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The Determinants of Plasma Plasminogen Activator Inhibitor 1 Levels Differ for American and Japanese Men Aged 40–49

Tomoko Takamiya, MD¹, Takashi Kadowaki, MD^{1,2}, Wahid R. Zaky, MD¹, Hirotugu Ueshima, MD², Rhobert W. Evans, PhD¹, Tomonori Okamura, MD², Atsunori Kashiwagi, MD³, Yasuyuki Nakamura, MD⁴, Yoshiyuki Kita, PhD², Russell P. Tracy, PhD⁵, Lewis H. Kuller, MD¹, and Akira Sekikawa, MD¹

¹Department of Epidemiology, University of Pittsburgh

²Department of Health Science, Shiga University of Medical Science

³Department of Internal Medicine, Shiga University of Medical Science

⁴Department of Living and Welfare, Kyoto Women's University

⁵Departments of Pathology and Biochemistry, University of Vermont, School of Medicine

Abstract

Background—Elevated plasma plasminogen activator inhibitor-1 (PAI-1) levels were associated with higher incidence of type II diabetes. Elucidating the determinants of PAI-1 in various ethnicities may help to understand the susceptibility to developing diabetes. The aim of our study was to compare PAI-1 levels between Americans and the Japanese in the post-war generation and to elucidate the determinants of the PAI-1 levels.

Methods—We conducted a cross-sectional study on a total of 198 men aged 40–49 in the U.S. (Body-mass index (BMI): 27.0 ± 3.3 kg/m²) and Japan (BMI: 23.3 ± 3.1 kg/m²). Examination included physique measurement (BMI and waist girth), blood analysis (lipid profiles, glucose, insulin, C-reactive protein, and PAI-1), and life-style assessment by self-administered questionnaires.

Results—PAI-1 levels were significantly lower in American than in Japanese men, even after adjustment for age, waist girth, cigarette smoking, habitual alcohol drinking, and other factors. In the Americans, waist girth, insulin, and cigarette smoking were significantly associated with PAI-1 levels, while waist girth and triglycerides were significantly associated with PAI-1 levels in the Japanese.

Conclusions—PAI-1 levels were significantly lower in American than in Japanese men and the determinants of PAI-1 levels differ for American and Japanese men aged 40–49.

Keywords

PAI-1; US; Japan; epidemiology; post-war generation

Introduction

Plasminogen activator inhibitor 1 (PAI-1) is an inhibitor of plasminogen activation and is considered to be an important regulatory element in plasmin generation. It may play an

important role in settings where plasmin is important such as fibrinolysis¹ and extravascular plasmin-mediated collagenase activation in atherosclerosis and cancer²³. PAI-1 levels increases in obese subjects with insulin resistance as well as patients with type II diabetes⁴. A recent study reported that elevated plasma PAI-1 levels were associated with higher incidence of type II diabetes independent of insulin resistance and other known risk factors for diabetes⁵.

Ethnic differences in the circulating PAI-1 levels⁶⁷ were reported as well as in the susceptibility to developing type II diabetes⁸⁹. Festa et al. reported that blacks had lower PAI-1 levels and Hispanics had higher PAI-1 levels compared to non-Hispanic whites even after adjustment of waist, insulin sensitivity and other associated factors⁶. Iso et al. reported a decade ago that Americans had higher PAI-1 levels as well as higher cholesterol levels compared to Japanese⁷. Most of their subjects in their study were born before World War II and therefore, the results may not be applicable to the post-war generation, especially to the Japanese who have experienced westernization. In the post-war generation, levels of blood cholesterol in the Japanese have been reaching levels similar to those in Americans, according to recent national survey data in the U.S. and Japan^{10–12}. In our study, among the post-war generation, several metabolic risk factor profiles were even better in American men than in Japanese men¹³, although American men were more obese than Japanese men.

Therefore, within a decade following 1990, we expected to see changes in American and Japanese PAI-1 levels that reflected variations in exposure to metabolic risk factors experienced by the post-war generation. To our knowledge, there have not been prior studies that have compared PAI-1 levels between Americans and the Japanese in the post-war generation. The aim of this study was 1) to examine whether PAI-1 levels are different between the post-war generation of Americans and the Japanese, and 2) to reveal the determinants of PAI-1 levels in Americans and the Japanese.

Methods

Subjects

The research design and methods have been described in detail¹³. Briefly, we examined 100 men in Allegheny County, PA, U.S., aged 40–49, who volunteered for this study from June to October 2002, and 98 male Japanese residents in Kusatsu City, Shiga, Japan, who were randomly selected using the Basic Residents' Register from May 2001 to December 2002. Among the 100 participants at the U.S. site, 99 were Caucasians. At the Japan site, all of the participants were Japanese. Exclusion criteria were: 1) clinical cardiovascular disease, 2) type 1 diabetes, 3) cancer (except skin cancer) in the past two years, 4) renal failure, and 5) genetic familial hyperlipidemias. Informed consent was obtained from all participants. The study was approved by the Institutional Review Board of the University of Pittsburgh, Pittsburgh, U.S., and Shiga University Medical Science, Otsu, Japan.

Study protocol

BMI was calculated as weight (kg) divided by height squared (m²). Waist girth was measured at the level of the umbilicus while participants were standing erect. Blood pressure (BP) was measured twice with a standard mercury sphygmomanometer. The average of two measurements of the first (systolic) and fifth (diastolic) Korotkoff sounds was used for the analysis.

Venipuncture was performed early in the clinic visit after a 12-hour fast. Serum samples were kept at room temperature for 45 minutes. Serum samples were analysed at the Heinz Laboratory, Department of Epidemiology, University of Pittsburgh. Lipid levels were determined using the standardized methods of the Centers for Disease Control and

Prevention, including total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG). Low-density lipoprotein cholesterol (LDL-C) was estimated by the Friedewald equation ¹⁴. When the value of TG exceeded 400 mg/dl, LDL-C was determined directly using an automated spectrophotometric assay (Equal Diagnostics, Exton, PA). Fasting serum glucose was determined using an enzymatic procedure ¹⁵, and insulin level was determined using radio-immunoassay (Linco Research Inc., St. Charles, U.S.).

Plasma samples were analysed at the Laboratory for Clinical Biochemistry Research, University of Vermont. PAI-1 levels was determined as the free form (both latent and active) with an assay originally developed by Dr. Desire Collen and colleagues ¹⁶. C-reactive protein (CRP) was determined by a colorimetric competitive enzyme-linked immunosorbent assay ¹⁷, and fibrinogen in an automated clot-rate assay by the ST4 instrument (Diagnostica Stago, Parsippany, U.S.).

Insulin resistance was estimated by homeostasis model assessment (HOMA) score ¹⁸.

Self-administered questionnaires were used to obtain current medication lists, current smoking status (Yes=1, No=0), habitual alcohol drinking (Yes=1, No=0), and demographic information.

Statistical Analysis

Two-sample t tests for normally distributed variables and the Mann-Whitney U test for skewed variables, including PAI-1 levels, were performed to compare the risk factors between the Americans and the Japanese. Spearman correlation coefficients between PAI-1 levels and the other variables were calculated. Log PAI-1 levels were used as a dependant variable in regression analyses since the residuals with the model, in which PAI-1 levels were used, were not normally distributed. Association of log PAI-1 levels and ethnicity (American or Japanese), after adjusting for selected risk factors including age, waist girth, diastolic blood pressure (DBP), TG, HDL-C, glucose, insulin, CRP, cigarette smoking, and habitual alcohol drinking, was analyzed by the multiple regression model. These variables for adjustment were selected based on the correlation analysis and the previous study ⁷. Associations of log PAI-1 levels with the selected risk factors were examined both in the Americans and the Japanese separately, to reveal the determinants of log PAI-1 levels in each ethnicity. Significance was considered to be at a level of $p < 0.05$. All statistical analyses were performed with SAS version 8.2 software (SAS Institute, Inc., Cary, North Carolina, U.S.)

Results

PAI-1 levels were significantly lower in the Americans than in the Japanese ($p < 0.0001$) (Table 1, Figure 1). Excluding those who had medications for hypertension, hyperlipidemia, and diabetes which can affect PAI-1 levels from the analysis did not change the results ($p < 0.0001$). We also found that PAI-1 levels were still lower in the Americans than in the Japanese in all comparisons stratified by cigarette smoking and habitual alcohol drinking which are factors known to influence PAI-1 levels ¹⁹. Due to the small sample size in the stratified analysis, a significant difference was observed only in non-smokers and drinkers: among non-smokers ($N=85$; 31.5 ± 23.2 and $N=51$; 53.2 ± 37.3 $\mu\text{g/L}$) ($p < 0.001$), smokers ($N=15$; 47.0 ± 26.1 $\mu\text{g/L}$ and $N=47$; 60.7 ± 46.5 $\mu\text{g/L}$) ($p < 0.47$), non-drinkers ($N=53$; 31.0 ± 24.2 $\mu\text{g/L}$ and $N=15$; 43.6 ± 42.3 $\mu\text{g/L}$) ($p = 0.19$), drinkers ($N=47$; 37.0 ± 24.1 $\mu\text{g/L}$ and $N=82$; 58.8 ± 41.8 $\mu\text{g/L}$) ($p < 0.01$) and non-smokers and non-drinkers ($N=11$; 34.0 ± 18.3 $\mu\text{g/L}$ and $N=9$; 54.4 ± 52.0 $\mu\text{g/L}$) ($p = 0.45$). No significant difference was found in medication status between the Americans and the Japanese (for hypertension 7% and 5%, diabetes 0% and 0%, and hypercholesterolemia 8% and 3%, respectively).

Waist girth, BMI, TC, HDL-C, insulin, HOMA, and CRP were significantly correlated with PAI-1 levels both in the Americans and the Japanese (Table 2). Age and cigarette smoking correlated with PAI-1 levels only in the Americans, habitual alcohol drinking only in the Japanese.

The multiple regression analysis, conducted in the Americans and the Japanese, together in the same model, showed a significant association between PAI-1 levels and ethnicity, even after adjustment for age, waist girth, DBP, TG, HDL-C, glucose, insulin, CRP, cigarette smoking, and habitual alcohol drinking (overall $P < 0.001$) (Table 3). This analysis revealed that log PAI-1 levels were significantly higher in the Japanese (log PAI-1=3.987) than in the Americans (log PAI-1=3.073), even after adjustment for the selected variables. Also, waist girth, TG, insulin, and cigarette smoking were significantly associated with PAI-1 levels.

The multiple regression analysis, conducted separately in the Americans and the Japanese, showed that waist girth, insulin, and cigarette smoking in the Americans and waist girth and TG in the Japanese were significantly and independently associated with PAI-1 levels (Table 3). This variability of PAI-1 levels explained by the model was 0.482 in the Americans and 0.310 in the Japanese.

Discussions

We found that PAI-1 levels are significantly lower in the Americans than in the Japanese in the post-war generation. This is the first study which has compared PAI-1 levels between Americans and the Japanese in the post-war generation with a standardized measurement. Obesity is one of the determinants of PAI-1 levels⁴ and therefore, the current finding is notable because the Americans were more obese than the Japanese. The difference in PAI-1 levels between these ethnic groups remained even after adjustment for age, waist girth, DBP, TG, HDL-C, glucose, insulin, CRP, cigarette smoking, and habitual alcohol drinking.

We also found that waist girth, insulin, and cigarette smoking are significantly and independently associated with PAI-1 levels in the Americans, while waist girth and TG are significantly associated with PAI-1 levels in the Japanese. Significant correlations of PAI-1 levels with age, BMI, TG, fasting plasma glucose, and insulin in the current study agrees with the results in previous studies^{7,20–26}. A significant and independent association of PAI-1 levels with waist girth in both ethnic groups supports the results in previous studies, showing that elevated PAI-1 levels are more evident in subjects with abdominal pattern of body fat independent of total body fat^{25,27}. In our study, after adjustment for selected risk factors, insulin was significantly associated with PAI-1 levels only in the Americans but not in the Japanese. Contrasting results for the Americans and the Japanese may be explained by the difference in the levels of obesity between these two ethnic groups. Subsequently when we conducted a multiple regression analysis on Japanese subjects whose BMIs were greater than 25 kg/m², we observed a marginal association of insulin with PAI-1 levels (data not shown). Studies in human adipocyte indicate that PAI-1 synthesis is upregulated by insulin²⁸ but the upregulation of PAI-1 synthesis by insulin may be evident only in obese subjects.

PAI-1 levels were lower in the Americans than in the Japanese in all comparisons stratified by smoking and drinking status. A significant association between PAI-1 levels and cigarette smoking only in the Americans in our study may be explained by the large difference in the prevalence of smokers between these two ethnic groups: 16 % for the Americans and 46 % for the Japanese, respectively. The lack of the significant association between PAI-1 levels and habitual alcohol drinking in the Americans observed in our study agrees with the previous study by Iso et al⁷. Thus, PAI-1 levels were higher in the Japanese compared to the

Americans regardless of smoking and drinking status. The determinants of PAI-1 levels, however, may vary depending on smoking or drinking status among the populations.

A few hypotheses explaining lower PAI-1 levels in the Americans compared to the Japanese were speculated. First, it may be explained by less dominance in abdominal pattern of body fat among the Americans compared to the Japanese²⁹ as secretion of PAI-1 levels from the visceral fat may largely contribute to the PAI-1 levels. Second, there may be the differences in the fat cell size between these two ethnic groups. Americans may have smaller fat cells²⁸ than the Japanese as smaller fat cells produce less PAI-1 compared to larger fat cells^{30–32}. Third, it may be explained by the differences in genetic factors between these ethnic groups. Subjects homozygous for the 4G allele at position -675 in the promoter have higher PAI-1 levels³³ and ethnic differences in the distribution of 4G/5G polymorphism have been reported⁶. Although our study did not conduct genotyping, one mechanism for lower PAI-1 levels in Americans may be explained by lower prevalence of 4G/4G genotype in Americans compared to the Japanese³⁴. There may be, however, other multifactorial genes, which are determinants of insulin resistance and PAI-1 levels as PAI-1 levels are related to insulin resistance³⁵.

Lower PAI-1 levels in the Americans compared to the Japanese agrees with the fact that Americans, especially Caucasians are less susceptible to developing diabetes than Asians³⁶, when taking into account the fact that PAI-1 levels predict diabetes⁵. In fact, Hispanics who are also more susceptible to developing diabetes than Caucasians³⁷ showed higher PAI-1 levels compared to Caucasians⁶. Therefore, lower PAI-1 levels in the Americans compared to the Japanese in the post-war generation observed in our current study is highly plausible although this result contrasts with the result in the study conducted on their forebears in the early '90s⁷.

There are some limitations in this study. First, the sample size of this study was relatively small. Second, our subjects at the U.S. site were volunteers and therefore may be healthier than the general population. However, the prevalence of subclinical atherosclerosis measured with computed tomography in our U.S. population was similar to that in the general U.S. population¹³. It is therefore unlikely that our U.S. population is very different from a randomly selected population. Third, our study included only men. Finally, we can not determine the causal relationships due to the cross-sectional nature of the study.

In conclusion, PAI-1 levels were significantly lower in American than in Japanese men, aged 40–49 although the Americans were more obese than the Japanese. Varying constellations of risk factor profile and genetic factors may lead to the significant differences in PAI-1 levels found between American and Japanese ethnic groups.

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Figure 1.

The distribution of plasma PAI_1 levels

PAI-1 levels were significantly lower in the Americans than in the Japanese ($p < 0.0001$).

Table 1

The comparison of the characteristic of the subjects (American men and Japanese men aged 40–49)

Metabolic risk factors	American (N=100)	Japanese (N=98)	P value
	Mean SD	Mean SD	
Age (years)	44.6 ± 2.9	44.7 ± 2.8	0.79
Body Mass Index (kg/m ²)	27.0 ± 3.3	23.3 ± 3.1	<0.0001
Waist Girth (cm)	96.4 ± 9.8	84.7 ± 8.5	<0.0001
Systolic blood pressure (mmHg)	113.7 ± 9.6	122.6 ± 14.1	<0.0001
Diastolic blood pressure (mmHg)	78.4 ± 5.8	78.6 ± 10.4	0.25
Total cholesterol (mg/dl)	192.8 ± 31.3	220.9 ± 37.6	<0.0001
Triglycerides (mg/dl)	139.1 ± 82.9	151.0 ± 84.0	0.17
HDL cholesterol (mg/dl)	45.9 ± 11.6	54.7 ± 14.9	<0.0001
LDL cholesterol (mg/dl)	119.7 ± 30.0	136.0 ± 39.0	<0.001
Fasting glucose (mg/dl)	95.3 ± 9.1	103.4 ± 8.8	<0.0001
Fasting insulin (μU/ml)	12.5 ± 6.6	8.2 ± 3.8	<0.0001
HOMA *	3.0 ± 1.7	2.1 ± 1.1	<0.0001
C-reactive protein (mg/L)	1.9 ± 2.9	0.9 ± 2.8	<0.0001
Fibrinogen (mg/dl)	241.3 ± 66.4	236.3 ± 62.9	0.47
PAI-1 (μg/L)	33.9 ± 24.2	56.8 ± 41.9	<0.0001

* Homeostasis Model Assessment Score

Table 2

Correlations between cardiovascular risk factors and PAI-1 levels

cardiovascular risk factors	American (N=100)	Japanese (N=98)
Age	0.20 [†]	−0.03
Waist Girth	0.57 [‡]	0.46 [‡]
Body Mass Index	0.58 [‡]	0.37 [‡]
Systolic blood pressure	0.02	−0.01
Diastolic blood pressure	0.05	−0.07
Total Cholesterol	0.13	−0.05
Triglycerides	0.50 [‡]	0.39 [‡]
HDL-Cholesterol	−0.26 [‡]	−0.24 [†]
LDL-Cholesterol	0.01	−0.12
Fasting Glucose	0.30 [‡]	0.09
Fasting Insulin	0.49 [‡]	0.28 [‡]
HOMA Score [*]	0.52 [‡]	0.27 [‡]
C-Reactive Protein	0.41 [‡]	0.53 [‡]
Fibrinogen	0.00	0.13
Cigarette Smoking	0.23 [†]	0.07
Habitual alcohol drinking	0.14	0.21 [†]

^{*} Homeostasis Model Assessment Score

[†] p<0.05,

[‡] p<0.01

Spearman correlation coefficients between cardiovascular risk factors and PAI-1 levels in American men and Japanese men aged 40–49

Table 3

The relationship between logPAI-1 levels and risk factors

Dependent Variables; logPAI-1			(N=198)
Independent Variables	Regression coefficients	SE	P value <0.001
	Multivariate model R ² =0.462		
Ethnicity	0.913	0.132	<0.001
Age	0.018	0.015	0.227
Waist Girth	0.031	0.006	<0.001
Diastolic Blood Pressure	-0.009	0.005	0.077
Triglycerides	0.002	0.001	0.007
HDL-Cholesterol	0.004	0.004	0.263
Fasting Glucose	-0.002	0.005	0.672
Fasting Insulin	0.031	0.009	0.001
C-Reactive Protein	0.024	0.015	0.123
Cigarette Smoking	0.248	0.098	0.013
Habitual Alcohol Drinking	0.056	0.099	0.571

The relationship between logPAI-1 levels and risk factors by multivariate regression model

Table 4

The relationship between logPAI-1 levels and risk factors

Dependent Variables; logPAI-1							
Independent Variables	American (N=100) Regression coefficients		SE	P value <0.001	Japanese (N=98) Regression coefficients		P value <0.001
	Multivariate model R2=0.482				Multivariate model R2=0.310		
Age	0.028		0.021	0.187	0.009	0.023	0.706
Waist Girth	0.028		0.008	<0.001	0.032	0.009	<0.001
Diastolic Blood Pressure	-0.01		0.011	0.335	-0.009	0.006	0.157
Triglycerides	0.001		0.001	0.086	0.002	0.001	0.031
HDL-Cholesterol	0.005		0.006	0.427	0.005	0.005	0.346
Fasting Glucose	0.003		0.007	0.671	-0.008	0.008	0.315
Fasting Insulin	0.033		0.011	0.002	0.029	0.020	0.155
C-Reactive Protein	0.022		0.022	0.327	0.028	0.023	0.232
Cigarette Smoking	0.422		0.171	0.015	0.153	0.128	0.238
Habitual Alcohol Drinking	0.062		0.124	0.617	0.060	0.187	0.750

The relationship between log PAI-1 levels and risk factors by multivariate regression models in the Americans and the Japanese