between 30 µg /mg and 300 µg/mg.[15] Urine concentrations of albumin were measured by immunoturbidimetric method. [1]

Fasting blood samples were drawn for serum creatinine, total cholesterol, high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and C-reactive protein levels.

Echocardiography

All echocardiographic studies were performed using a Mylab 50 ultrasonography machine (Esaote, Genova, Italy). Echocardiographies were obtained at rest with the patient at the supine left lateral position, using standard parasternal and apical views. The overall monodimensional left ventricular measurements and the 2-dimensional (apical 4- and 2-chamber) views were obtained according to the recommendations of the American Society of Echocardiography.[16,17] All tracings were obtained and read by one observer blinded to the clinical characteristics of the patients under observation. The left ventricular mass was derived in grams using the formula described by Devereux and coworkers[21]:

Left ventricular mass = $0.80 \times 1.04 [(VST_d \times LVID_d \times PWT_d)^3 - (LVID_d)^3] + 0.6$

where VST is ventricular septal thickness, LVID is left ventricular internal dimension, and PWT is posterior wall thickness. We also tested the prognostic value of LVH, defined as a binary variable, after correction for body surface area (a left ventricular mass ≥ 125 g/m^2 in men and ≥ 110 g/m^2 in women).[22] Body surface area (in square meters) was estimated according to Briars equation.[23]

Statistical Analyses

Analyses were performed using the SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA). Differences between continuous variables were tested by the Student *t* test or the Mann-Whitney *U* test when appropriate. Differences in proportions were tested using the chi-square test or the Fisher exact test. Logistic regression analysis was performed to determine the adjusted odds ratio (OR) for independent predictors of LVH. Variables with a *P* value less than .01 in the univariable analysis entered in the multivariable regression analysis except for the left ventricular mass and left ventricular internal dimension, because of the high correlation with the dependent variable. Data are expressed as OR and 95% confidence interval (CI). A 2-tailed *P* value less than .05 was considered as the level of significance.

RESULTS

Table 1 shows the demographic, clinical, and echocardiographic characteristic of the patients with and without LVH. The mean age of patients in the LVH and non-LVH groups was 42.97 ± 11.02 years and 45.13 ± 10.15 years, respectively. A total of 110 patients were enrolled in each group. Male-female ratio in the LVH group was 1:1.56 % and in patients without LVH was 1:1.17. As compared with those without LVH, the patients with LVH had significantly increased DBP (107.64 ± 97.45 mm Hg versus 92.31 ± 10.68 mm Hg; $P < .001$), total serum cholesterol level (198.23 ± 38.66 mg/dl versus 180.55 ± 53.83 mg/dL; $P < .001$), plasma LDLC level (121.05 ± 35.35 mg/dL versus 108.65 ± 23.41 mg/dL; $P = .008$), and serum creatinine level (0.82 ± 0.22 mg/dL versus 0.75 ± 0.2 mg/dL; $P = .02$). The mean HDLC level was significantly lower in patients with LVH than patients without LVH (31.69 ± 88.57 mg/dL versus 23.29 ± 59.27 mg/dL; $P < .001$). Smoking was more common in patients with LVH (41.8% versus 27.3%, $P = .02$).

The overall prevalence of microalbuminuria in patients with LVH and without LVH was 59.1% and 33.6%, respectively. Patients with LVH had significantly higher microalbuminuria level compared with those without LVH (ACR, 54.4 ± 39.48 µg/mg versus 33.56 ± 21.73 µg/mg; $P < .001$). A multivariable logistic regression model was built to assess the relationship between LVH and urine albumin level, controlled for smoking status as a categorical variable and serum creatinine, total serum cholesterol, DBP, LDLC, and HDLC as continuous independent variables. The analysis

Table 1. Comparison of Demographic, Clinical and Echocardiographic Characteristics of Hypertensive Patients With and Without Left Ventricular Hypertrophy

Variable	Left Ventricular Hypertrophy		*P*
	No	Yes	
Age, y	65.13 ± 10.15	62.97 ± 11.02	.13
Sex			
Male	51 (46.4)	43 (39.1)	
Female	59 (53.6)	67 (60.9)	.17
Smoking	30 (27.3)	46 (41.8)	.02
Family History of essential hypertension	45 (40.9)	47 (42.7)	.45
Body mass index, kg/m^2	29.63 ± 4.66	29.02 ± 4.27	.66
Systolic blood pressure, mm Hg	174.00 ± 16.02	189.97 ± 156.10	.75
Diastolic blood pressure, mm Hg	92.31 ± 10.68	107.64 ± 97.45	< .001
Serum triglyceride, mg/dL	185.35 ± 61.28	197.95 ± 84.94	.49
Serum cholesterol, mg/dL	180.55 ± 53.83	198.23 ± 38.66	< .001
High-density lipoprotein, mg/dL	52.20 ± 7.28	47.60 ± 9.53	< .001
Low-density lipoprotein, mg/dL	108.65 ± 23.41	121.05 ± 35.35	.008
Fasting blood glucose, mg/dL	94.5 ± 6.67	96.07 ± 8.36	.13
Serum creatinine (mg/dL	0.75 ± 0.20	0.82 ± 0.22	.02
Albumin-creatinine ratio, µg/mg	33.56 ± 21.73	54.4 ± 39.48	< .001
Microalbuminuria	37 (33.6)	65 (59.1)	< .001
Ejection fraction, %	60.72 ± 6.92	59.99 ± 7.45	.45
Left ventricular mass, g	232.86 ± 59.27	316.78 ± 88.57	< .001
Left ventricular mass index, g/m^2	100.62 ± 15.93	188.99 ± 44.88	< .001

Table 2. Multivariable Logistic Regression Analysis for Prediction of Left Ventricular Hypertrophy

Variable	Odds Ratio	95 % Confidence Interval	*P*
Smoking	1.517	0.780 to 2.949	.22
Diastolic blood pressure, mm Hg	1.049	1.020 to 1.079	< .001
Serum cholesterol, mg/dL	1.002	0.995 to 1.009	.58
High-density lipoprotein, mg/dL	0.934	0.896 to 0.974	< .001
Low-density lipoprotein, mg/dL	1.016	1.004 to 1.027	.008
Serum creatinine, mg/dL	5.221	1.124 to 24.25	.04
Albumin-creatinine ratio, µg/mg	1.028	1.015 to 1.041	< .001

showed that the patients with a higher urine ACR were more likely to have LVH (OR, 1.028; 95% CI, 1.015 to 1.041; $P < .001$). Other predictive factors for LVH were DBP, LDLC, HDLC, and serum creatinine (Table 2).

DISCUSSION

In this study we have demonstrated that microalbuminuria levels were higher in patients with LVH compared to patients without LVH. The study also documents that the microalbuminuria levels were increased in patients with hypertension and correlated with LVH. Moreover, in our multivariate analyses, microalbuminuria displayed a stronger association with LVH. These associations confirm the role of microalbuminuria as a marker of increased cardiovascular risk and subclinical organ damage. This may help to explain the high incidence of morbid events reported in hypertensive patients with increased urinary albumin excretion.

Microalbuminuria was previously shown to be a concomitant factor of several metabolic and nonmetabolic cardiovascular risk factors in patients with essential hypertension.[6] Tsioufis and colleagues showed patients with microalbuminuria had significantly greater left ventricular internal dimension (by 21 g/m^2) and relative wall thickness (by 0.05 cm) compared to patients without microalbuminuria ($P < .001$).[10] In a more recent study, Ratto and colleagues showed that the deviation of left ventricular mass from the predicted value was positively related to albuminuria ($P < .001$). Patients with microalbuminuria showed a higher prevalence of inappropriate LVH compared to other left ventricular geometries (appropriate LVH and absence of LVH; $P < .001$).[5] Wachtell and associates found microalbuminuria in 1844 of 8029patients (23%) with stage 2-3 hypertension. In patients with moderately severe hypertension, LVH on two consecutive electrocardiographies was associated with increased prevalence of microalbuminuria compared to patients without persistent electrocardiography markers of LVH. High albumin excretion was related to LVH independent of age, blood pressure, diabetes mellitus, race, serum creatinine, and smoking, suggesting parallel cardiac damage and albuminuria.[10]

We also found that patients with LVH compared with those without LVH had significantly higher serum creatinine levels ($P = .02$). Smilde and coworkers reported that kidney dysfunction was independently related to a 1.47-fold increased risk of LVH (95% CI, 1.15 to 1.88, $P = .009$). In addition, both creatinine clearance (OR, 1.56; 95% CI, 1.07 to 2.2; $P = .04$) and microalbuminuria (OR, 1.37, 95% CI, 1.04 to 1.80; $P = .02$) were independently associated with the presence of LVH.[14] Multivariable regression analysis demonstrated that serum creatinine was independently related to LVH ($P = .04$). Determination of serum creatinine concentration is recommended in all patients with hypertension as a marker of target organ damage. A serum creatinine value within the reference range is a predictor of cardiovascular morbidity in white patients with essential hypertension.[21] Schillaci and colleagues showed a powerful and independent relationship between baseline serum creatinine concentration and cardiovascular risk in initially untreated men and women with essential hypertension who were free of overt cardiovascular disease and with creatinine values below commonly accepted upper limits of normal.[21] Leoncini and colleagues showed that lower creatinine clearance was associated with longer reported duration of disease; higher levels of SBP, serum glucose, total cholesterol, and LDLC; early signs of target organ damage, namely LVH; and retinal vascular changes.[22] In contrast, Wachtell and colleagues found that serum creatinine was not associated with the different geometric patterns.[10] Also, another study showed

that serum creatinine did not have a significant difference between patients with LVH and without LVH. They used electrocardiographies rather than echocardiography to identify subjects with LVH. Therefore, the possibility exists that several cases of LVH were not detected or were falsely identified.[14]

In regression analysis, DBP emerged as a predictor of the risk for having LVH; patients with higher DBP may have higher risk for having LVH ($P < .001$). Tsioufis and coworkers showed DBP was significantly associated with left ventricular mass index.[23] Whereas another study showed a direct relationship between LVH and SBP as measured either by ambulatory blood pressure or office blood pressure averaged over a 30-year period.[24]

With multivariate analysis, elevated HDLC levels were protective against the development of LVH. Whereas, elevated LDLC levels were independent predictor of LVH development. This observation agrees with the previous reports, which found a relationship between low HDLC levels, a feature of insulin resistance syndrome and cardiovascular disease in hypertensive patients. The cardioprotective effects of HDLC are mainly related to its ability to inhibit LDLC oxidation and to improve endothelial dysfunction.[25] Horio and coworkers showed only low HDLC among several lipid levels was an independent predictor of both left ventricular mass and left ventricular diastolic dysfunction. Triglyceride levels showed no significant correlation with left ventricular mass and diastolic function, although total or LDLC was not associated with these echocardiographic indexes at all. In addition, LVH and left ventricular diastolic dysfunction were most advanced in a subgroup with both low HDLC and high triglycerides.[26]

Our study limitation was the relatively small number of participants. Thus, our results cannot be extrapolated to the general essential hypertensive population. Another limitation of the study was lack of an assessment of ambulatory blood pressure measurement throughout the 24 hours and we only measured clinic blood pressure. In some studies, ambulatory blood pressure is a better predictor of LVH than clinic blood pressure. [24] The strong points of this study, however, are first of all, the presence of a control group. Second, we used echocardiography to identify subjects with LVH that is a reliable means of measuring LVH. Compared with electrocardiography, echocardiography shows a higher sensitivity and an equally high specificity for the diagnosis of LVH.[27]

CONCLUSIONS

The present study suggests that microalbuminuria exhibits comparable strengths of association with LVH in patients with essential hypertension. Predicting LVH via an easily obtained laboratory test such as microalbuminuria can be clinically useful. Thus, a strategy to reduce the risk of cardiovascular events warrants monitoring the microalbuminuria and if levels of microalbuminuria are elevated, treatment regimen that lowers microalbuminuria, including a renin-angiotensin system blocker and lipid-lowering agent therapy should be considered.[8,28-30] There is evidence to suggest that early preventive measures would direct at lifestyle changes such as weight reduction, increasing physical activity, reducing dietary salt and fat intake, and pharmacotherapy might halt the progression of LVH or induce its regression in hypertensive people.[28,31] The findings from this study are intriguing and should prompt further study into the association between microalbuminuria and LVH in patients with essential hypertension and suggest that future studies should focus also on the LVH and its regression in patients with essential hypertension.

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CONFLICT OF INTEREST

The authors declare that they have no competing financial interests in relation to the work described.

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