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Original Article

Asymmetric Dimethylarginine Predicts One-year Recurrent Cardiovascular Events: Potential Biomarker of "Toxin Syndrome" in Coronary Heart Disease*

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ABSTRACT **Objective:** To examine the prognostic value of serum levels of asymmetric dimethylarginine (ADMA) in patients with stable coronary heart disease (CHD) thus explore a potential biomarker of "toxin syndrome" in CHD. **Methods:** In this prospective nested case-control study, 36 of 1,503 Chinese patients with stable CHD experienced at least 1 recurrent cardiovascular event (RCE) during 1-year follow-up. Serum levels of ADMA at the start of follow-up were compared between these 36 cases and 36 controls which matched to cases in terms of gender, age, history of hypertension, and myocardial infarction. **Results:** Based on the crude model, subjects in the 2 highest ADMA quartiles showed significantly higher risk of developing RCE than those in the lowest ADMA quartile [odds ratio (OR) 4.09, 95% confidence interval (CI) 1.01 to 16.58; OR 6.76, 95% CI 1.57 to 29.07]. This association was also observed in the case-mix model (OR 5.51, 95% CI 1.23 to 24.61; OR 7.83, 95% CI 1.68 to 36.41) and multivariable model (OR 6.64, 95% CI 1.40 to 31.49; OR 13.14, 95% CI 2.28 to 75.71) after adjusting for confounders. The multivariable model which combined ADMA and high-sensitivity C-reactive protein (hsCRP) showed better predictive power with areas under the receiver operator characteristic curves (0.779) than the model of either ADMA (0.694) or hsCRP (0.636). **Conclusion:** Serum ADMA level may be a potential biomarker of "toxin syndrome" in CHD which shows favorable prognostic value in predicting 1-year RCE in patients with stable CHD. [The registration number is ChiCTR-PRNRC-07000012]

KEYWORDS asymmetric dimethylarginine, recurrent cardiovascular event, nested case-control study, coronary heart disease, toxin syndrome

Coronary atherosclerosis begins with endothelial dysfunction. Increasing evidence suggest that elevated serum levels of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of endothelial nitric oxide (NO) synthase, can inhibit NO synthesis and thereby prevent recruitment of endothelial progenitor cells to repair vascular lesions. In this way, excessive levels of ADMA may contribute to atherosclerotic vascular disease.[1-3]

Patients with previous cardiovascular events are prone to recurrent cardiovascular events (RCEs), leading many research groups to search for prognostic factors that may help predict risk of RCEs and thereby aid in the identification and management of high-risk populations. For example, elevated levels of high-sensitivity C-reactive protein (hsCRP) at the time of percutaneous coronary intervention predicts 10-year mortality and myocardial infarction.[4] Elevated level of C-reactive protein within 72 h of onset of acute coronary syndrome is associated with moderately increased long-term risk of RCE or death.[5] N-terminal B-type natriuretic levels have been associated with risk of cardiovascular events and mortality in senile patients with coronary heart disease (CHD).[6]

Several additional biomarkers may have diagnostic and prognostic value for patients with CHD.[7] For example, elevated levels of ADMA have been linked to several conditions, including stroke, dyslipidemia, chronic renal insufficiency, diabetes mellitus, metabolic syndrome, atherosclerosis, hypertension, and myocardial ischemia/reperfusion injury,[8-13] some of which are independent risk

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factors for CHD. The potential association between ADMA and cardiovascular events[14] requires further study, since previous work has been limited mostly to healthy subjects[15,16] or to patients with unstable angina.[17] The research team headed by Academician CHEN Ke-ji first proposed that "blood-stasis transforming into toxin" was the key pathological mechanism for RCEs in stable CHD patinets. In order to verify this hypothesis, we conducted a nested case-control study to examine the prognostic value of ADMA in patients with stable CHD and compare the predictive power of ADMA with that of hsCRP, so as to provide a potential biomarker of "toxin syndrome" for early identifying high-risk CHD patients.

METHODS

Study Design and Study Population

Study protocol was approved by Ethics Committee of China-Japan Friendship Hospital affiliated to the National Ministry of Health. Participants provided informed consent before being enrolled. The methods were carried out in accordance with the approved guidelines. This study was registered on Chinese Clinical Trial Registry. The registration number is ChiCTR-PRNRC-07000012. (URL:http://www.chictr.org.cn/showproj.aspx?proj=9513)

This prospective cohort study involved 1,503 outpatients with stable CHD who were admitted to one of the following 5 hospitals between October 2007 to July 2010: Xiyuan Hospital, China-Japan Friendship Hospital, Anzhen Hospital, Tongren Hospital and Fujian Institute of Integrative Medicine (the first four hospitals located in Beijing, the last hospital located in Fujian Province).

Outpatients were recruited as described.[18-20] For inclusion in the cohort, outpatients (1) had to be younger than 80 and (2) had to be diagnosed with stable CHD, which was defined as asymptomatic, stable angina or a period of stability lasting at least 1 month after acute coronary syndrome. Outpatient condition was assessed using World Health Organization criteria, which take into account symptoms as well as either changes in diagnostic electrocardiography or the presence of elevated levels of cardiac enzymes. Outpatients also (3) had to have a history of myocardial infarction or at least one coronary artery stenosis ⩾50% confirmed by coronary angiography.

Outpatients were excluded from the cohort if they presented with any of the following: (1) infection, fever, trauma, burns, or surgery within the preceding month; (2) active tuberculosis or rheumatic autoimmune disease; (3) severe heart failure, with an ejection fraction <35%; (4) severe valvular heart disease or myocardiopathy; (5) severe chronic obstructive pulmonary disease, pulmonary heart disease or respiratory failure; (6) renal insufficiency, defined as serum creatinine (Cr) >2.5 mg/dL (221 μmol/L) in men or >2.0 mg/dL (177 μmol/L) in women; (7) hepatic insufficiency, defined as alanine transaminase (ALT) levels more than 3 times the normal upper limit, or the presence of liver cirrhosis; (8) severe blood disorder; (9) severe mental illness; (10) malignancy; (11) a history of organ transplantation; or (12) life expectancy shorter than 3 years.

Follow-up lasted for 1 year. Serum samples were collected at the start. Participants filled out standardized questionnaires to provide clinicodemographic data. Researchers analyzing samples and collecting data were blinded to the objectives of the study.

Cases and Controls

The cases in this study were 36 subjects who experienced at least 1 RCE during the 1-year follow-up. As controls, 36 subjects who did not experience an RCE and who were matched to cases in terms of gender, age, and history of hypertension, diabetes, and myocardial infarction were selected. This sample size of 36 cases and 36 controls should provide 90% power to detect a standardized difference of 1.64 μmol/L in mean ADMA levels, assuming a two-sided type Ⅰ error rate of 5%.

Outcomes and Primary Exposure Variable

The primary outcome was RCE, defined as cardiac death, nonfatal myocardial infarction, or ischemic stroke. The primary exposure variable was baseline serum level of ADMA, measured using a commercially available enzyme-linked immunosorbent assay kit (ELISA, BioVendor, Brno, Czech Republic; lot No. AAE138) and a SpectraMax-M2 spectrophotometer (Molecular Devices, Sunnyvale, Canada).

Clinicodemographic Factors

Potential involvement of other clinicodemographic factors in risk of RCE was assessed using data from the questionnatires filled out at baseline. Body mass index (BMI) was calculated as mass in kilograms divided by squared height in meters. Atherogenic index (AI) was calculated as AI = [total cholesterol (TC) – high-density lipoprotein (HDL)] / HDL. Personal exercise was defined as at least 30 min of moderately intense physical activity one day.[21,22]

Biochemical Factors

The central laboratory of the China-Japan Friendship Hospital determined levels of hsCRP, low-density lipoprotein (LDL), HDL, TC, triglyceride (TG), blood glucose (GLU), fibrous protein (FIB), and Cr. Laboratory personnel were blinded to the case/control status of each sample.

Statistics

A statistician blinded to the case/control status of data performed all statistical analyses using SPSS 19.0 (IBM, Chicago, USA). The threshold of significance was defined as a 2-sided $P<0.05$. Differences between cases and controls in categorical variables were assessed for significance using the Chi-squared test. Differences in continuous variables were assessed using Student's *t*-test when data were normally distributed and showed homogeneous variance; otherwise, differences were assessed using a non-parametric test.

Potential associations between ADMA levels and risk of RCE were tested using Spearman or Pearson correlation based on 3 alternative risk models of logistic regression.[23] In these analyses, ADMA concentration was divided into quartiles. The crude risk model involved no adjustments to the data. The case-mix model incorporated critical factors that might affect the outcome.[24] The multivariable model incorporated potential confounding factors present at baseline. Using these models, logistic regression was performed to generate odds ratios (ORs). To verify the robustness of the results, models were examined using forward, backward, and stepwise selection procedures, and goodness-of-fit were assessed using the Hosmer-Lemeshow statistic. Receiver operating characteristic (ROC) curves were generated to assess the predictive ability of the logistic regression models.

RESULTS

Baseline Characteristics of Cases and Controls

Baseline characteristics of the entire cohort of 1,503 as well as of the 36 cases and 36 controls are summarized in Table 1. Levels of hsCRP were significantly higher in cases than in controls ($P<0.05$). The same was true of ADMA level (1.91 ± 0.31 *vs.* 1.65 ± 0.40 μmol/L, $P=0.00$).

Table 1. Baseline Clinical Characteristics

Characteristic	All of group (*n*=1,503)	Control group (*n*=36)	Case group (*n*=36)	*P* value
BMI (kg/ m^2)	25.46 ± 3.14	25.59 ± 3.34	25.71 ± 3.44	0.89
HsCRP (mg/L)	2.56 ± 5.17	0.85 (0.32, 1.65)	1.73 (0.50, 4.26)	0.04
LDL (mmol/L)	2.59 ± 0.95	2.79 (2.19, 3.31)	2.31 (1.96, 2.90)	0.07
HDL(mmol/L)	1.11 ± 0.32	1.17 ± 0.28	1.07 ± 0.34	0.20
TC (mmol/L)	4.29 ± 1.11	4.49 (3.72, 5.07)	4.08 (3.62, 4.87)	0.32
TG (mmol/L)	1.76 ± 1.32	1.72 (1.01, 2.06)	1.88 (1.12, 3.03)	0.11
AI	3.08 ± 1.78	2.07 (0.00, 3.15)	1.92 (0.00, 2.99)	0.38
GLU (mmol/L)	6.35 ± 2.05	5.83 (5.17, 7.49)	6.32 (5.27, 8.41)	0.36
ADMA (μmol/L)	NR	1.65 ± 0.40	1.91 ± 0.31	0.00
FIB (g/L)	3.31 ± 0.88	3.41 ± 1.10	3.23 ± 1.13	0.50
Cr (μmol/L)	82.90 ± 20.24	81.00 (69.50,93.75)	79.65 (66.50,96.83)	0.88
Smoking history (%)	57.15	52.78	58.33	0.64
Personal exercise (%)	58.82	69.44	36.11	0.85
Family history of CHD (%)	35.79	38.89	52.78	0.34
Diuretics (Case)	80	1	1	1
ACE inhibitors/ARB (Case)	740	10	9	0.79
Lipid-lowering drugs (Case)	1,110	23	16	0.10
Beta-blocking drugs (Case)	1,022	16	14	0.63
Aspirin (Case)	1,388	25	22	0.46

Notes: Data were presented as frequencies (percentages) for categorical variables and as means ± SD and medians (25th, 75th percentiles) for continuous variables. Categorical data were presented as the number of people who used specific drugs in each group. Paired. BMI: body mass index; hsCRP: sensitivity C reactive protein; LDL: low density lipoprotein; HDL: high density lipoprotein; TC: total cholesterol; TG: triglyceride; AI: atherogenic index; GLU: glucose; ADMA: asymmetric dimethylarginine; FIB: fibrin; Cr: Creatinine; CHD: coronary heart disease. AI=(TC–HDL)/HDL; NR: no report; ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker

ADMA Levels and Risk of RCE

Univariate analysis was used to identify factors associated with the significantly higher baseline ADMA level in cases than in controls. The following factors showed an association (P<0.21): hsCRP, HDL, LDL, TG, ADMA. These 5 factors were entered into the regression analysis using a case-mix adjusted model. Confounders[25] previously shown to affect ADMA level (gender, age, LDL, hsCRP, FIB and Cr) were checked for correlation with ADMA levels in our cases and controls. Significant associations of ADMA level with gender and age were detected (P<0.05, Table 2), so these two factors were included in the multivariable adjusted model. During regression, ADMA levels were treated categorically as quartiles (in μmol/L): <1.526, 1.526–1.766, 1.766–2.058, and >2.058.

Table 2. Correlation of ADMA and Potential Confounders

Index	Gender	Age	LDL-C	hs-CRP	FIB	Cr
correlation coefficient	0.284	0.265	0.144	0.210	0.132	0.093
P value	0.016	0.025	0.227	0.077	0.272	0.438

Note: Spearman and pearson correlation were used, and P<0.05 was considered significant.

Results of ADMA hierarchical regression modeling are shown in Figure 1. Finally, only ADMA and TG included in the regression equation (Table 3). In the crude model, relative risk increased with ADMA level. Subjects in the 2 highest ADMA quartiles were at significantly higher risk of RCE than those in the lowest quartile [OR 4.09, 95% confidence interval (CI) 1.01 to 16.58; OR 6.76, 95% CI 1.57 to 29.07]. This association was also observed in the case-mix model (OR 5.51, 95% CI 1.23 to 24.61; OR 7.83, 95% CI 1.68 to 36.41) and multivariable model, which adjusted for gender and age (OR 6.64, 95% CI 1.40 to 31.49; OR 13.14, 95% CI 2.28 to 75.71). Hosmer-Lemeshow testing showed good fit for all 3 models (P>0.1).

Predictive Ability of Risk Models

Since hsCRP is a traditional biomarker for cardiovascular events, it was used to benchmark the predictive ability of the 3 risk models based on ADMA quartile. ADMA quartile or hsCRP alone showed similar predictive power in the cohort, with respective areas of 0.694 and 0.636 under the ROC curves (Figure 2). Predictive power was greater for the multivariable model (0.768) or case-mixed model (0.753) based on ADMA quartile. The greatest predictive power was the multivariable model which combined ADMA and hsCRP (0.779) with sensitivity of 0.806 and specificity of 0.694.

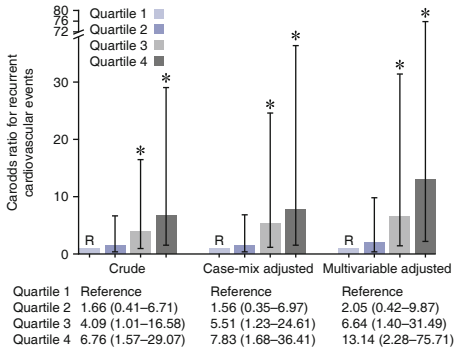

Figure 1. Odds Ratio of ADMA for Recurrent Cardiovascular Events (RCE)

Notes: Odds ratios of crude, case-mix adjusted, and multivariable adjusted models for RCE were shown according to quartiles of ADMA. The case-mix adjusted model included the following variables: hsCRP, HDL, LDL, TG, AI, ADMA. The multivariable adjusted model was based on the case-mix model considering confounders of gender and age. Bars represent 95% confidence intervals. *P<0.05. R means reference.

Table 3. Unadjusted and Adjusted OR for Recurrent Cardiovascular Events

Model	Index	*P* value	OR	CI
Crude	ADMA (Q1)	0.04		
	ADMA (Q2)	0.48	1.66	0.41–6.71
	ADMA (Q3)	0.049	4.09	1.01–16.58
	ADMA (Q4)	0.01	6.76	1.57–29.07
Case-mix	ADMA (Q1)	0.02		
	ADMA (Q2)	0.56	1.56	0.35–6.97
	ADMA (Q3)	0.03	5.51	1.23–24.61
	ADMA (Q4)	0.01	7.83	1.68–36.41
	TG	0.04	1.78	1.03–3.07
Multivariable (only ADMA)	ADMA (Q1)	0.01		
	ADMA (Q2)	0.37	2.05	0.42–9.87
	ADMA (Q3)	0.02	6.64	1.40–31.49
	ADMA (Q4)	0.00	13.14	2.28–75.71
	TG	0.03	1.96	1.07–3.57
	Gender	0.43	0.62	0.19–2.04
	Age	0.28	0.97	0.90–1.03

Notes: CI: confidence interval; Q: quartile. Bivariate regression analysis was used, and P<0.05 was considered significant.

Subgroup Analysis

Analysis of 54 subjects (23 cases and 31 cotrols) with baseline hsCRP levels <3 mg/L showed the highest quartile of ADMA significantly related to RCE in the crude model (OR 5.50, 95% CI 1.05 to 28.88), case-mix model (OR 6.39, 95% CI 1.12 to 36.59) and multivariable model (OR 14.96, 95% CI 1.84 to 121.68).

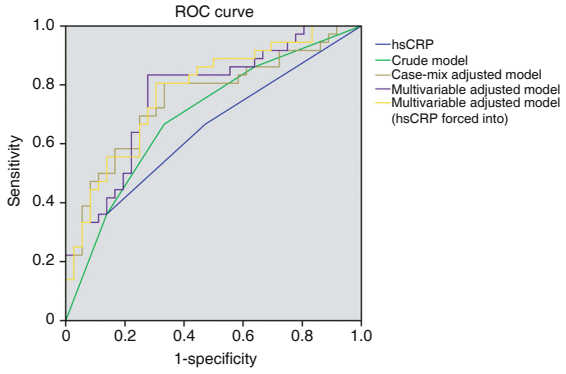

Figure 2. Predictive Ability of Risk Models (ROC Curve)

Notes: Areas under the ROC curve respectively are: crude model of hsCRP: 0.636; crude model of ADMA: 0.694; case-mix adjusted model of ADMA: 0.753; multivariable adjusted model of ADMA: 0.768; multivariable adjusted model which combined ADMA and hsCRP: 0.779

DISCUSSION

In this nested case-control study involving Chinese patients with stable CHD, high ADMA quartile was associated with increased risk of RCE, regardless of the risk model used and even after adjusting for confounders.

The present study extends the literature linking elevated ADMA levels with cardiovascular events. One meta-analysis found significantly higher ADMA levels in patients with CHD than in healthy controls [weighted mean difference (WMD) 0.248, 95% CI 0.156 to 0.340, $P<0.001$].[26] This relationship was also observed separately for subgroups of patients with myocardial infarction (WMD 0.397, 95% CI 0.112 to 0.683, $P=0.0106$), stable angina pectoris (WMD 0.197, 95% CI 0.031 to 0.364, $P=0.02$) and unstable angina pectoris (WMD 0.857, 95% CI 0.293 to 1.420, $P=0.003$). Similar results were reported by Schulze, et al.[27] Instead of comparing patients with healthy individuals, Valkonen, et al[28] examined ADMA levels and RCE risk in a cohort of middle-aged, non-smoking Finnish men. Their prospective, nested case-control study showed that subjects in the highest ADMA quartile (>0.62 μmol/L) were at 3.9-fold higher risk of RCE (95% CI 1.25 to 12.3, $P=0.02$) than those in the other quartiles. A study looking at ADMA levels and risk of RCE among patients with CHD reported that ADMA level correlated with the occurrence of significant coronary artery disease, as well as with severity of coronary atherosclerosis.[29]

Aside from case-control studies, several large-scale prospective studies have shown ADMA to be a biomarker of cardiovascular events,[30,31] including the AtheroGene study[32] and Ludwigshafen Risk and Cardiovascular Health Study.[33] The Framingham Study, involving 3,320 subjects followed up for 11 years, found relationships between ADMA levels and all-cause mortality.[34] This extensive literature contrasts with some studies showing that symmetrical dimethylarginine (SDMA), but not ADMA, is associated with cardiovascular events.[16,35] For example, 1 trial in 1,148 patients with stable CHD found no significant association between serum ADMA levels and risk of RCE: a 1 standard deviation increase in ADMA level was associated with a hazard ratio of 1.02 (95% CI 0.86 to 1.21).

The present study extends previous work showing an association between elevated ADMA levels and prognosis of patients with CHD:[36-39] unlike most previous work, our study involved subjects with stable disease. Our results add to the already wide range of disease backgrounds in which ADMA predicts clinically important outcomes. For example, ADMA is a strong independent predictor of mortality in older healthy individuals,[40] and ADMA levels in patients with CHD are lower in the presence of a stent placement compared with angiography alone.[41]

ADMA levels in our cohort were higher than those reported in other studies. While this may reflect differences in ethnicity and other clinicodemographic characteristics, it may also reflect the fact that we used ELISA to assay ADMA, which gives significantly higher readings than HPLC.[42]

Combined with previous work, the present study suggests that serum levels of ADMA may be an independent predictor of RCE in patients with stable CHD with hsCRP levels below 3 mg/L, which indicates its additional prognostic value in this population. At the same time, our findings should be treated with caution, since we looked only at risk of RCE during 1 year. This raises the question of whether ADMA levels continue to have predictive power in the long term. Further prospective studies involving larger cohorts and longer follow-up are needed to verify and extend our results.

According to Chinese medicine (CM) theory, blood stasis is one of the most important pathogenesis of CHD and it almost runs through the development of CHD. The vascular endothelial damage, oxidative stress injury, inflammatory reaction and myocardial

necrosis involved in the process of vulnerable plaque rupture and thrombosis as well as subsequent myocardial infarction is closely related to the "toxin syndrome" of CM theory. Therefore, ADMA elevation might be regarded as a potential biomarker and microscopic representation of "toxic syndrome" in stable CHD patients which deserves further study.

One challenge to validating ADMA as a biomarker of RCEs is determining the range of normal values in order to establish clear risk thresholds and treatment targets. Lowering ADMA to target levels is another formidable challenge: although some drugs may reduce ADMA levels,[43,44] no specific ADMA inhibitors are known. Clearly much work remains to be done before ADMA monitoring and treatment can become a weapon against RCEs.

Conflict of Interest

The authors have declared that no conflict of interest exists.

Author Contributions

Chen KJ and Shi DZ conceived and designed the trials and performed interpretation of the results; Xu H and Chen Z carried out the project, drafted the paper and analyzed data; Shang QH and Gao ZY collected the information of all volunteers; Yu CA performed the experiments in this trial.

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