Original Article

Statin Treatment Decreased Serum Asymmetric Dimethylarginine (ADMA) Levels in Ischemic Stroke Patients

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***Aim*: It remains unclear whether the decrease in the ADMA level associated with statin treatment results from the LDL-C-lowering effect or the pleiotropic effects of statins. A prospective, controlled study was conducted to examine whether statin treatment affects serum ADMA concentrations in ischemic stroke patients.**

***Methods*: Consecutive outpatients with non-cardiogenic ischemic stroke who had never been treated with statins and whose LDL-cholesterol level was higher than 140 mg/dL were enrolled and compared with control patients whose LDL-cholesterol level was lower than 140 mg/dL. Overall, 114 patients were enrolled in the study (56 and 58 in statin-treated and non-statin-treated groups, respectively). Patients in the statin group were treated with pravastatin 10 mg/day ($n=15$), fluvastatin 20 mg/day ($n=14$), pitavastatin 1 mg/day ($n=14$), or atorvastatin 10 mg/day ($n=13$).**

***Results*: The serum ADMA concentration and LDL-C level were significantly decreased by statin treatment ($p=0.003$ and $p<0.001$, respectively), and the ADMA concentration in subjects treated with statins was significantly lower than that of the control ($p=0.028$). Multiple linear regression analysis showed that age ($\beta=0.26$, $p<0.05$) and statin use ($\beta=-0.20$, $p<0.05$) were independently associated with the ADMA level.**

***Conclusions*: A significant relation between statin treatment and decreased levels of ADMA was demonstrated in ischemic stroke patients with an adequately controlled lipid profile, suggesting the statin treatment might prevent atherosclerotic disease in ischemic stroke patients through suppression of ADMA concentration.**

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Key words; Ischemic stroke, Statin, ADMA, Pleiotropic effect

Introduction

Although 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) decrease low-density lipoprotein cholesterol (LDL-C) levels and the incidence of vascular events in both the primary and secondary prevention of coronary heart disease (CHD)[1, 2] and stroke[3], their beneficial effect on CHD risk cannot be explained by a decrease in LDL-C alone[4, 5]. In fact, statins reduce the risk of myocardial infarction and stroke even in patients with average or lower-than-average cholesterol concentrations, and a wide range of evidence suggests that statins protect against the progression of vascular disease and improve vascular endothelial function via pleiotropic effects that are independent of any lipid-lowering mechanism. In particular, these drugs decrease the risk of vascular events in patients with cardiovascular disease and ischemic stroke irrespective of the baseline LDL-C level[6].

The maintenance of physiological vascular tone

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and structure depends on endothelial production and the release of nitric oxide (NO)[7]. Asymmetric dimethylarginine (ADMA) was recently characterized as an endogenous, competitive inhibitor of NO synthase and is now considered a novel independent risk factor for endothelial dysfunction[8]. Among the convincing evidence, some studies have reported associations between elevated plasma ADMA and impaired NO synthesis in hypercholesterolemia, coronary heart disease[9, 10], and vascular risk factors[11], while another found an independent association between a 1-mmol/L increase in plasma ADMA and 26% increase in the risk of all-cause mortality in patients with end-stage renal disease[12]. More recent studies indicated that ADMA is an independent marker for acute stroke and transient ischemic attack[13]. In our previous study, it was demonstrated that a higher ADMA concentration may be a useful marker of the future development of ischemic stroke[14]. Elevated ADMA concentrations are highly prevalent in patients with hypercholesterolemia, and a positive correlation between plasma LDL-C and ADMA concentration has been reported[8]. Statins treatment for patients with hypercholesterolemia may thus lead to a significant decrease in the plasma ADMA level[15].

Nevertheless, it remains unclear whether the decrease in the ADMA level results from the LDL-C-lowering effect of statins or from their pleiotropic effects. Indeed, the relation between the ADMA level and statin therapy remains highly controversial[15-17], probably due to variations in baseline lipid profiles in the various study populations.

Here, we conducted a prospective, controlled study to examine whether statin treatment affects serum ADMA concentrations in ischemic stroke patients.

Methods

Study patients

Consecutive outpatients with non-cardiogenic ischemic stroke who had never been treated with statins and whose LDL-cholesterol level was higher than 140 mg/dL were enrolled during the period of January 2004 through March 2006 at Shioda Hospital (Chiba, Japan). Patients in the chronic stage (at least 3 months after ischemic stroke) and who were able to look after own affairs without assistance (modified Rankin Scale 0-2) were enrolled in the study. After measurement of serum ADMA and LDL-cholesterol and other clinical factors in the morning fasting state as described later, the subjects were treated with pravastatin, fluvastatin, pitavastatin, or atorvastatin for more than 3 months. The first 15 patients enrolled were administered pravastatin, the second 15, fluvastatin, the third 15, pitavastatin, and the rest, atorvastatin, and changing drugs was not allowed during the study period. ADMA and LDL-cholesterol were measured before and after statin treatment. This statin group was compared with the non-statin-treated control group, which consisted of consecutive outpatients with non-cardiogenic ischemic stroke who had never been treated with statins, with LDL-cholesterol levels under fair to good control (less than 140 mg/dL), who were enrolled during almost the same period at the same hospital. The patients were in a chronic stage of ischemic stroke and had no symptoms to slight disability (modified Rankin Scale 0-2).

Neuroimaging study, including brain magnetic resonance imaging (MRI), was performed to confirm the clinical diagnosis of ischemic stroke. Patients were excluded if they had TIA or a known cardiac source of embolus (chronic or paroxysmal atrial fibrillation, mitral stenosis, mechanical valve, intracardiac clot or vegetation, myocardial infarction within 3 months of enrollment, dilated cardiomyopathy, or left atrial spontaneous echo contrast). The study was approved by the ethics committee of Shioda Hospital and written informed consent was obtained either from the patients or their relatives.

Data collection

Ischemic stroke and the type of stroke were diagnosed by two or more certified neurologists. Prior use of medications for hypertension (HT), hyperlipidemia (HL), or diabetes mellitus (DM) was recorded for all patients. To evaluate the detailed mechanisms of the effect of statins on ADMA, we measured total cholesterol (TC), high-density cholesterol (HDL-C), LDL-C, triglycerides, fasting blood sugar, body mass index (BMI), and estimated glomerular filtration rate (eGFR) by the newly derived creatinine-based GFR-estimating equation for Japanese, at baseline and at month 3[18].

Analysis of ADMA

ADMA was measured by high-performance liquid chromatography using ortho-phthalaldehyde for fluorescence determination (SRL, Tokyo, Japan) in accordance with a previously described method with several modifications[19]. Briefly, HPLC was performed on a Hitachi L-7100 system equipped with a Jasco FP-2025 fluorescence detector for excitation at 348 nm and emission at 450 nm with a PEGASIL ODS (4.6 mm i.d. x 250 mm; Chemical Inspection and Testing Institute). Samples were eluted with 75

Table 1. Patient Characterisics

	Non-statin group ($n=58$)	Statin group ($n=56$)	p value
Mean age, y (SD)	73.1 (10.1)	70.4 (10.6)	0.180
Female, %	34.5	44.6	0.267
Hypertension, %	86.2	75.5	0.193
Diabetes, %	15.5	14.3	0.854
Smoking, %	31.0	26.7	0.617
Ischemic heart diseases, %	3.5	5.4	0.676
Type of cerebral infarction (ATI), %	17.2	25.0	0.310
Total cholesterol, mg/dL (SD)	181.8 (26.6)	184.7 (35.7)	0.617
LDL cholesterol, mg/dL (SD)	108.7 (24.0)	110.3 (28.4)	0.741
HDL cholesterol, mg/dL (SD)	52.9 (13.4)	53.8 (14.2)	0.719
Triglycerides, mg/dL (SD)	101.6 (47.6)	114.1 (50.0)	0.175
FBS, mg/dL (SD)	109.8 (32.8)	113.9 (46.9)	0.587
BMI, kg/m^2 (SD)	22.2 (2.9)	22.3 (2.5)	0.831
eGFR (mL/min/1.73m^2) (SD)	68.6 (18.7)	67.3 (18.3)	0.724

ATI: atherothrombotic infarction, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FBS: fasting blood sugar, BMI: body mass index, eGFR: estimation of glomerular filtration rate

mmol/L aqueous sodium acetate buffer.

Statistical analysis

Group statistical comparisons were assessed by paired *t*-test before and after treatment with statins. Results are presented as the mean ± SD for continuous variables and the percentage of total patients for categorical variables. Categorical data were expressed as the percentage of the total. Fisher's exact test was used to compare the categorical variables between groups. The relationship between the ADMA and the cerebrovascular risk factors was assessed by means of Pearson's moment correlation coefficient. Analysis of covariance was used to test the difference between statin and non-statin groups. Multiple linear regression analysis was conducted to identify independent relations between variables, with ADMA as the dependent variable and age, sex, HT, DM, smoking, ischemic heart disease, LDL-C, high density lipoprotein (HDL)-C, and triglycerides as the independent variables. Statistical significance was accepted at $p<0.05$ for all analyses. There were no missing data in any of the analyses described. All analyses were performed with the SPSS software program, version 11.0.1 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

Overall, 117 patients were enrolled in the study (59 and 58 in statin-treated and non-statin-treated groups, respectively). All patients in both groups were treated with aspirin 100 mg/day monotherapy and no other antithrombotic agents were administered. Two patients were lost to follow-up, one patient dropped out because of urinary hemorrhage in the statin group, and 56 patients were followed for the 3-month study period. Patients in the statin group were treated with pravastatin 10 mg/day ($n=15$), fluvastatin 20 mg/day ($n=14$), pitavastatin 1 mg/day ($n=14$), or atorvastatin 10 mg/day ($n=13$). Patient characteristics at baseline for the control group and at month 3 for the statin group are shown in **Table 1**. Mean ages in the statin and control groups were 73.1 ± 10.1 and 70.4 ± 10.6 years, respectively, without a significant difference between groups ($P=0.180$). The statin group consisted of 25 women (44.6%) and 31 men (55.4%), and the control group of 20 women (34.5%) and 38 men (65.5%), also without a significant difference ($P=0.267$). Additionally, no significant differences were seen between the groups in the prevalence of HT or DM, smoking, ischemic heart disease, type of cerebral infarction, FBS, BMI, eGFR, TC, LDL-C, MDA-LDL-C, HDL-C, or TG.

Effect of statins on ADMA

Effects of statins on ADMA and LDL-C are shown in **Fig. 1**. Serum ADMA concentration was significantly decreased from 0.512 ± 0.098 μmol/mL to 0.457 ± 0.065 μmol/mL by statin treatment for over 3 months ($p=0.003$). The LDL-C level was also significantly decreased from 154.9 ± 15.4 mg/dL to 110.3 ±

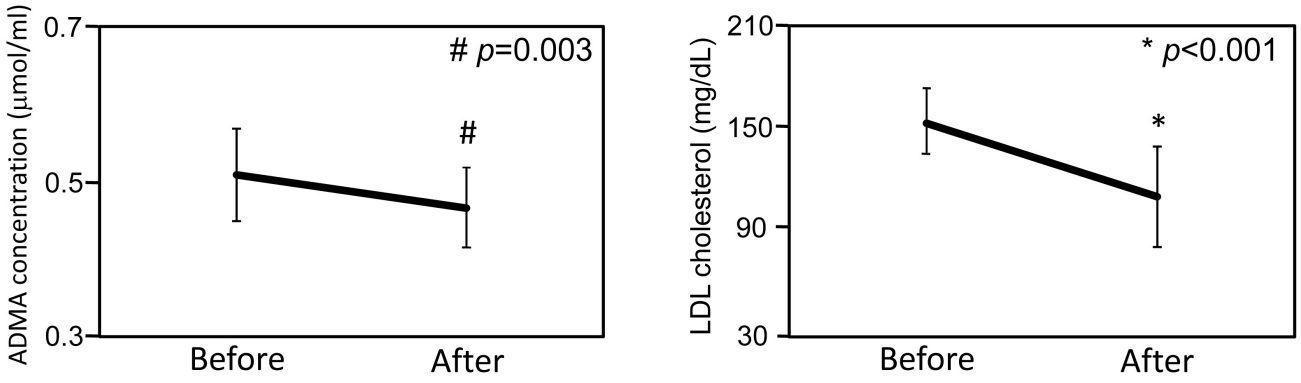

Fig. 1. Asymmetric dimethylarginine (ADMA) and LDL-C before and after treatment with statins for more than 3 months.

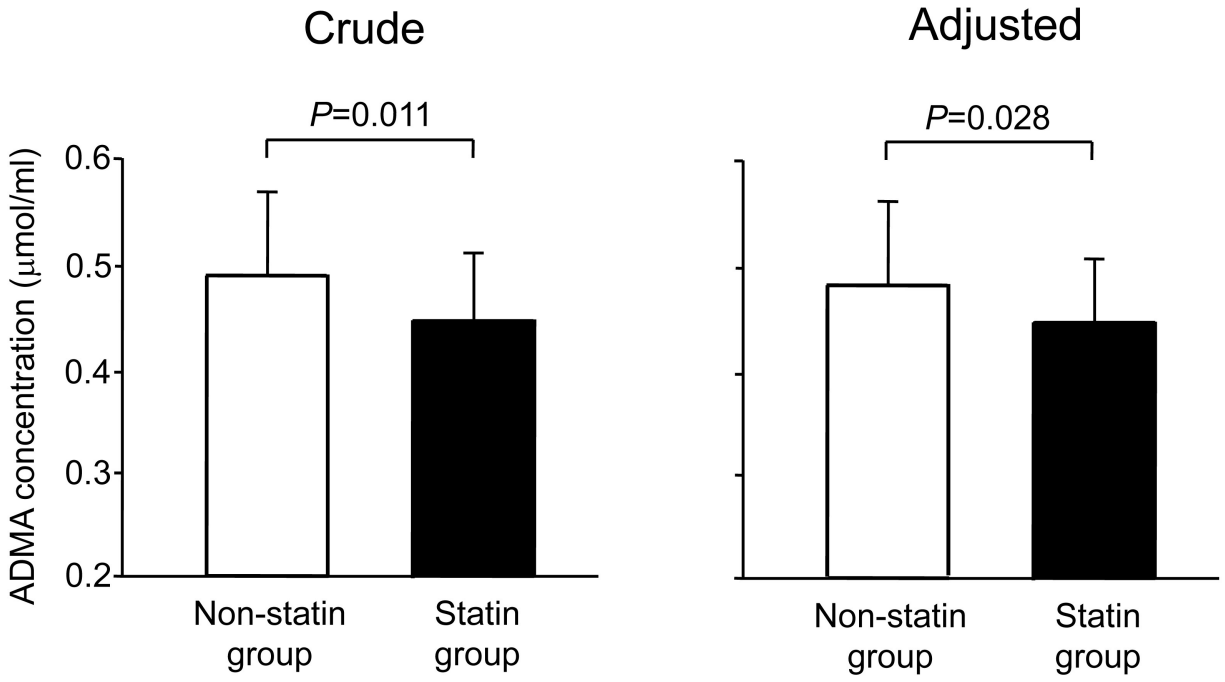

Fig. 2. Differences in serum ADMA between statin and non-statin groups.

Subjects treated with statins had lower serum ADMA concentrations than the control group (left panel). After adjusting for age, gender, HT, DM, smoking, ischemic heart disease, type of cerebral infarction, LDL-C, HDL-C, TG, FBS, BMI, and eGFR, the ADMA concentration in subjects treated with statins was significantly lower than that of the control (right panel).

28.4 mg/dL with statins ($p<0.001$). No differences were seen among the effects of the four statins on LDL-C and ADMA levels (data not shown).

Differences in serum ADMA between statin and non-statin groups

Subjects treated with statins had lower serum ADMA concentrations than the control group (0.457 ± 0.065 μmol/mL vs 0.493 ± 0.082 μmol/mL, $p=0.011$, **Fig. 2**, left panel), in spite of similar levels of LDL-C. After adjusting for age, gender, HT, DM, smoking, ischemic heart disease, type of cerebral infarction, LDL-C, HDL-C, TG, FBS, BMI, and eGFR, the ADMA concentration in subjects treated with statins was significantly lower than that of the control (0.459 ± 0.10 μmol/mL vs 0.490 ± 0.095 μmol/mL, $p=0.028$, **Fig. 2**, right panel).

Table 2. Relationship between ADMA and the clinical parameters

	Pearson's correlation coefficient		Multiple linear regression analysis	
	r	*p* value	*β*	*p* value
Age	0.37	<0.001	0.26	<0.05
Gender (Female=0, Male=1)	−0.10	0.29	0.00	1.00
Hypertention (No=0, Yes=1)	0.17	0.07	0.14	0.13
Diabetes (No=0, Yes=1)	−0.17	0.07	−0.09	0.47
Smoking (No=0, Yes=1)	−0.21	<0.05	−0.11	0.26
Ishemic heart diseases (No=0, Yes=1)	−0.03	0.79	0.07	0.49
Type of cerebral infarction (ATI=0, LI=1)	0.05	0.59	−0.06	0.53
Statin use (No=0, Yes=1)	−0.24	<0.05	−0.20	<0.05
Total cholesterol	−0.13	0.17	*N*	
LDL cholesterol	−0.07	0.46	0.00	0.98
HDL cholesterol	0.07	0.44	0.15	0.14
Triglycerides	−0.15	0.11	−0.01	0.91
FBS	−0.18	0.05	−0.13	0.29
BMI	−0.07	0.45	−0.08	0.41
eGFR	−0.21	<0.05	−0.11	0.29
				(model R^2=0.270)

N: not included in the model, ATI: atherothrombotic infarction, LI: lacunar infarction, LDL: low-density lipoprotein, HDL: high-density lipoprotein, FBS: fasting blood sugar, BMI: body mass index, eGFR: estimation of glomerular filtration rate

Relationship between serum ADMA and the Clinical Factors

Pearson's correlation coefficients of serum ADMA with clinical parameters are shown in **Table 2**. There was a mild to moderate correlation of serum ADMA with age, smoking, statin use, and eGFR. In multiple linear regression analysis, age and statin use were independently associated with serum ADMA, with age correlating positively and statin use correlating negatively. When stepwise multiple linear regression analysis was conducted, the results did not change materially; age (β=0.348, p<0.001) and statin use (β=−0.193, p=0.029) were independently associated with the ADMA level and other variables were removed from the model.

Discussion

In this study, statin treatment significantly decreased serum ADMA levels. Additionally, the ADMA levels were significantly lower in patients after treatment with statins than in those without statin treatment, although the LDLC levels were similar between the groups. Given the role of ADMA elevation in the pathogenesis of cerebrovascular disease, these findings raise the possibility that statin treatment might prevent atherosclerotic disease even in patients who have suffered a stroke. Our findings might explain the findings of several large prospective trials conducted previously. Patients in the WOSCOPS study receiving pravastatin had a lower risk of CHD than those receiving a placebo, regardless of the LDL-C level (140 to 180 mg/dL)[4], while the relative risk reduction conferred by atorvastatin treatment in the ASCOT/LLA study was independent of pretreatment lipid levels[5]. These findings suggest that the beneficial effects of statins may be attributable to mechanisms beyond cholesterol reduction.

Among candidates for non-cholesterol-related mechanisms, NO, a potent biological vasodilator produced by endothelial nitric oxide synthase (eNOS) from L-arginine in the vascular endothelium, has been reported to play a key role in the regulation of vascular tone, and the growth and maintenance of a thrombo-resistant interface between the bloodstream and the vessel wall via various mechanisms, namely the inhibition of platelet aggregation, leukocyte migration, cellular adhesion, and vascular smooth muscle cell proliferation[8, 20]. Given that the main cause of endothelial dysfunction is the decreased bioavailability of NO, an association between eNOS and vascular disease has been recognized. Deficiency of NO in the endothelium may produce endothelial dysfunction via two general mechanisms[21], namely, decreased synthesis of endothelial NO due to reduced eNOS expression or activity, and increased breakdown of eNOS-derived NO due to oxidative stress. Indeed, endothelial dysfunction is also a risk factor for cerebrovascular

events[22].

In addition to these mechanisms, however, the endogenous NO inhibitor ADMA has also recently emerged as a key factor in NO biosynthesis. Various findings suggest that ADMA increases the risk of atherosclerosis by inhibiting endothelial NO increase. Among them, high ADMA concentrations block NO synthase activity *in vitro*[23] and inhibit endothelium-dependent vasodilation in humans[8]. An increase in ADMA levels may be related to the inactivation of eNOS enzyme. Additionally, in individuals with overt atherosclerotic vascular disease, ADMA concentration is associated with the degree of endothelial dysfunction and decrease in NO elaboration[8, 24]. Regulation of eNOS activity by ADMA is therefore likely to modulate the progression of atherosclerosis.

Age was also independently associated with ADMA levels, which is consistent with the findings from several previous studies that showed age to be a strong positive predictor of ADMA elevation[11]. Further, elevated ADMA concentrations have also been confirmed in patients with hypercholesterolemia, hypertension, type II diabetes, and insulin resistance[8, 25, 26]. A prospective study showed that ADMA elevation was a predictor of severe cardiovascular events and total mortality[9]. With regard to cerebrovascular disease, high ADMA levels have been identified in patients with ischemic stroke, transient ischemic attack, and cerebral small vessel disease[13, 27]. To date, however, an association between ADMA and ischemic stroke has not been reported.

Although the mechanisms of the beneficial effects of statin therapy on endothelial dysfunction remain unclear, it is speculated that statin therapy is accompanied by increased NO bioavailability[28]. Direct upregulation of eNOS by statins has recently been reported, and this may represent an important mechanism by which these compounds preserve eNOS activity. Prophylactic statin therapy was shown to enhance cerebral blood flow, reduce infarct size, and improve neurological outcome in normocholesterolemic animals[29]. Similarly, atorvastatin was shown to reduce stroke size in normocholesterolemic mice through a cholesterol-independent mechanism[30]. These findings suggest that the effects of statins on atherosclerotic disorders, including ischemic stroke, might be explained by an improvement in NO bioavailability, which is independent of the LDL-C lowering effect of statins.

Several limitations of this study warrant mention. First, our sample size was small and confirmation of the findings will require further studies in larger populations. Second, we measured serum ADMA, but not arginine (Arg). Some reports showed that a low ratio of Arg to ADMA (Arg/ADMA ratio) is a marker of endothelial dysfunction; however, elevated plasma ADMA concentration alone is thought to be an independent risk marker of the progression of atherosclerosis. Third, due to its design, the study provides no indication of the predictive value of ADMA levels. Finally, the results of this study may not be extrapolated to other populations, such as other ethnic groups or patients with moderate or more severe disability. Regardless of the limitations, the present study may provide novel findings of one of the possible pleiotropic effects of statin treatment.

Allowing for these limitations, the present study showed a significant relation between statin treatment and decreased levels of ADMA as well as a strong relation between aging and ADMA elevation in ischemic stroke patients with an adequately controlled lipid profile. Given the role of ADMA elevation in the pathogenesis of cerebrovascular disease, statin treatment might prevent atherosclerotic disease in ischemic stroke patients through the suppression of ADMA concentration, even in patients with normal LDL-C levels.

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