Serum soluble RAGE level inversely correlates with left ventricular hypertrophy in essential hypertension patients

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ABSTRACT. Soluble receptor for advanced glycation end-products (sRAGE) acts as a decoy to prevent interaction between RAGE and its pro-inflammatory ligands. sRAGE levels have been found to decrease in chronic inflammatory diseases, including hypertension. However, few data have been reported concerning the association between serum sRAGE levels and hypertensive left ventricular hypertrophy (LVH). Fasting blood samples were obtained from 209 essential hypertensive patients, and sRAGE levels were measured using a commercially available double-sandwich enzyme-linked immunosorbent assay kit. All patients underwent complete transthoracic echocardiographic examination. LVH was defined as a left ventricular mass index >115 g/m² for men and >95 g/m² for women. Eighty-one hypertensive patients (38.76%) were categorized in the LVH(+) group. Age ($P = 0.009$),

hypertension duration ($P = 0.013$), triglyceride levels ($P = 0.028$), and systolic blood pressure ($P = 0.026$) were higher, and sRAGE and high-density lipoprotein cholesterol levels were lower in the LVH(+) group compared with the LVH(-) group. Multivariate logistic regression analysis showed that sRAGE level [odds ratio (OR) = 0.916; 95% confidence interval (CI) = 0.864-0.984; $P = 0.003$], hypertension duration (OR = 1.024; 95%CI = 1.003-1.052; $P = 0.027$), and triglyceride level (OR = 1.017; 95%CI = 1.005-1.039; $P = 0.018$) were independent predictors of LVH in hypertensive patients. In conclusion, serum sRAGE level was inversely associated with LVH in hypertensive patients.

Key words: Receptor for advanced glycation end-products; Left ventricular hypertrophy; Hypertension

INTRODUCTION

Essential hypertension is a major cause of cardiac damage, and left ventricular hypertrophy (LVH) resulting from systemic hypertension is characterized by structural remodeling of the heart. In hypertension, LVH is initially a transitional phase and a compensatory process, but it eventually proceeds to overt disease (Rosei and Muiesan, 2011). Individuals with LVH are at two to four times higher risk of having adverse cardiovascular events compared to patients without this condition (Gradman and Alfayoumi, 2006). Hypertensive LVH is a multi-factor pathological process, and identifying the key determinants involved is critically important for developing strategies to prevent heart failure. Acknowledged LVH risk factors include blood pressure, duration of hypertension, age, obesity, diet, and pharmacologic treatment (Schirmer et al., 1999; Ozawa et al., 2009).

Advanced glycation end-products (AGEs) derive from a non-enzymatic reaction between sugars and the free amino groups of proteins. AGEs and their specific receptor, RAGE, were initially reported to be involved in vascular complications of patients with diabetes mellitus and renal failure (Boulanger et al., 2004; Wautier et al., 2004). Soluble RAGE (sRAGE), consisting of RAGE's extracellular domain, exists in circulation in humans and acts as a decoy receptor to prevent interaction between RAGE and its pro-inflammatory ligands (Miyata et al., 2000). sRAGE levels have been found to be low in chronic inflammatory diseases, including atherosclerosis and diabetes, as well as during the aging process (Maillard-Lefebvre et al., 2009). Recent clinical investigations have revealed sRAGE to be involved in hypertension as well (Geroldi et al., 2005; Germanová et al., 2010). The aim of the present study was to determine the relationship between serum sRAGE concentrations and LVH in hypertensive patients.

MATERIAL AND METHODS

Subjects

Patients with essential hypertension ($N = 209$; 128 women and 81 men; mean age: 68.4 ± 7.8 years) were recruited from the outpatient hypertension department of our hospital. Essential hypertension was diagnosed when systolic blood pressure (SBP) was greater than

140 mmHg, diastolic blood pressure was greater than 90 mmHg, or both, based on repeated measurements, and irrespective of anti-hypertensive treatment. Participants were excluded if they had any of the following: diabetes mellitus, severe renal dysfunction (i.e., creatinine >2.5 mg/dL), cardiomyopathy, congenital heart disease, congenital valvular disease, active malignancy, chronic liver failure, or chronic or acute inflammatory states (such as sepsis, autoimmune diseases, or inflammatory bowel diseases). The study was approved by the local Ethics Committee and written informed consent was obtained from all patients.

Echocardiographic examination

All patients underwent complete transthoracic echocardiographic evaluation (Vivid 7 system; GE Healthcare, Fairfield, CT, USA), using a 2.5-4.0-MHz transducer. Patients were in the left lateral decubitus position. Two-dimensional, color flow and spectral Doppler measurements were performed according to the recommendations of the American Society of Echocardiography (Devereux, 1987). Readings were taken by two trained investigators unaware of each patient's clinical information. The following parameters were assessed using M-mode recordings: left ventricular end-diastolic diameter (LVEDD), left ventricular end-systolic diameter, left ventricular posterior wall thickness (PWT), interventricular septum thickness (IVST), and left ventricular mass (LVM). LVM was calculated using the Penn convention with the following regression-corrected cube formula: $LVM (g) = 1.04 \times [(IVST - LVEDD - PWT)^3 - LVEDD^3] - 14 g$. The left ventricular mass index (LVMI) was calculated as follows: $body\ surface\ area\ (BSA; m^2) = 0.06 \times height\ (cm) + 0.0128 \times weight\ (kg) - 0.1529$; $LVMI (g/m^2) = LVM/BSA$. LVH was defined as an $LVMI >115 g/m^2$ for men and $>95 g/m^2$ for women (Mancia et al., 2013).

Biochemical measurements

A venous blood sample was collected from each participant under fasting conditions. Levels of fasting blood glucose, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol, triglycerides (TG), urea nitrogen, and creatinine were measured. Serum sRAGE levels were determined using a double-sandwich enzyme-linked immunosorbent assay kit (96T/Kit, Yifeng Ltd., Shanghai, China) following the manufacturer protocol. Intra- and inter-assay coefficients of variation were 4 and 10%, respectively. The lower limit for detection of sRAGE was 25 pg/mL.

Statistical analysis

Data are reported as means $\pm$ standard deviation and were assessed for normal distribution using the Kolmogorov-Smirnov test. Comparisons between patients were performed using the Student independent *t*-test (two-tailed) for normally distributed data, or the Mann-Whitney U-test for parameters with non-normal distribution (fasting glucose, HDL-C, TG, blood urea nitrogen, and creatinine). Data reported as numbers of patients were analyzed by the chi-square test. Variables significantly associated with LVH in hypertensive patients were tested for independence by multivariate logistic regression analysis. Data were analyzed using SPSS for Windows (version 13.0; SPSS Inc., Chicago, IL, USA). P values <0.05 were considered significant.

RESULTS

The demographic and clinical characteristics of the 209 hypertensive patients are presented in Table 1. Eighty-one patients were categorized in the LVH(+) group. Coronary heart disease was more frequent among these patients than among those in the LVH(-) group (Table 2). There were no significant differences in gender or use of anti-hypertensive drugs between the two groups (Table 2).

Table 1. Clinical and analytical characteristics of the 209 hypertensive patients included in this study.

Parameter	Mean $\pm$ SD
Age	68.42 $\pm$ 7.83
Body mass index (kg/m ²)	26.67 $\pm$ 4.45
Hypertension duration (years)	11.34 $\pm$ 5.82
SBP (mmHg)	149.71 $\pm$ 12.06
DBP (mmHg)	92.36 $\pm$ 11.42
Total cholesterol (mg/dL)	196.54 $\pm$ 18.71
LDL-C (mg/dL)	121.63 $\pm$ 17.02
HDL-C (mg/dL)	47.11 $\pm$ 10.39
Triglycerides (mg/dL)	144.70 $\pm$ 19.72
Fasting glucose (mg/dL)	97.28 $\pm$ 7.41
Plasma creatinine (mg/dL)	0.98 $\pm$ 0.25
Blood urea (mg/dL)	14.39 $\pm$ 6.81
Serum sRAGE (pg/mL)	293.72 $\pm$ 34.66

SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, sRAGE = soluble receptor for advanced glycation end-products, SD = standard deviation.

Table 2. Baseline characteristics of the 209 hypertensive patients with or without left ventricular hypertrophy.

Characteristic	LVH(-) [N = 128]	LVH(+) [N = 81]	P value
Gender			0.154
Male	56 (43.8%)	32 (39.5%)	
Female	72 (56.2%)	49 (60.5%)	
Coronary heart disease			0.004
Yes	51 (39.8%)	46 (56.8%)	
No	77 (60.1%)	35 (43.2%)	
ACEI/ARB use			0.249
Yes	94 (73.4%)	59 (72.8%)	
No	34 (26.6%)	22 (27.2%)	
CCB use			0.091
Yes	66 (51.6%)	43 (53.1%)	
No	62 (48.4%)	38 (46.9%)	
Diuretic use			0.158
Yes	28 (21.9%)	18 (22.2%)	
No	100 (78.1%)	63 (77.8%)	
β -blocker use			0.329
Yes	59 (46.1%)	37 (45.7%)	
No	69 (53.9%)	44 (54.3%)	
Aspirin use			0.275
Yes	72 (56.3%)	50 (61.7%)	
No	56 (43.7%)	31 (38.3%)	

LVH = left ventricular hypertrophy, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blocker, CCB = calcium channel blocker.

Age ($P = 0.009$), hypertension duration ($P = 0.013$), TG ($P = 0.028$), and SBP ($P < 0.026$) were higher, and serum sRAGE and HDL-C lower in the LVH(+) group compared to the LVH(-) group (Table 3).

Table 3. Clinical variables of the 209 hypertensive patients with or without left ventricular hypertrophy.

Parameter	LVH(-) [N = 128]	LVH(+) [N = 81]	P value
Age	66.14 ± 2.37	70.31 ± 5.20	0.009
Body mass index (kg/m ²)	25.26 ± 4.01	26.84 ± 7.18	0.062
Hypertension duration (years)	7.19 ± 3.42	10.26 ± 4.18	0.013
SBP (mmHg)	132.03 ± 12.36	146.78 ± 11.24	0.026
DBP (mmHg)	78.42 ± 10.33	79.21 ± 9.45	0.173
Total cholesterol (mg/dL)	186.49 ± 26.58	195.82 ± 32.17	0.236
LDL-C (mg/dL)	115.04 ± 21.72	106.83 ± 22.81	0.415
HDL-C (mg/dL)	56.85 ± 13.38	42.16 ± 14.72	0.039
Triglycerides (mg/dL)	112.75 ± 36.02	163.21 ± 47.39	0.028
Fasting glucose (mg/dL)	103.24 ± 37.34	110.87 ± 34.82	0.311
Plasma creatinine (mg/dL)	0.98 ± 0.22	1.04 ± 0.18	0.162
Blood urea (mg/dL)	14.67 ± 4.48	13.85 ± 5.26	0.204
Serum sRAGE (pg/mL)	302.94 ± 37.28	225.61 ± 43.17	0.004

LVH = left ventricular hypertrophy, SBP = systolic blood pressure, DBP = diastolic blood pressure, LDL-C = low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, sRAGE = soluble receptor for advanced glycation end-products.

Multivariate logistic regression analysis of factors significantly associated with LVH (coronary heart disease, age, hypertension duration, TG, SBP, HDL-C, and sRAGE) showed that sRAGE concentration [odds ratio (OR) = 0.916; 95% confidence interval (CI) = 0.864-0.984; P = 0.003], hypertension duration (OR = 1.024; 95%CI = 1.003-1.052; P = 0.027), and TG level (OR = 1.017; 95%CI = 1.005-1.039; P = 0.018) were independent predictors of LVH in hypertensive patients (Table 4).

Table 4. Multivariate logistic regression analysis of factors correlated with left ventricular hypertrophy among the 209 hypertensive patients included in this study.

Variable	Odds ratio	95%CI	P value
sRAGE (pg/mL)	0.916	0.864-0.984	0.003
Hypertension duration (years)	1.024	1.003-1.052	0.027
Triglycerides (mg/dL)	1.017	1.005-1.039	0.018

CI = confidence interval, sRAGE = soluble receptor for advanced glycation end-products.

DISCUSSION

Our study showed that in hypertensive patients, serum sRAGE levels were lower in those with LVH than in those without this condition. Moreover, we found that serum sRAGE concentration, hypertension duration, and TG level were independent predictors of LVH among hypertensive patients.

LVH is an independent risk factor for hypertension-related cardiovascular morbidity and mortality (Mancia et al., 2008; Tovillas-Morán et al., 2010). A recent analysis of 30 echocardiography studies (from January 1, 2000 to December 1, 2010) including 37,000 hypertensive patients showed that LVH prevalence was not statistically different between women and men (ranging 37.9-46.2% vs 36.0-43.5%, respectively; Cuspidi et al., 2012). Epidemiological studies have also demonstrated that the prevalence of LVH in Chinese hypertensive patients is approximately 25 to 35% (Zhan et al., 2002). In this study, 38.76% of hypertensive patients were categorized as having LVH, and there was no difference in terms of gender between LVH(+) and LVH(-) groups. We found the incidence of coronary heart disease to be higher in the LVH(+) group, possibly because atherosclerosis patients are exposed to risk

factors common to this condition and hypertensive LVH. Accumulating evidence has shown that LVH occurrence depends not only on hypertension duration and blood pressure levels, but also on other comorbidities, such as TG, age, gender, genetics, insulin resistance, obesity, physical inactivity, increased salt intake, and chronic stress, which play cooperative roles (Lovic et al., 2014). Besides these established risk factors, researchers have gradually begun to pay attention to the utility of certain inflammatory or oxidative mediators for early screening of populations at high risk of hypertension. Lately, it has been found that high-sensitivity C-reactive protein, oxidized LDL, and apelin levels are closely related to the pathogenesis of primary hypertension (Pang et al., 2015). In the current study, we focused on the inflammatory biomarker sRAGE in this condition.

AGEs result from non-enzymatic glycation and glycoxidation of proteins and lipids. Accumulation of AGEs was first noticed in humans as a result of aging, and at an accelerated rate in diabetics (Schleicher et al., 1997; Wautier and Schmidt, 2004). Interaction between AGEs and RAGE can activate a range of signaling pathways that trigger the generation of reactive oxygen species (Wautier et al., 2001), and the resulting cellular response promotes inflammation through overexpression of various cell adhesion molecules (Chavakis et al., 2003). RAGE is composed of an intracellular domain, a short transmembrane domain, and an extracellular domain. sRAGE consists of the latter; thus, it may act as a decoy preventing pro-inflammatory ligands from reaching RAGE (Miyata et al., 2000). Accordingly, the administration of sRAGE has been reported to prevent the development of AGE-mediated diseases in animal studies (Taguchi et al., 2000; Goova et al., 2001; Bucciarelli et al., 2002). sRAGE also exists in circulation in humans, and numerous studies have revealed strong correlations between sRAGE levels and some chronic inflammatory diseases, including inflammatory bowel diseases, systemic lupus erythematosus, and atherosclerosis (Maillard-Lefebvre et al., 2009). However, the role of the AGE-RAGE axis in hypertensive cardiac damage has been less intensively investigated in clinical studies.

In 2005, Geroldi et al. (2005) carried out a cross-sectional study of 147 never-treated hypertensive patients and 177 normotensive controls. The association between sRAGE and pulse pressure was found to be strong even after multiple-regression analysis. This raises the possibility that sRAGE, in a similar manner to AGEs, may influence arterial stiffness in hypertension. Similarly, in a study of 415 patients, Yoon et al. (2012) established that log-transformed sRAGE levels significantly correlate with heart to femoral pulse wave velocity, a marker of central aortic stiffness. A recent clinical investigation (Cai et al., 2015) indicated that serum levels of endogenous secretory RAGE (esRAGE), which, like sRAGE, is a C-terminal truncated form of RAGE, are inversely associated with blood pressure, especially SBP, in male nondiabetic patients with obstructive sleep apnea. This suggests that esRAGE may protect against hypertension in patients with this sleep condition.

As far as the relationship between sRAGE levels and hypertensive LVH is concerned, even fewer clinical data are available. However, the link between the AGE-sRAGE system and LVH has been investigated in regard to other diseases. For example, high AGE levels are associated with concentric LVH in end-stage renal dysfunction patients (Zoccali et al., 2001). In addition, Leonardis et al. (2012) identified a significant inverse relationship between sRAGE and LVMI in chronic renal disease patients, while no such association was established in their control group. In our investigation, we found that sRAGE level was lower in the LVH(+) group, and constituted an independent predictor of LVH in hypertensive patients. Our study consisted of clinical observations, and we did not investigate the mechanism by which

sRAGE levels decrease in hypertensive LVH patients. However, our findings provide support for the hypothesis that the RAGE pathway could be a causal risk factor for hypertensive LVH. Based on previous research indicating crosstalk between the AGE-RAGE axis and the renin-angiotensin-aldosterone system (RAAS; Nakamura et al., 2005), we might explore the underlying mechanism through AGE/RAGE-producing inflammatory effects leading to myocardial hypertrophy, or RAAS-related volume and pressure overload, or complicated interactions between these factors.

Limitations

Certain limitations to the current study should be considered. First, this was an observational, single-center study in which only a small number of hypertensive patients were available for analysis. Second, a cross-sectional design was used. Although cross-sectional studies can measure association, they are not powerful enough to demonstrate causality. Ideally, serial echocardiograms and sRAGE levels would have been obtained to show cause and effect. Third, although we recorded data concerning anti-hypertensive drug treatment, we did not collect those regarding physical exercise habits, which may have an effect on LVH. Further long-term prospective studies are needed to elucidate the causal relationship between sRAGE level and LVH in hypertensive patients.

CONCLUSION

The present study showed that serum sRAGE level was inversely correlated with hypertensive LVH. Further large-scale studies are required to assess the effect of the AGE-RAGE axis on the development of LVH in essential hypertension.

Conflicts of interest

The authors declare no conflict of interest.

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