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Plasma Fibrinogen, Ambulatory Blood Pressure, and Silent Cerebrovascular Lesions

The Ohasama Study

Yoko Aono, Takayoshi Ohkubo, Masahiro Kikuya, Azusa Hara, Takeo Kondo, Taku Obara, Hirohito Metoki, Ryusuke Inoue, Kei Asayama, Yoriko Shintani, Junichiro Hashimoto, Kazuhito Totsune, Haruhisa Hoshi, Hiroshi Satoh, Shin-Ichi Izumi, Yutaka Imai

Objective—Twenty-four-hour ambulatory blood pressure (24-hour ABP) values are considered a powerful predictor of stroke. Silent cerebrovascular lesions are associated with an increased risk of stroke. Because fibrinogen is a major determinant of plasma viscosity, an elevated fibrinogen level might also be associated with stroke risk. We evaluated the association of 24-hour ABP and plasma fibrinogen levels with the risk of silent cerebrovascular lesions (white matter hyperintensity and lacunar infarct) detected by MRI.

Methods and Results—The study cohort comprised 958 individuals from the general population of Ohasama, a rural Japanese community. Multiple logistic regression analysis adjusted for age, sex, smoking and drinking status, use of antihypertensive medication, body mass index, 24-hour ABP, and a history of hypercholesterolemia, diabetes mellitus, and atrial fibrillation demonstrated that each 1-SD increase in fibrinogen level was associated with a significantly increased risk of silent cerebrovascular lesions (odds ratio, 1.26; $P=0.001$). The 24-hour ABP was also significantly and independently associated with the risk of silent cerebrovascular lesions. Even when 24-hour ABP values were within normal range ($<135/80$ mm Hg), elevated fibrinogen levels were associated with an increased risk of silent cerebrovascular lesions. Fibrinogen and 24-hour BP had additive effects on silent cerebrovascular lesions.

Conclusion—The 24-hour ABP and plasma fibrinogen levels were closely and independently associated with the risk of silent cerebrovascular lesions including white matter hyperintensity and lacunar infarct. (*Arterioscler Thromb Vasc Biol.* 2007;27:963-968.)

Key Words: ambulatory blood pressure ■ lacunar infarct ■ plasma fibrinogen ■ silent cerebrovascular lesions ■ white matter hyperintensity

Silent cerebrovascular lesions as white matter hyperintensity (WMH) and lacunar infarcts are frequently observed on MRI scans of elderly individuals. Silent cerebrovascular lesions constitute an independent predictor of the risk of symptomatic stroke,^{1,2} and are associated with cognitive impairment or dementia.³

Fibrinogen is involved in primary hemostasis, platelet aggregation, and leukocyte–endothelial cell interaction, and it is the major determinant of whole blood and plasma viscosity.^{4,5} Elevated fibrinogen levels induce a state of hypercoagulability,^{6,7} and may reflect the progression of atherosclerosis.

Growing evidence indicates that fibrinogen is a risk factor for coronary heart disease.^{8–10} A large meta-analysis¹¹ has shown close associations between elevated

plasma fibrinogen levels and the risk of coronary heart disease and stroke mortality. However, findings regarding the incidence of stroke,^{12–14} as well as the relationship between fibrinogen and silent cerebrovascular lesions^{15–18} are inconsistent. The latter studies included patients with a history of cerebrovascular diseases,¹⁶ or a comparatively small study cohort.^{15–17} One study has found that fibrinogen predicts coronary heart disease in Asian countries including Japan,¹⁹ but the association between silent cerebrovascular lesions and fibrinogen in the Asian general population has not been described.

Hypertension is a major risk factor for silent cerebrovascular lesions,^{18,20} and ambulatory blood pressure (ABP) is more closely correlated with target organ damage than casual blood pressure (CBP).^{21,22}

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From the Departments of Clinical Pharmacology and Therapeutics (Y.A., M.K., A.H., T.O., H.M., Y.S., K.T., Y.I.), Planning for Drug Development and Clinical Evaluation (T.O., K.A., J.H.), Environmental Health Sciences (H.S.), and Physical Medicine and Rehabilitation (T.K., S.I.), Tohoku University Graduate School of Pharmaceutical Sciences and Medicine; Tohoku University 21st Century COE Program “Comprehensive Research and Education Center for Planning of Drug Development and Clinical Evaluation” (T.O., A.H., T.O., H.M., R.I., J.H., K.T., H.S., Y.I.), Sendai, Japan; Ohasama Hospital (H.H.), Iwate, Japan.

Correspondence to Dr Takayoshi Ohkubo, Department of Clinical Pharmacology and Therapeutics, Tohoku University Hospital, 1-1 Seiryō-cho, Aoba-ku, Sendai, 980-8574, Japan. E-mail tohokubo@mail.tains.tohoku.ac.jp

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We conducted a cross-sectional study to determine the association between plasma fibrinogen and silent cerebrovascular lesions in a general population. We also evaluated the association between silent cerebrovascular lesions and the risk conferred by combined fibrinogen and ABP levels.

Methods

Design

This investigation was a part of the Ohasama study. The socioeconomic and demographic characteristics of this region and full details of the project have been described elsewhere.²³ The study protocol was approved by the Institutional Review Board of Tohoku University School of Medicine, Sendai, Japan, and by the Department of Health of the Ohasama Town Government.

Study Population

The population of Ohasama in 1998 was 7202. Of those, 3077 were 55 years or older. Individuals ($n=492$) who were not at home during the normal working hours of the study nurses, and those hospitalized, mentally ill, or bedridden ($n=185$), were not eligible for inclusion. Of the remaining 2400 eligible individuals, 1174 subjects (49%) gave informed consent and participated in the MRI examination. We excluded 173 subjects whose BP and fibrinogen levels were not adequately measured. We also exclude 43 subjects with history of previous stroke or transient ischemic attack. Therefore, a total of 958 individuals (40%; mean age 66.0 ± 5.7 years; 32% men) were included in the present analysis.

MRI

We obtained MR images using a superconducting magnet with a main 0.5 T. The brain was imaged in the axial plane in 10-mm-thick slices and we collected T1- and T2-weighted images. A lacunar infarct was defined as an area of low signal intensity measuring ≤ 15 mm and ≥ 3 mm on T1-weighted images and that was visible as a hyperintense lesion on T2-weighted images. Hyperintense punctate lesions evident only on the T2-weighted images were not counted as lacunar infarcts. We defined WMH as hyperintensities on only T2-weighted images, and graded it according to Fazekas²⁴ as follows: absent (grade 0), punctate (grade 1), early confluent (grade 2), and confluent (grade 3). Small caps ($< 5 \times 10$ mm) on the horns of the lateral ventricles and pencil-thin lining around the ventricles were considered normal. Larger caps ($\geq 5 \times 10$ mm) were considered as grade 2. A neurosurgeon and 4 technical experts directed by the neurosurgeon independently evaluated the MRI findings in a blinded manner. In the case of disagreement, a consensus reading was held. Both intra-reader and inter-reader studies ($n=111$) showed good agreement. Kappa statistics were between 0.68 and 0.86 for lacunar infarct, and between 0.72 and 0.86 for WMH. We defined silent cerebrovascular lesions as: (1) WMH of grade 1 or more; (2) presence of lacunar infarcts; or (3) any combination of these findings.

BP Measurements

ABP was monitored using a fully automatic ABPM630 device (Nippon Colin, Komaki, Japan)²⁵ preset to measure BP every 30 minutes. Mean 24-hour, daytime, and nighttime values for ABP were calculated for each participant. Daytime and nighttime values were estimated from the subjects' diaries.

CBP was measured twice consecutively in the sitting position, after a minimum 2-minute interval of rest, by a doctor using a mercury sphygmomanometer or an automatic device (HEM907; Omron Healthcare Co. Ltd, Kyoto, Japan) at the time of MRI examination. The average of the 2 readings was defined as the CBP.

Devices used to measure ABP and CBP have been validated^{25,26} and met the criteria of Association for the Advancement of Medical Instrumentation.²⁷

Physical and Biochemical Examination

Fibrinogen (mg/dL) was measured by the Clauss method. Hypercholesterolemia was defined as total cholesterol ≥ 220 mg/dL, use of medication for hypercholesterolemia, and/or a history of hypercholesterolemia. Diabetes mellitus was defined as a nonfasting glucose level of ≥ 200 mg/dL, HbA1c level of $\geq 6.5\%$, use of medication for diabetes, and/or a history of diabetes mellitus.

Statistical Analysis

To analyze the relationship between silent cerebrovascular lesions and patient characteristics, we used the χ^2 test for categorical data and the Student t test for continuous data. We examined the associations between fibrinogen and silent cerebrovascular lesions using logistic regression analysis. Quartiles were initially analyzed, where the lowest quartile was treated as the reference category. We then entered fibrinogen as a linear term (per SD) into the model. We adjusted for age (continuous variable), sex (men, women), cardiovascular risk factors including smoking status (ever, never), drinking status (ever, never), use of antihypertensive medication (treated, untreated), body mass index (≥ 25 kg/m², < 25 kg/m²), 24-hour ABP (continuous variable), and a history of hypercholesterolemia, diabetes mellitus, and atrial fibrillation (present, absent). We also examined the combination of fibrinogen and 24-hour ABP levels using logistic regression analysis. All statistical analyses were conducted using SAS software, version 9.1 (SAS Institute Inc, Cary, NC). Values are expressed as means \pm SD. $P < 0.05$ was considered statistically significant.

Results

Fibrinogen and Silent Cerebrovascular Lesions

Individuals with silent cerebrovascular lesions were significantly older, had higher frequencies of use of antihypertensive medication, cardiovascular disease, lower body mass index, and higher 24-hour, daytime, nighttime ABP (both systolic and diastolic BP), and fibrinogen levels (Table 1). In individuals with silent cerebrovascular lesions, serum creatinine levels were significantly higher. Other biochemical factors were not associated with silent cerebrovascular lesions.

Figure 1 shows the adjusted odds ratios (ORs) and 95% CIs for silent cerebrovascular lesions among the quartiles of fibrinogen. The highest quartiles of fibrinogen were associated with a significant increase in the risk for silent cerebrovascular lesions (OR, 1.99; 95% CI, 1.34 to 2.97; $P=0.0007$). The associations were also similar for WMH and lacunar infarct, respectively (Figure 2a, 2b). The highest quartiles of fibrinogen were associated with a significant increase in the risk for WMH (OR, 1.78; 95% CI, 1.20 to 2.65; $P=0.004$) and lacunar infarct (OR, 1.70; 95% CI, 1.09 to 2.65; $P=0.02$).

The logistic regression analysis showed that more advanced age, use of antihypertensive medication, lower body mass index, higher 24-hour ABP, and fibrinogen levels were significantly associated with silent cerebrovascular lesions (Table 2). Each 1-SD (62.0 mg/dL) increase in fibrinogen was significantly associated with a risk for silent cerebrovascular lesions (OR, 1.26; 95% CI, 1.09 to 1.46; $P=0.001$). When daytime or nighttime ABP or CBP was adapted to this model instead of 24-hour ABP, the trends were similar, although CBP was not significantly associated with silent cerebrovascular lesions (data not shown). When 24-hour ABP and CBP were adapted to the same model, the trends were similar, although only CBP was not significantly associated with silent cerebrovascular lesions (data not shown). The

TABLE 1. Population Characteristics (Ohasama Study, Japan, 1998)

				Silent Cerebrovascular Lesions		
				(-)	(+)	<i>P</i>
N of subjects				492	466	
Men, %				29	34	0.1
Age, y				64±5	68±5	<0.0001
BMI, kg/m ²				24±3	23±3	0.03
BP, mm Hg						
Ambulatory	24-hour	Systolic	123±12	128±13	<0.0001	
		Diastolic	72±7	74±7	<0.0001	
		Daytime	Systolic	129±13	134±14	<0.0001
			Diastolic	76±8	78±8	<0.0001
	Nighttime	Systolic	111±13	117±14	<0.0001	
		Diastolic	63±7	66±8	<0.0001	
	Casual	Systolic	140±21	142±20	0.09	
		Diastolic	78±11	78±11	0.9	
Ever smoker, %				17	21	0.07
Ever drinker, %				28	30	0.6
Antihypertensive medication, %				26	50	<0.0001
Hypercholesterolemia, %				36	38	0.6
Diabetes, %				14	17	0.2
Cardiovascular disease, %				7	12	0.007
Atrial fibrillation, %				2	3	0.3
Biochemical value						
Fibrinogen, mg/dL				289±54	306±69	<0.0001
Hematocrit, %				42±4	42±4	0.2
Total cholesterol, mg/dL				200±33	201±33	0.5
HDL cholesterol, mg/dL				57±15	56±16	0.8
Triglyceride, mg/dL				133±79	128±78	0.3
Lipoprotein(a), mg/dL				23±23	24±25	0.5
Serum creatinine, mg/dL				0.77±0.16	0.82±0.22	0.0001
Uric acid, mg/dL				4.4±1.2	4.5±1.3	0.3
High-sensitivity CRP, mg/L				0.39 (0.18–0.79)	0.47 (0.21–0.85)	0.5

Values for high-sensitivity CRP levels are medians (interquartile range).

N of biochemical examination: fibrinogen and lipoprotein(a), 958; hematocrit, 901; total cholesterol and triglyceride, 946; HDL cholesterol, 900; serum creatinine, 939; uric acid, 931; high-sensitivity CRP, 224.

BMI indicates body mass index; BP, blood pressure; CRP, C-reactive protein; HDL, high-density lipoprotein.

associations were also similar for WMH and lacunar infarct, respectively (data not shown).

Other biochemical factors were not significantly associated with silent cerebrovascular lesions in the multivariate analysis ($P>0.08$).

We also performed stratified analysis. Sex (men/women), age (<65 / ≥65 years), and use of antihypertensive medication (treated/untreated) did not significantly interact the association between fibrinogen and silent cerebrovascular lesions (all P for interaction >0.2).

Association of 24-Hour ABP and Plasma Fibrinogen Levels With the Risk of Silent Cerebrovascular Lesions

Higher fibrinogen (≥328 mg/dL) and higher 24-hour ABP (≥135/80 mm Hg²⁸) levels were independently associated

with an increase risk for silent cerebrovascular lesions (Figure 3). Even when 24-hour ABP values were within normal range (<135/80 mm Hg), elevated fibrinogen levels were associated with an increased risk of silent cerebrovascular lesions. There were no significant interactions between 24-hour ABP and fibrinogen on the risk of silent cerebrovascular lesions ($P>0.8$). Fibrinogen and 24-ABP had additive effects on silent cerebrovascular lesions.

Discussion

The present cross-sectional study found that 24-hour ABP and fibrinogen levels were significantly and independently associated with prevalence of silent cerebrovascular lesions, including WMH and lacunar infarct, in a comparatively large general population.

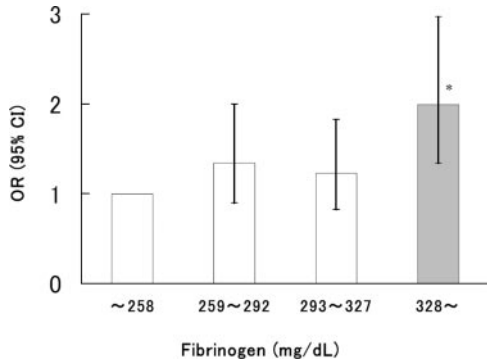


Figure 1. Adjusted ORs and 95% CIs for silent cerebrovascular lesions among the quartiles of fibrinogen. ORs for silent cerebrovascular lesions were adjusted for age, sex, smoking status, drinking status, use of antihypertensive medication, body mass index, 24-hour ABP, and history of hypercholesterolemia, diabetes mellitus, and atrial fibrillation. Cut-off for quartiles of fibrinogen: 1st, ≤ 258 mg/dL; 2nd, 259 to 292 mg/dL; 3rd, 293 to 327 mg/dL; 4th, 328 mg/dL. * $P<0.05$ vs. 1st quartile.

The findings of previous studies^{15–18} that investigated the association between fibrinogen and silent cerebrovascular lesions are inconsistent. For example, Schmidt et al¹⁵ found that higher fibrinogen levels are associated with WMH and lacunes in a multivariate analysis of 349 individuals. Meanwhile, in a population-based study of 3301 elderly individuals, Longstreth et al¹⁸ found that fibrinogen levels were not

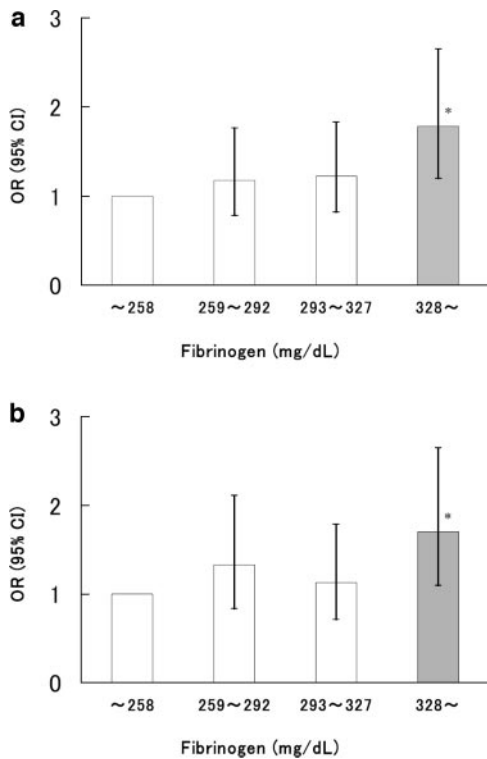


Figure 2. Adjusted ORs and 95% CIs for (a) WMH and (b) lacunar infarct among the quartiles of fibrinogen. ORs for (a) WMH and (b) lacunar infarct were adjusted for age, sex, smoking status, drinking status, use of antihypertensive medication, body mass index, 24-hour ABP, and history of hypercholesterolemia, diabetes mellitus, and atrial fibrillation. Cut-off for quartiles of fibrinogen: 1st, ≤ 258 mg/dL; 2nd, 259 to 292 mg/dL; 3rd, 293 to 327 mg/dL; 4th, 328 mg/dL. * $P<0.05$ vs. 1st quartile.

independently related to white matter grade in fully adjusted multivariate models. In this study, associations between fibrinogen and silent cerebrovascular lesions remained statistically significant even after adjustment for various confounding variables in the general population.

Recently, Sato et al demonstrated in a prospective study of Japanese subjects with no history of stroke and/or coronary heart disease that high plasma fibrinogen concentration was a predictor for risk of intraparenchymal hemorrhage but not of cerebral infarction.¹⁴ However, the clear mechanism responsible to the difference between cerebral hemorrhage and cerebral infarction was not described. The present study found that fibrinogen levels were associated with silent cerebrovascular lesions. Because silent cerebrovascular lesions constitute an independent predictor of the risk of cerebral infarction,¹ it is possible that fibrinogen would be a risk of cerebral infarction. We are following-up the present subjects to clarify this question.

The exact mechanism by which elevated fibrinogen might contribute to WMH and lacunar infarct remains unknown. However, these lesions are considered to reflect ischemic small vessel disease. Fibrinogen triggers a variety of atherogenic processes such as endothelial injuries.¹⁰ Thus, fibrinogen might promote atherogenesis not only in large vessels but also in small vessels. Elevated fibrinogen levels induce a state of hypercoagulability,^{6,7} and might reflect the progression of atherosclerosis. Such hemorheological impairments caused by increased levels of fibrinogen would aggravate cerebral hypoperfusion.

Hyperfibrinogenemia can be alleviated using drugs and by making lifestyle modifications, such as stopping smoking and starting to exercise.²⁹ Fibrinogen levels are inversely associated with dietary consumption of seafood.³⁰ Miura et al reported that higher intake of iron, sugar, and caffeine, in addition to obesity, account largely for higher fibrinogen levels.³¹ Several drugs reduce fibrinogen levels, including bezafibrate and ticlopidine.^{4,5,32} However, no reliable evidence yet supports the routine use of fibrinogen-lowering agents to reduce the risk of cerebrovascular diseases. Further study is needed to clarify this issue.

The present study indicated that ABP values are more closely associated with silent cerebrovascular lesions than with 2 measurements of CBP at one visit. This finding is consistent with those of a previous study.²² Furthermore, the present study discovered that 24-hour ABP and plasma fibrinogen levels are closely and independently associated with a risk of silent cerebrovascular lesions. Even when 24-hour ABP values were within normal range, elevated fibrinogen levels were associated with an increased risk of silent cerebrovascular lesions. These findings suggest that both factors are strong risk factors for silent cerebrovascular lesions.

Possibility of selection bias needs to be considered to generalize the present findings, because there were differences in age between the study subjects and those excluded (958 study subjects, 66.0 ± 5.7 years; 216 excluded subjects, 69.2 ± 7.0 years; $P<0.0001$). In addition, marked differences exist in the epidemiologies of cerebrovascular disease between Japan and US or European countries. Further research

TABLE 2. Multivariate ORs and 95% CIs for Silent Cerebrovascular Lesions With Cardiovascular Risk Factors

	OR	95% CI	P
Sex, men (n=303):women (n=655)	1.01	0.64–1.60	1.0
Age, per 10-year increase	2.90	2.22–3.80	<0.0001
Smoker, ever smokers (n=181):never smokers (n=777)	1.19	0.74–1.90	0.5
Drinker, ever drinkers (n=276):never drinkers (n=682)	1.19	0.80–1.79	0.4
Diabetes, present (n=149):absent (n=809)	1.06	0.72–1.55	0.8
Hypercholesterolemia, present (n=356):absent (n=602)	1.20	0.89–1.61	0.2
Atrial fibrillation, present (n=27):absent (n=931)	1.06	0.44–2.52	0.9
Antihypertensive medication, treated (n=362):untreated (n=596)	2.02	1.49–2.75	<0.0001
BMI, ≥ 25 kg/m ² (n=305):<25 kg/m ² (n=653)	0.72	0.53–0.97	0.03
24-hour average ambulatory SBP, per 10-mm Hg increase	1.23	1.10–1.39	0.0006
Fibrinogen, per 1-SD increase	1.26	1.09–1.46	0.001

SBP indicates systolic blood pressure.

These variables were simultaneously included multiple logistic regression model.

in other ethnic and cultural populations is needed to confirm the generalizability of our findings.

In conclusion, the present study demonstrated that 24-hour ABP and plasma fibrinogen levels are closely and independently associated with the risk of silent cerebrovascular lesions, suggesting that fibrinogen is an independent risk factor or predictor of silent cerebrovascular lesions.

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Disclosures

None.

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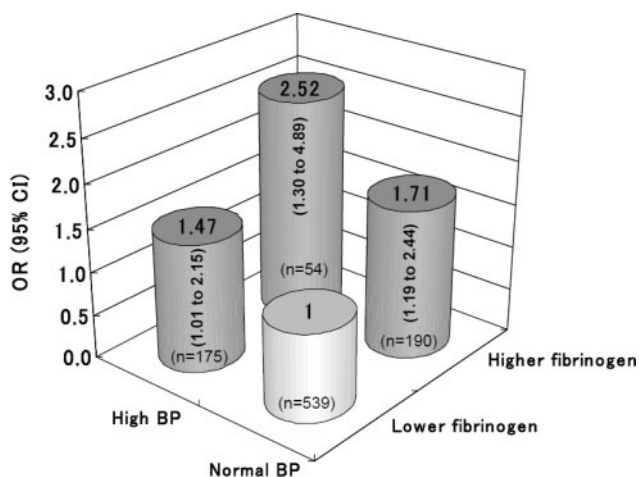


Figure 3. Adjusted ORs and 95% CIs (inside the bars) for silent cerebrovascular lesions associated with combination of fibrinogen levels and 24-hour ABP levels. ORs for silent cerebrovascular lesions were adjusted for age, sex, smoking status, drinking status, use of antihypertensive medication, body mass index, and history of hypercholesterolemia, diabetes mellitus, and atrial fibrillation. n=number of participants in group. Higher fibrinogen was defined ≥ 328 mg/dL (dichotomized at upper quartiles). Normal 24-hour ABP is defined as 24-hour ABP levels <135/80 mm Hg.

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