ORIGINAL RESEARCH

Serum Mimecan Is Associated With Arterial Stiffness in Hypertensive Patients

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***Background*—**Mimecan plays an important role in endothelial and vascular smooth muscle cell integrity and may be involved the pathology of arterial stiffness. However, the role of mimecan in arterial stiffness in patients with hypertension is not well defined.

***Methods and Results*—**A total of 116 hypertension patients and 54 healthy controls were enrolled in the investigation. Hypertensive patients were divided into 2 groups: the with arterial stiffness group (brachial-ankle pulse wave velocity [baPWV] ≥1400 cm/s; n=83) and the without arterial stiffness group (baPWV <1400 cm/s; n=33). A noninvasive measure of vascular stiffness was performed using pulse wave velocity (PWV) measurement of baPWV. Hypertensive patients had higher baPWV, mimecan, and endothelin 1 (ET-1) than healthy controls. The arterial stiffness group had higher mimecan and endothelin 1 (ET-1) and lower ankle-brachial pressure index (ABI) than those without stiffness. In hypertensive patients, mimecan was inversely correlated with ABI ($P<0.05$) and positively correlated with baPWV, ET-1, and total cholesterol. On multivariable logistic regression analysis, diastolic blood pressure, mimecan, ET-1, and creatinine were independent predictors of arterial stiffness in hypertensive patients ($P<0.05$).

***Conclusions*—**Mimecan levels are higher in hypertensive patients than in healthy controls. Increased plasma mimecan levels are independently associated with increased arterial stiffness as assessed by baPWV. **(*J Am Heart Assoc*.2015;4:e002010 doi: 10.1161/JAHA.115.002010)**

Key Words: arterial stiffness • ET-1 • hypertension • mimecan

Mimecan, also known as osteoglycin, is encoded by the osteoglycin gene on human chromosome 9q22.[1] The protein product isolated from demineralized bone is a corneal keratan sulfate proteoglycan and is present in many non-corneal tissues without keratan sulfate chains, such as the aorta and myocardium.[2] In normal adult rat carotid artery, osteoglycin is expressed in both the media and adventitia. Osteoglycin has been identified as a new marker of differentiated vascular smooth muscle cells (VSMCs) and may be an essential component of normal vascular matrix.[3] Increasing evidence has demonstrated that mimecan has a close relationship with the risk of cardiovascular (CV) disease (CVD). Osteoglycin is a major candidate regulator of rat left ventricular mass (LVM), with increased osteoglycin protein expression associated with elevated LVM.[4] In atherosclerotic lesions, osteoglycin mRNA was up-regulated in the activated endothelium and thickened neointima. The investigators concluded that osteoglycin is a basic component of the vascular extracellular matrix (ECM) and also plays a role in atherosclerosis.[5] Further research has shown that down-regulation of osteoglycin is required for arteriogenesis.[6] Currently, clinical investigation of mimecan expression has shown that it is decreased in patients with calcified abdominal aortic aneurysms.[7] However, there are no studies that investigate the relationship between arterial stiffness and mimecan.

Arterial stiffness is recognized to be an independent risk factor for CV morbidity and mortality. It is the root cause of a range of CV complications, including myocardial infarction (MI), left ventricular hypertrophy, stroke, renal failure, dementia, and death, as well as a hallmark of the aging process.[8] It is also plays an important role in hypertension. Arterial stiffness has long been viewed as a consequence of long-standing hypertension. However, recent studies have suggested that

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arterial stiffness may contribute to the pathogenesis of hypertension.[9] Arterial stiffness resulting from alterations in ECM is one of the mechanisms responsible for increased peripheral resistance in hypertension.[10] Mimecan, as a basic component of the vascular ECM, has a close relationship with the endothelium and VSMCs.[3,5] However, the association between plasma mimecan levels and arterial stiffness in patients with hypertension has not been established.

This study investigated the association between serum mimecan concentration and arterial stiffness, as measured by brachial-ankle pulse wave velocity (baPWV), in patients with hypertension.

Methods

Subjects

A total of 116 subjects, diagnosed with primary hypertension on the basis of World Health Organization criteria (systolic blood pressure [BP] (SBP) ≥140 mm Hg and/or diastolic BP (DBP) ≥90 mm Hg), were enrolled in the cross-sectional study. These patients were assessed in the clinic or in-patient department of the Second Affiliated Hospital of Soochow University (Suzhou, China) between December 2011 and December 2013. Exclusion criteria were based on the presence of any of the following: (1) secondary hypertension; (2) hyperlipidemia; (3) kidney disease; (4) cancer; (5) lung disease; and (6) liver disease. Secondary hypertension was excluded on the basis of clinical and biochemical assessments. In addition, 54 normotensive subjects who were evaluated in the physical examination center of the same hospital were recruited as a parallel control group, with the same exclusion criteria applied. All study participants were >18 years of age. The study protocols for human subjects were approved by the ethics committee of the Second Affiliated Hospital of Soochow University. All subjects provided written consent before participating in the study.

Clinical and Biochemical Assessment

Demographic and clinical data were verified by reviewing the electronic medical records. Body mass index (BMI) was calculated by dividing the patients' weight in kilograms by their height in meters squared. BP was measured after 5 minutes of rest, and hypertension was defined as an SBP equal to or greater than 140 mm Hg, a DBP equal to or greater than 90 mm Hg, or the use of antihypertensive medication(s). Hyperlipidemia was defined as a total cholesterol (TC) concentration of greater than 5.69 mmol/L, triglyceride (TG) concentration of greater than 1.7 mmol/L, low-density lipoprotein (LDL) concentration of greater than 3.1 mmol/L, and/or the use of cholesterol-lowering medication. CVD was defined as previous MI, coronary revascularization, or stroke. After overnight fasting, venous blood was taken for laboratory measurements. Routine biochemical measurements were performed on each blood sample using an AU5400 automated chemistry analyzer (Beckman Coulter, Fullerton, CA). TC and TGs were measured using a standard enzymatic method, and high-density lipoprotein (HDL) cholesterol was measured using an enzymatic colorimetric method. LDL cholesterol was indirectly measured using the Friedewald formula in participants with plasma TG concentrations below 400 mg/mL. Plasma creatinine concentration was measured using a modified kinetic Jaffe method. Blood samples were collected from the antecubital vein in the morning after an overnight fast. Blood samples were transferred immediately into pyrogen-free blood collection tubes (Becton Dickinson, Franklin Lakes, NJ) containing EDTA-2Na (1 mg/mL) as an anticoagulant and aprotinin (a competitive serine protease inhibitor; 500 U/mL) and then centrifuged immediately at 1500*g* for 15 minutes at 4°C. The resulting plasma samples were stored frozen at −80°C in multiple aliquots until use. Circulating mimecan concentrations were determined using the mimecan (human) ELISA kit (catalog no. 2260; antibodies-online Inc., Atlanta, GA), according to the manufacturer's instructions. The detection range of this kit is 0.313 to 20 ng/mL and sensitivity is 0.133 ng/mL. Circulating endothelin 1 (ET-1) concentrations were determined using the ET-1 (human) ELISA kit (catalog no. QET00B; R&D Systems, Minneapolis, MN), according to the manufacturer's instructions. The detection range for this kit is 0.34 to 250 pg/mL and its sensitivity is 0.102 pg/mL.

Measurement of baPWV

The baPWV was measured using an automated PWV/ankle brachial index (ABI) analyzer (ST-203AT III-230V; Colin Co Ltd, Komaki, Japan) after the subjects had rested in the supine position for at least 5 minutes. Electrocardiogram electrodes were placed on both wrists and both ankles, and BP cuffs were wrapped around both upper arms and both ankles. To measure the baPWV, pulse waves obtained from the brachial and tibial arteries were recorded simultaneously, and the transmission time (DTba) was calculated as the time interval between the initial increase in the brachial and ankle waveforms. The path length from the suprasternal notch to the brachium (Lb) and from the suprasternal notch to the ankle (La) was automatically obtained based on the subject's height. The baPWV was calculated using the equation baPWV=(La−Lb)/DTba (cm/s), and the mean baPWVs for the left and right sides were used for the analysis. Arterial stiffness was defined as baPWV ≥1400 cm/s.[11]

Statistical Analysis

Statistical analyses were performed using SPSS software (version 22.0; SPSS, Inc., Chicago, IL). Data are presented as the mean±SD or as a percentage, and $P<0.05$ was considered statistically significant. Comparisons of 2 continuous variables were performed using the Student t test, and categorical variables were analyzed using the chi-squared test to compare the characteristics of the study population. Pearson correlation analyses were performed to examine the association between PWV and various parameters. Multivariable logistic regression analyses were performed to estimate the odds ratio (OR) and the 95% confidence interval (CI) for high PWV. $P<0.05$ was considered statistically significant. The final multivariable model was selected using backward selection. All variables in the final model are significant at $P<0.05$.

Results

Patient Characteristics

The clinical and biochemical characteristics of the study subjects are presented in Table 1. There were 116 participants (mean age, 63.6±11.5 years) in the hypertensive group and 54 healthy participants (mean age, 60.3±11.7 years) in the control group. There were no significant differences in age, gender, current smoking status, TC, and LDL-C between the 2 groups. However, compared to the control group, hypertensive patients had greater SBP, DBP, BMI, and TG ($P<0.01$ for all measurements). Arterial stiffness was assessed noninvasively by established methods, including baPWV and the ABI. In the present study, baPWV was markedly increased in hypertensive patients, compared to the control group (1612.75±310.12 vs. 1221.30±189.75 cm/s; $P<0.001$), whereas ABI was decreased (1.11±0.11 vs. 1.23±0.09; $P<0.001$). Hypertensive patients had a higher arterial stiffness incidence than the control group (71.6% vs. 22.2%; $P<0.001$). In addition, both plasma mimecan and ET-1 concentrations were significantly increased in hypertensive patients, compared to the control group (13.71±7.15 vs. 8.32±4.78 ng/mL, respectively, for mimecan; 2.46±1.04 vs. 1.45±0.88 pg/mL, for ET-1; $P<0.001$).

Comparison of Patient Characteristics Between High baPWV and Low baPWV Groups

The demographic, biochemical, and clinical characteristics of the 116 hypertensive patients are presented in Table 2. Eighty-three patients were assigned to the arterial stiffness group (baPWV ≥1400 cm/s) and 33 were assigned to the group without arterial stiffness (baPWV <1400 cm/s). Of note, creatinine (Cr; $P=0.006$), baPWV ($P<0.001$), plasma mimecan ($P<0.001$), and ET-1 ($P=0.001$) were higher in the arterial stiffness group than in the group without arterial stiffness, whereas ABI ($P=0.014$) was lower in the arterial stiffness group than in the group without arterial stiffness.

Table 1. Clinical and Biochemical Characteristics of the 54 Healthy Participants and the 116 Hypertensive Patients

	Healthy Participants (n=54)	Hypertensive (n=116)	*P* Value
Age, y	60.3±11.7	63.6±11.5	0.08
Gender, M/F	30/24	60/56	0.742
Smoke (%)	10 (18.5)	24 (20.7)	0.838
BMI, kg/m^2	22.10±3.24	23.60±2.59	0.004
SBP, mm Hg	111.1±11.4	144.0±19.5	<0.001
DBP, mm Hg	69.9±8.1	80.9±11.6	<0.001
TC, mmol/L	4.26±1.15	4.20±0.95	0.74
LDL, mmol/L	2.17±0.90	2.45±0.80	0.052
TG, mmol/L	1.25±0.38	1.58±0.75	<0.001
Cr, μmol/L	63.03±14.07	63.31±14.20	0.908
BaPWV, cm/s	1221.30±189.75	1612.75±310.12	<0.001
BaPWV ≥1400 cm/s (%)	12 (22.2)	83 (71.6)	<0.001
ABI	1.23±0.09	1.11±0.11	<0.001
Mimecan, ng/mL	8.32±4.78	13.71±7.15	<0.001
ET-1, pg/mL	1.45±0.88	2.46±1.04	<0.001

The data are presented as either mean±SD or numbers. *P* value for comparison between groups using independent t test or chi-square test; $P<0.05$ was considered to be statistically significant. ABI indicates ankle-brachial pressure index; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; Cr, creatinine; DBP, diastolic blood pressure; ET-1, endothelin 1; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

Correlations Between Mimecan Levels and Other Variables

Correlation coefficient analysis results for mimecan levels and other clinical variables for the 116 hypertensive patients are given in Table 3. Plasma mimecan concentrations were negatively correlated with ABI ($r=-0.36$; $P<0.001$), but positively correlated with baPWV ($r=0.37$; $P<0.001$), ET-1 ($r=0.22$; $P=0.035$), and TC ($r=0.2$; $P=0.029$).

Multivariable Regression Analysis of Determinants of baPWV

The initial multivariable logistic model for the 116 hypertensive patients and 54 healthy participants was adjusted for the following covariates (gender, age, hypertension, TC, TG, LDL,

Table 2. Clinical and Biochemical Characteristics of the 116 Hypertensive Patients With and Without Arterial Stiffness

	Without Arterial Stiffness Group (n=33)	With Arterial Stiffness Group (n=83)	*P* Value
Age, y	65.4±12.0	62.9±11.2	0.305
Gender, M/F	18/15	42/41	0.837
Smoke, Y/N (%)	7 (21.2)	17 (20.5)	0.930
BMI, kg/m^2	23.29±2.93	23.72±2.45	0.456
SBP, mm Hg	145.2±20.4	143.5±19.2	0.670
DBP, mm Hg	76.1±7.4	82.8±12.4	0.001
TC, mmol/L	4.19±0.84	4.19±0.99	0.964
LDL, mmol/L	2.49±0.74	2.44±0.82	0.754
TG, mmol/L	1.74±0.85	1.51±0.70	0.173
Cr, μmol/L	57.94±12.20	65.45±14.44	0.006
BaPWV, cm/s	1239.33±109.19	1761.18±227.62	<0.001
ABI	1.15±0.11	1.09±0.11	0.014
Mimecan, ng/mL	10.36±5.16	15.04±7.42	<0.001
ET-1, pg/mL	2.02±0.76	2.63±1.09	0.001
ACEI	6 (18.2%)	12 (14.5%)	0.617
ARB	11 (33.3%)	27 (32.5%)	0.934
Beta-blocker	10 (30.3%)	31 (37.3%)	0.474
CCB	13 (39.4%)	34 (40.9%)	0.877
Diuretic	8 (24.2%)	26 (31.3%)	0.450

The data are presented as mean±SD, numbers, or numbers with percentages. *P* value for comparison between groups were determined using *t* test or chi-square test; *P*<0.05 was considered to be statistically significant. ABI indicates ankle-brachial pressure index; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; baPWV, brachial-ankle pulse wave velocity; BMI, body mass index; CCB, calcium-channel blocker; Cr, creatinine; DBP, diastolic blood pressure; ET-1, endothelin 1; LDL, low-density lipoprotein; SBP, systolic blood pressure; TC, total cholesterol; TG, triglyceride.

smoking, Cr, mimecan, ET-1, and BMI). Table 4 shows a regression analysis of those factors that were associated with arterial stiffness. Hypertension (OR, 3.3; 95% CI, 1.5 to 8.0; *P*=0.009), gender (OR, 2.8; 95% CI, 1.1 to 7.0; *P*=0.03), mimecan (OR, 1.1; 95% CI, 1.0 to 1.2; *P*=0.001), ET-1 (OR, 3.6; 95% CI, 2.0 to 6.4; *P*<0.001), and Cr (OR, 1.1; 95% CI, 1.0 to 1.1; *P*=0.001) were independent predictors of arterial stiffness in these study subjects.

Table 3. Pearson Correlation Coefficients Between Mimecan Levels and Clinical Variables in Hypertensive Patients

Variables	Pearson Coefficient of Correlation	*P* Value
baPWV	0.37	<0.001
ABI	−0.36	<0.001
ET-1	0.2	0.035
TC	0.2	0.029

P<0.05 was considered to be statistically significant. ABI indicates ankle-brachial pressure index; baPWV, brachial-ankle pulse wave velocity; ET-1, endothelin 1; TC, total cholesterol.

Table 4. Multivariable Logistic Regression Analysis of Factors Correlated With Arterial Stiffness in the 54 Healthy Participants and the 116 Hypertensive Patients

Variables	Odds Ratio	95% Confidence Interval	*P* Value
Hypertension	3.3	1.3 to 8.0	0.009
Gender	2.8	1.1 to 7.0	0.03
Mimecan	1.1	1 to 1.2	0.001
ET-1	3.6	2 to 6.4	<0.001
Cr	1.1	1.0 to 1.1	0.001

P<0.05 was considered to be statistically significant in the multivariate logistic regression analysis. Cr indicates creatinine; ET-1, endothelin 1.

The initial multivariable logistic model for the 116 hypertensive patients was adjusted for the following covariates (gender, age, SBP, DBP, TC, TG, LDL, smoking, Cr, mimecan, ET-1, and BMI). Table 5 shows the regression analysis of those factors that were associated with arterial stiffness in the hypertensive participants. DBP (OR, 1.1; 95% CI, 1.0 to 1.2; *P*=0.003), mimecan (OR, 1.1; 95% CI, 1.0 to 1.2; *P*=0.009), ET-1 (OR, 2.9; 95% CI, 1.3 to 6.4; *P*=0.007), and Cr (OR, 1.1; 95% CI, 1.0 to 1.1; *P*=0.005) were independent predictors of arterial stiffness in these patients.

Discussion

Arterial stiffness is a useful predictive maker for CV morbidity and mortality and baPWV has been proposed as a simple, noninvasive method for estimating arterial stiffness.[12] In this study, we report 2 important findings. First, our study showed that DBP, Cr, mimecan levels, and ET-1 were positively correlated with arterial stiffness in hypertensive patients based on the baPWV value. Second, we report that DBP, mimecan, ET-1, and Cr are independent predictors of arterial stiffness in these patients.

Table 5. Multivariable Logistic Regression Analysis of Factors Correlated With Arterial Stiffness in the 116 Hypertensive Patients

Variables	Odds Ratio	95% Confidence Interval	*P* Value
DBP (per 1 mm Hg)	1.1	1.0 to 1.2	0.003
Mimecan	1.1	1.0 to 1.2	0.009
ET-1	2.9	1.3 to 6.4	0.007
Cr	1.1	1.0 to 1.1	0.005

P<0.05 was considered to be statistically significant in the multivariate logistic regression analysis. Cr indicates creatinine; DBP, diastolic blood pressure; ET-1, endothelin 1.

Hypertension is the leading cause of morbidity, disability, and premature death. Epidemiological studies have reported that arterial stiffness is closely correlated with surrogate markers of atherosclerosis and that baPWV, a measure of arterial stiffness, is an independent predictor of adverse CV events in hypertensive patients.[13,14] Arterial stiffness, measured by baPWV, increases in hypertensive patients.[13,15] Our results corroborate these findings. We show that hypertensive patients had a higher baPWV than healthy controls, hypertension is a independent predictor of arterial stiffness; moreover, DBP is an independent predictor of arterial stiffness in hypertensive patients.

It is well-known that hypertension can induce end-organ damage, such as stroke and kidney failure. Kidney disease is closely associated with hypertension and arterial stiffness.[16,17] Moreover, Karras et al. have reported that arterial stiffness is an independent predictor of mortality in patients with chronic kidney disease.[18] These findings are also supported by our results, which show that the high arterial stiffness group had a higher Cr level and that Cr is an independent predictor for arterial stiffness.

From the correlation analysis, we found that mimecan had a positive relationship with TC. We are the first to report this finding. Cholesterol is known to be an independent factor for coronary arterial disease (CAD) and can induce atherosclerotic plaque formation. In atherosclerotic lesions, osteoglycin mRNA was up-regulated in the activated endothelium.[5] Cheng et al. also reported that circulating mimecan is a predictor for CAD.[19] All these findings indicate that mimecan has the potential to affect cholesterol and, in turn, contribute to progression of coronary heart disease. In contrast, Moncayo-Arlando et al. reported that lack of osteoglycin does not affect e progression of atherosclerosis in mice.[20] Thus, the underlying mechanism(s) between mimecan and cholesterol require further investigation.

Our study show that the high baPWV group had higher plasma mimecan levels than the lower baPWV group and that mimecan is an independent predictor of arterial stiffness. However, the biological mechanisms that link high plasma mimecan levels and arterial stiffness remains to be elucidated.

There are several potential explanations for the role of mimecan in arterial stiffness. First, high mimecan levels may be linked to arterial stiffness through a close association with CV risk factors: High serum mimecan levels have been shown to be positively correlated with CAD, hyperlipidemia, and cardiac hypertrophy.[4,19,21] All of these diseases are characterized by high arterial stiffness.[22–24] However, this may not constitute a comprehensive explanation, because our multivariable logistic regression analyses show that plasma mimecan levels are an independent predictor of baPWV.

Second, and perhaps more important, high mimecan levels might be directly linked to vascular complications. We have reported that silencing mimecan expression in VSMCs increased VSMC proliferation, indicating that high levels of mimecan reduce the VSMC proliferation.[25] VSMCs contribute significantly to aortic stiffness. Thoracic and abdominal aortic dilatation with loss of VSMC density result in increased vascular stiffness.[26] Thus, vascular remodeling induced by increasing mimecan levels may be responsible for the high degree of arterial stiffness observed in hypertension.

Third, endothelial dysfunction may constitute another explanation for the effect of mimecan on arterial stiffness. The cause-and-effect relationship between endothelial dysfunction and vascular stiffness has been commonly accepted. Endothelial dysfunction was correlated with increased aortic stiffness,[27] and treatments that improve endothelial function are associated with a significant improvement of PWV in patients with metabolic syndrome.[28] In our study, mimecan had a positive correlation with ET-1, and both ET-1 and mimecan are independent predictors of arterial stiffness. As we know, in atherosclerotic lesions, osteoglycin mRNA was up-regulated in the activated endothelium.[29] ET-1 is strongly corelated with aortic elasticity parameters.[30] Thus, increasing mimecan levels can increase arterial stiffness by reducing endothelial function.

Last, the ECM plays an important role in vascular remodeling and arterial stiffness.[31] Mimecan has been implicated in the integrity of the ECM and has demonstrated effects on collagen. Adenoviral overexpression of osteoglycin in mice significantly improved cardiac collagen maturation.[32,33] Deposition of collagen in ECM remodeling plays an important role in progression of arterial stiffness. Thus, mimecan's potential to stimulate both the amount of collagen and its quality represents another mechanism by which mimecan may alter arterial stiffness.

There are several limitations associated with this study. First, every hypertensive patient was prescribed some kind of medication. Although there were no statistical differences in the medication used between the high arterial stiffness group and the low arterial stiffness group, we cannot exclude the influence of drugs, such as angiotensin converting enzyme inhibitors or angiotensin II receptor blockers, which are known to reduce arterial stiffness.[34] Second, we measured baPWV rather than aortic stiffness. The measurement of baPWV has some limitations; it has poor sensitivity and is influenced by heart rate and height of the patient. Also, owing to the small number of subjects in the healthy control group, we were not able to assess any differences in risk factors for arterial stiffness between the hypertensive and control groups. Finally, only a single plasma mimecan measurements was available, which is not as desirable as using the mean of several measurements. However, the use of standardized methods in a single center and taking measurements from fasting subjects likely improved the reliability of the data.

In conclusion, the present findings indicate that increased plasma mimecan levels are independently associated with increased arterial stiffness measured according to the baPWV in patients with hypertension.

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Disclosures

None.

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