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Original Article

Increased Plasma 8-Isoprostane Levels in Hypertensive Subjects: the Tsurugaya Project

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To examine the relationship between 8-isoprostane and blood pressure, we measured plasma 8-isoprostane concentration and home blood pressure levels in an elderly Japanese population. Our study population comprised 569 subjects aged 70 years and over who were not receiving antihypertensive medication. On the basis of their blood pressure values, the participants were classified into three groups: normotensive (home blood pressure <135/85 mmHg), hypertensive (home blood pressure 135/85–160/90 mmHg), and severely hypertensive (home blood pressure ≧160/90 mmHg). The mean plasma 8-isoprostane level in the severely hypertensive group (21.1±5.2 pg/ml) was significantly higher than that in the normotensive (20.2±4.9 pg/ml) or hypertensive (19.7±5.1 pg/ml) group, and this result was unchanged when we adjusted for possible confounding factors such as age, sex, use of vitamin A, C or E supplements, smoking status, drinking status, body mass index, use of non-steroidal anti-inflammatory drugs, history of diabetes, hypercholesterolemia, home heart rate and serum creatinine level. Thus, the level of plasma 8-isoprostane appears to be elevated in older subjects with severe hypertension. (*Hypertens Res* 2004; 27: 557–561)

***Key Words*: hypertension, oxidative stress, isoprostanes, home blood pressure measurement, elderly**

Introduction

Data from a number of animal experiments and *in vitro* studies in humans support the hypothesis that increased oxidative stress may be related to elevated blood pressure (BP) (*1*, *2*).

However, few studies have investigated the relationship between 8-isoprostane and hypertension in a large sample of human subjects (*3*).

Isoprostanes are chemically stable lipid peroxidation products of arachidonic acid, and their quantification provides a novel approach to the assessment of oxidative stress *in vivo* (*4*). Isoprostanes are detectable in plasma and urine under normal conditions (*5*), and their levels increase during oxidative stress (*6*).

Recently, self-measurement of BP at home (home BP measurement) has been reported to have better reproducibility (*7*, *8*) and prognostic value (*9*) than BP measurement in clinics.

Our objective was to clarify the relationship between plasma 8-isoprostane concentration and home BP measurement in elderly people.

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Methods

Study Participants

Our study population comprised subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. At the time of the study, there were 2,730 individuals aged 70 years and older living in Tsurugaya. We invited all of these individuals to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status, and 1,179 of them did so, giving their informed consent for analysis of the data. The protocol of this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine. We excluded subjects whose plasma 8-isoprostane levels had not been measured ($n=29$). Home BP data were obtained from 968 of the remaining subjects, who collected their own data on more than 3 days during the 4-week study period. This criterion was based on our previous observation that average BP values for the first 3 days did not differ significantly from those obtained during the entire study period (*7*). Furthermore, since antihypertensive medication *per se* would affect the degree of oxidative stress, we excluded subjects who were receiving antihypertensive medication (*10*). Therefore, the study population comprised 569 subjects (mean age 75.2±4.6 years; men: 45%).

Home BP Measurements

We used the following procedure to ascertain the accuracy of the home BP measurement. First, physicians informed the population about home BP recording and taught them how to measure their own BP. The daily measurement was made within 1 h of awakening and before breakfast, with the subject seated and having rested for at least 2 min. In subjects receiving antihypertensive drugs, home BP was measured before taking the drugs. The home BP of an individual was defined as the mean of all measurements obtained for that person. The mean (±SD) number of home BP measurements was 15.3±10.2 (range, 3–48).

BP-Measuring Device

Home BP was measured with an HEM747IC device (Omron Life Science Co. Ltd., Tokyo, Japan), which uses the cuff-oscillometric method to generate a digital display of systolic and diastolic pressures. This device has been validated previously (*11*), and satisfies the criteria of the Association for the Advancement of Medical Instrumentation (*12*).

8-Isoprostane Measurement

Total (esterified plus free) 8-iso-prostaglandin (PG) $F_{2\alpha}$ concentrations were assayed in plasma by a specific enzyme immunoassay (EIA) kit (Cayman Chemical, Ann Arbor, USA) (*13*, *14*).

For total 8-iso-$PGF_{2\alpha}$ measurement, peripheral venous blood was collected in ethylenediaminetetraacetic acid 2Na (EDTA2Na)- and EDTA4Na-coated cold polyethylene tubes containing indomethacin, an inhibitor of cyclooxygenase, and aprotinin, an inhibitor of kallikreins, to prevent any *in vitro* formation of 8-iso-$PGF_{2\alpha}$. After collection, blood samples were immediately cooled at 4°C and transferred to the laboratory within 4 h. In the laboratory, the samples were centrifuged at $3,000\times g$ at 4°C for 10 min. The plasma fraction was removed and stored at −80°C for later 8-iso-prostane assay. The antiserum used in this assay has 100% cross-reactivity with 8-isoprostane, 0.2% with $PGF_{2\alpha}$, $PGF_{3\alpha}$, PGFI, and PGF_2 and 0.1% with 6-keto $PGF_{2\alpha}$. Both the intra-assay and interassay variabilities were within 6%. The detection limit of the assay was 4 pg/ml.

Classification of Subjects

On the basis of BP values, participants were classified into three groups: normotensive, home BP <135/85 mmHg; hypertensive, home BP 135/85–160/90 mmHg; and severely hypertensive, home BP ≧160/90 mmHg.

Data Analysis

Variables were compared by the *t*-test, analysis of variance, the χ^2 test, or analysis of covariance, as appropriate.

We used the following confounders as covariates: age, sex, use of vitamins A, C or E, use of non-steroidal anti-inflammatory drugs (NSAIDs), smoking habit, drinking habit, body mass index (BMI), history of diabetes or hypercholesterolemia, home heart rate (HR) and serum creatinine level. These factors were chosen because it is known that some lifestyle-related factors, such as obesity (*3*), smoking (*15*), supplementation with vitamins A, C or E (*16*), or use of NSAIDs (*17*), and disease conditions such as diabetes (*18*) or hypercholesterolemia (*19*) can affect the plasma 8-isoprostane level. We defined diabetes as a free blood glucose level of 200 mg/dl or over, or current use of antidiabetic medication. Similarly, we defined hypercholesterolemia as a level of total cholesterol of 220 mg/dl or over, or current use of lipid-lowering agents. The drug information was confirmed by a well trained pharmacist. The level of statistical significance was set at $p<0.05$. Data are given as the mean±SD. All statistical analyses were performed with SAS software, version 8.02.

Results

Descriptive Data for Plasma 8-Isoprostane

Table 1 shows the descriptive data for plasma 8-isoprostane.

Table 1. Descriptive Data for Plasma 8-Isoprostane

		N	Plasma 8-isoprostane	*p* value
Sex	Men	258	20.4±4.9	0.09*
	Women	311	19.7±5.0	
Age	70–79 years	462	20.0±5.0	0.43*
	80 years–	107	20.4±5.1	
Use of vitamins A, C or E supplements	With	74	19.7±5.1	0.47*
	Without	495	20.1±5.1	
Smoking	Current	76	20.7±4.9	0.046**
	Ex	165	20.6±4.8	
	Never	319	19.6±5.2	
Drinking	Current	227	20.0±5.0	0.63*
	Ex or Never	337	20.0±5.1	
Diabetes	With	46	21.0±4.4	0.16*
	Without	523	20.0±5.1	
Hypercholesterolemia	With	243	19.7±5.2	0.11*
	Without	326	20.3±4.9	
Use of NSAIDs	With	92	20.7±4.9	0.18*
	Without	477	19.9±5.1	

NSAIDs, non-steroidal anti-inflammatory drugs. * *t*-test; ** ANOVA.

Table 2. Baseline Characteristics

	Normotensive	Hypertensive	Severely hypertensive	*p* value
N	286	205	78	
Age	74.6±4.0	76.1±5.1	75.1±4.8	0.002*
Sex (% men)	47.6	42.0	46.2	0.46†
Use of vitamins A, C, or E supplements (%)	14.7	11.7	10.3	0.46†
Current smokers (%)	12.2	14.2	15.4	0.82†
Current drinkers (%)	37.4	41.5	44.9	0.18†
Diabetes (%)	8.0	7.8	9.0	0.95†
Hypercholesterolemia (%)	40.9	42.9	48.7	0.037†
BMI	22.9±3.1	24.1±3.5	24.5±3.1	<0.001*
Systolic blood pressure (mmHg)	120.6±9.7	144.1±7.0	167.3±12.4	<0.001*
Diastolic blood presure (mmHg)	70.5±6.5	77.5±7.7	90.8±8.1	<0.001*
Home heart rate (beat/min)	65.2±7.9	65.2±8.1	67.8±8.9	0.03*
Use of NSAIDs	15.7	17.6	14.1	0.75†
Serum creatinine (mg/dl)	0.76±0.20	0.76±0.44	0.73±0.15	0.71*

Normotensive: home blood pressure <135/85 mmHg; Hypertensive: home blood pressure 135/85–160/90 mmHg; Severely hypertensive: home blood pressure ≧160/90 mmHg. BMI, body mass index; NSAIDs, non-steroid anti-inflammatory drugs. * ANOVA; † χ^2 test.

The plasma 8-isoprostane level tended to be higher in men, elderly subjects and subjects with diabetes. Similarly, subjects who were using vitamin A, C or E supplements showed a lower plasma 8-isoprostane level than those who were not. Current smokers and ex-smokers showed higher levels of plasma 8-isoprostane than subjects who had never smoked.

Baseline Characteristics

Table 2 shows the baseline characteristics of the subjects. The normotensives were the youngest subjects, and the prevalence of diabetes was highest among the severely hypertensive subjects. The proportions of subjects who were taking antihypertensive medication were higher among subjects with severe hypertension or hypertension than among normotensive subjects. Among the three subject groups, the mean BMI was the highest in severe hypertensives. The plasma 8-isoprostane level in severely hypertensive subjects (21.1 pg/ml) was significantly higher than that in hypertensive (20.2 pg/ml) or normotensive (19.7 pg/ml) subjects.

Table 3. Relationship between Plasma 8-Isoprostane Level and Home BP Levels

	N	Plasma 8-isoprostane (95% C.I.)
All subjects (*N*=569)		
Normotensive	286	19.7 (19.1–20.3)*
Hypertensive	205	20.1 (19.4–20.8)
Severely hypertensive	78	21.0 (19.9–22.2)
p for trends		0.041
Men (*N*=258)		
Normotensive	136	20.4 (19.5–21.2)
Hypertensive	86	20.0 (18.9–21.0)
Severely hypertensive	36	21.7 (20.0–23.4)
p for trends		0.402
Women (*N*=311)		
Normotensive	150	19.1 (18.3–19.9)
Hypertensive	119	20.2 (19.2–21.1)
Severely hypertensive	42	20.6 (19.0–22.2)
p for trends		0.054
Limited population** (*N*=294)		
Normotensive	156	20.3 (19.5–21.0)
Hypertensive	95	20.0 (19.0–21.0)*
Severely hypertensive	43	21.9 (20.4–23.4)
p for trends		0.149

*$p<0.05$ *vs.* Severely hypertensive. **Subjects without HDL <40 mg/dl, total cholesterol ≧220 mg/dl, triglyceride ≧300 mg/dl or free blood glucose ≧200 mg/dl. Normotensive: home BP <135/85 mmHg; Hypertensive: home BP 135/85–160/90 mmHg; Severely hypertensive: home BP ≧160/90 mmHg. Adjusted for age, sex, use of vitamin A, C or E supplements, smoking habit, drinking habit, body mass index, home heart rate, diabetes, hypercholesterolemia, use of non-steroid anti-inflammatory drugs and serum creatinine level. *N*, number of subjects; C.I., confidence interval; BP, blood pressure; HDL, high-density lipoprotein.

Adjustment for Possible Confounders

Even after adjustment for confounding factors, there was no change in the finding that the plasma 8-isoprostane level in severely hypertensive subjects was higher than that in hypertensive or normotensive subjects (p for trend=0.041) (Table 3).

When we performed separate analyses for men and women, the finding that the plasma isoprostane level among severely hypertensive subjects was higher than that in normotensives or hypertensives was unchanged. Furthermore, even when we excluded the subjects with a high-density lipoprotein (HDL) cholesterol level <40 mg/dl, or with a level of total cholesterol ≧220 mg/dl, or with a high triglyceride level ≧300 mg/dl or a free blood glucose level ≧200 mg/dl , the tendency for the plasma isoprostane level in severely hypertensive subjects to be higher than that in normotensive or hypertensive was also unchanged.

Discussion

The plasma 8-isoprostane level in elderly subjects with severe hypertension was modestly but significantly higher than that in normotensive or hypertensive subjects, even when we adjusted for possible confounders.

Our study had several methodological advantages. First, the use of home BP measurement made it possible to obtain multiple measurements over a long observation period under well-controlled conditions. This approach has been reported to have better reproducibility (*7*, *8*) and prognostic value (*9*) than casual BP measurement, because it avoids observer bias, regression dilution bias (*8*) and the white-coat effect. Second, we adjusted for possible confounders such as age, sex, use of vitamin A, C or E supplements, smoking habit, drinking habit, BMI, use of NSAIDs, history of diabetes, history of hypercholesterolemia, home HR, and serum creatinine level, since these factors could affect the level of 8-isoprostane or BP.

Although many animal experiments have indicated a positive relationship between high BP levels and 8-isoprostane, few studies have supported such a relation in humans (*3*). Keaney *et al.* examined 2,828 subjects in the Framingham Heart Study and measured urinary creatinine-indexed 8-isoprostane as a marker of systemic oxidative stress (*3*). However, they did not find any meaningful positive association between oxidative stress and hypertension.

The difference between their findings and ours may be explained as follows. First, their diagnosis was based on clinic BP measurements, whereas we used home BP measurements. Therefore, our approach may have reduced the number of misclassifications (*8*).

Second, Keaney *et al.* considered that the proportion of individuals with oxidative-mediated hypertension, such as salt sensitivity, may have been too small to drive an association between hypertension and oxidative stress in their sample (*3*). On the other hand, our population comprised elderly Japanese individuals. The proportion of individuals with sodium sensitivity is known to be higher in Japanese than in Caucasian populations (*20*). Similarly, BP becomes salt-sensitive with age (*20*). Therefore, the proportion of subjects with salt sensitivity might have been higher in our subjects than in theirs, and this might have at least partly accounted for the difference between our results and those of Keaney *et al.* (*3*).

Our study also had some limitations. First, most of the participants were sufficiently active and healthy to participate in the survey, and this might have led to small inter-individual differences in the study effects. Second, since this study was a cross-sectional study, we cannot conclude that oxidative stress causes hypertension or that higher BP leads to increased oxidative stress. Third, we used EIA rather than gas chromatography/mass spectrometry, the gold standard for isoprostane analysis, and plasma obtained by centrifuga-

tion was stored at −80°C within 1 to 4 h—rather than immediately—after collection, because large numbers of samples had to be processed in a timely manner. Finally, we used plasma samples rather than urine samples. Although the plasma samples were prepared carefully (peripheral venous blood was collected in polyethylene tubes containing 1 mmol/ml indomethacin, cooled immediately at 4°C and transferred to the laboratory within 4 h; plasma obtained by centrifugation was aliquoted and stored at −80°C for later 8-isoprostane assay in the laboratory), some autoxidation might have occurred.

In conclusion, we have demonstrated that plasma 8-isoprostane levels are elevated in elderly subjects with severe hypertension. This is the first study to clarify the relationship between isoprostanes and hypertension in elderly individuals. However, as the difference in plasma 8-isoprostane levels among the three groups was modest, further study will be needed to clarify the clinical significance of this difference.

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Original Article

C-Reactive Protein and Peripheral Artery Disease among Japanese Elderly: the Tsurugaya Project

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We investigated the cross-sectional relationship between ankle brachial index and cardiovascular disease risk factors, including C-reactive protein (CRP), among Japanese elderly, a topic which has had little prior epidemiologic study. Our study population comprised 946 subjects aged at least 70 years in whom both CRP and ankle brachial index were measured. The participants were classified into a low (ankle brachial index<0.9) and normal ankle brachial index group. We found that current smoking, high-density lipoprotein cholesterol <40 mg/dl, a low body mass index (continuous variable), hypertension, diabetes and statin use were all significantly related to a lower ankle brachial index. Higher log-transformed CRP level was significantly related to a lower ankle brachial index after adjustment for the cardiovascular risk factors mentioned above ($p<0.01$). The odds ratios for low ankle brachial index compared to 0–1 risk factors were 5.79 (95% confidence interval [CI]: 2.99–11.20) for 2 risk factors and 17.45 (95% CI: 6.78–49.91) for 3 or more risk factors; independently of other risk factors, the odds ratio for CRP>1.0 mg/l was 2.10 (95% CI: 1.13–3.88) compared to lower CRP values. Thus, a high level of CRP is related to a low ankle brachial index among Japanese elderly as well as Western subjects. This is the first study to report the relationship between CRP and low ankle brachial index among Japanese elderly. (*Hypertens Res* 2004; 27: 955–961)

***Key Words*: C-reactive protein, cardiovascular risk factors, ankle brachial index, Japanese, elderly**

Introduction

In recent years, C-reactive protein (CRP) has become established as a risk factor for cardiovascular diseases (*1–14*). Higher levels of CRP predict future myocardial infarction and stroke independently of other cardiovascular disease risk factors, and it has been suggested that the measurement of CRP, in addition to cardiovascular disease risk factors, may improve our ability to predict cardiovascular diseases (*10, 13*).

Peripheral artery disease (PAD) is a severe atherosclerotic condition causing intermittent claudication and is associated with higher incidence of future cardiovascular and cerebrovascular diseases (*15–19*). The low ankle brachial systolic blood pressure index (ABI) has been used as a measure of lower limb PAD (*20*). In Western countries, some prospective studies have demonstrated a positive relationship between CRP and low ABI (*21, 22*) as well as a relationship

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between CRP and cardiovascular diseases (*1–14*).

In Japan, however, epidemiological data about risk factors for low ABI among Japanese have been limited (*23*, *24*). Furthermore, no studies have investigated the relationship between CRP and low ABI. Therefore, in the present study, we investigated the relationship between ABI and cardiovascular disease risk factors, including CRP, among Japanese elderly.

Methods

Study Participants

Our study population comprised subjects aged 70 years and older who were living in the Tsurugaya area of Sendai, one of the major cities in the Tohoku area of Japan. At the time of the study, there were 2,730 people aged 70 years and older living in Tsurugaya (*25*, *26*). We invited all of these individuals to participate in a comprehensive geriatric assessment, which included medical status, physical function, cognitive function and dental status, and 1,178 of these people agreed to participate and give their informed consent for analysis of the data. The protocol for this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine. We excluded subjects whose CRP had not been measured ($n=29$) and subjects whose ABI had not been measured ($n=21$). We assessed hypertension using home blood pressure (BP) data, and subjects who did not measure their BP on at least 3 days during the 4-week study period were excluded ($n=176$). This criterion was based on our previous observation that the average BP values for the first 3 days did not differ significantly from those obtained during the entire study period (*27*). Furthermore, we excluded subjects who did not complete the questionnaire about alcohol consumption ($n=6$). Therefore, the study population comprised 946 subjects (mean age 75.2± 4.6 years, men: 45%).

CRP Measurement

We collected the blood sample under non-fasting conditions. Serum CRP levels were determined using an immunotechnique on a Behring BN II analyzer (Dade Behring, Tokyo, Japan). The BN II high sensitivity assay utilizes a monoclonal antibody coated on polystyrene particles and fixed-time kinetic nephelometric measurements (*28*). The BN II nephelometer makes a 1:400 dilution to measure CRP concentrations between 3.5 and 210 mg/l. The assay has been approved by the US Food and Drug Administration for use in assessing the risk of cardiovascular and peripheral vascular disease.

ABI Measurement

Bilateral ABI was measured in all subjects using a new device, the FORM ABI/PWV (Colin Co., Komaki, Japan), which incorporates an automatic oscillometer (*29*). The FORM ABI/PWV is a device with four cuffs that can measure BP levels simultaneously in both arms and both legs, and automatically calculates the ABI. This device is useful for mass medical examinations and population-based studies because it enables measurements of ABI and brachial ankle pulse wave velocity in a short time and is not affected by the operator's technique. This device has been used in other Japanese epidemiological studies (*24*, *30*, *31*).

Classification of Subjects

We treated the lowest ABI in either leg as the ABI value. We defined the subjects with an ABI<0.90 as the "low ABI" subjects, and we classified serum CRP levels into three groups, <1 mg/l, 1 to 2.9 mg/l and 3 mg/l and over, according to the previous reports (*10*, *13*).

Data Analysis

Variables were compared by the χ^2 test, *t*-test or analysis of variance, as appropriate. The odds ratio (OR) of PAD was calculated using multiple logistic regression analysis.

We used the following variables as confounding factors: age, sex, smoking habit, drinking habit, hypertension, hypercholesterolemia, a low level of high density lipoprotein (HDL) cholesterol, body mass index (BMI), diabetes, prior cardiovascular diseases and use of statin drugs.

Subjects were considered hypertensive if their home systolic BP (SBP) was at least 135 mmHg and/or home diastolic BP (DBP) was at least 85 mmHg, or if they were using antihypertensive agents (*32*, *33*). Subjects were considered diabetic if their non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Subjects were considered hypercholesterolemic if their level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol was defined as a level of HDL cholesterol below 40 mg/dl. The information on smoking status, drinking status and history of prior cardiovascular diseases was obtained using questionnaire surveys. Current drinkers were also asked about drinking frequency, beverage types usually consumed, and amount consumed on a single occasion. From these responses we calculated the average daily alcohol consumption in grams. Since statins have been reported to lower CRP levels (*34*, *35*), we treated them as independent confounding factors. When we analyzed the relationship between low ABI and CRP as a continuous variable, we used the log-transformed value (CRP value+1), because the CRP distribution was skewed to the right among Japanese (*36*); we added 1 before transformation because the log-transformation expands the scale for values below 1. Since the CRP level has been reported to be related to risk clustering (*37*), we analyzed the relationship between low ABI and a combi-

Table 1. Association between Lower Ankle Brachial Index and Cardiovascular Disease Risk Factors, for 946 Subjects, the Tsurugaya Project, Sendai, Japan, 2002

	Ankle brachial index		
	<0.9	≧0.9	*p*
Number of subjects	54	892	
Age (years)	77	76	0.049*
Sex (male %)	67	43	<0.01**
Current smoker (%)	26	12	<0.01**
Ex-smoker (%)	43	30	
Never smoker (%)	31	58	
Mean alcohol consumption (g)	14	10	0.37*
Body mass index (kg/m^2)	24	24	0.46*
Hypertension (%)	91	69	<0.01**
Diabetes (%)	26	9	<0.01**
Hypercholesterolemia (%)	31	36	0.49**
Low HDL cholesterol (%)	33	11	<0.01**
Use of statin drugs (%)	30	16	0.01**
History of cardiovascular diseases (%)	31	15	<0.01**

* *t*-test, ** χ^2-test. Hypertension: home systolic blood pressure (BP) was at least 135 mmHg and/or home diastolic BP was at least 85 mmHg, or they were using antihypertensive agents. Diabetes: non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Hypercholesterolemia: level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol: level of high density lipoprotein cholesterol below 40 mg/dl.

Table 2. Association between C Reactive Protein (CRP) and Cardiovascular Disease Risk Factors

	CRP (mg/l)			*p*
	−0.9	1.0–2.9	3.0−	
Number of subjects	637	201	108	
Age (years)	76	76	76	0.70*
Sex (male %)	43	47	47	0.44**
Current smoker (%)	11	17	12	0.02*
Ex-smoker (%)	29	32	40	
Never smoker (%)	60	51	47	
Alcohol consumption (g)	11	13	7	0.22*
Body mass index (kg/m^2)	24	25	25	<0.01*
Hypertension (%)	68	74	81	0.01**
Diabetes (%)	8	11	16	0.03**
Hypercholesterolemia (%)	33	42	40	0.047**
Low HDL cholesterol (%)	11	14	16	0.20**
Use of statin drugs (%)	18	13	19	0.27**
History of cardiovascular diseases (%)	15	17	24	0.051**

* ANOVA, ** χ^2-test. Hypertension: home systolic blood pressure (BP) was at least 135 mmHg and/or home diastolic BP was at least 85 mmHg, or they were using antihypertensive agents. Diabetes: non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Hypercholesterolemia: level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol: level of high density lipoprotein cholesterol below 40 mg/dl.

nation of cardiovascular disease risk factors and CRP level. In this analysis, we treated hypertension, diabetes, current smoking or low HDL cholesterol as cardiovascular disease risk factors.

The drug information was confirmed by an experienced pharmacist. The level of statistical significance was set at $p<0.05$. All statistical analyses were performed with SAS software, version 8.2 (SAS Institute, Cary, USA).

Results

Association between ABI and Atherosclerosis Risk Factors

Table 1 shows the association between low ABI and cardiovascular disease risk factors. The mean age was significantly higher in subjects with low ABI than those without low ABI. The proportions of never smokers and females were lower in low ABI subjects. Similarly, the proportions of subjects with hypertension, diabetes, and low HDL cholesterol, and the proportions of statin users or subjects with a history of prior cardiovascular diseases, were higher in low ABI subjects. The proportions of subjects with hypercholesterolemia did not differ between subjects who had a low ABI and subjects who did not. Neither alcohol consumption nor BMI differed between subjects with or without a low ABI.

Association between CRP and Other Cardiovascular Disease Risk Factors

The median (interquartile range) of CRP was 0.61 (0.17–1.37) mg/l. Table 2 shows the association between CRP value and cardiovascular disease risk factors. The proportion of never smokers was lower in subjects with high CRP, and the proportions of ex-smokers or subjects with hypertension, hypercholesterolemia, diabetes or prior cardiovascular diseases were higher in subjects with the highest CRP level. The proportions of each gender, subjects with low HDL cholesterol or statin users did not differ among the CRP groups. Mean age or alcohol consumption also did not differ among the CRP groups. BMI was lower in the subjects of the lowest CRP group.

OR of Low ABI Was Associated with CRP and Cardiovascular Disease Risk Factors

Table 3 shows the results of the multiple logistic regression analysis. Compared with the lowest CRP group, the moder-

Table 3. Odds Ratio of Low Ankle Brachial Index Associated with Cardiovascular Disease Risk Factors

	Odds ratio	95% CI	*p*
Age (5 years)	1.23	0.91–1.67	0.18
Sex (male=1)	1.77	0.74–4.23	0.20
Current smoker	3.10	1.16–8.32	0.02
Ex-smoker	1.51	0.62–3.71	0.50
Alcohol consumption (23 g/day)	1.01	0.79–1.29	0.97
Body mass index (kg/m^2)	0.89	0.80–0.99	0.03
Hypertension	4.29	1.60–11.50	<0.01
Diabetes	3.73	1.82–7.66	<0.01
Hypercholesterolemia	1.10	0.56–2.14	0.79
Low HDL cholesterol	3.39	1.69–6.81	<0.01
Use of statin drugs	3.51	1.71–7.19	<0.01
History of cardiovascular diseases	1.74	0.89–3.40	0.10
CRP			
–0.9 mg/l	1.00		
1–2.9 mg/l	2.20	1.10–4.41	0.03
3– mg/l	2.06	0.90–4.75	0.09
p for trend			0.03
CRP log-transformed (continuous)	2.15	1.21–3.82	<0.01

CI, confidence interval. Hypertension: home systolic blood pressure (BP) was at least 135 mmHg and/or home diastolic BP was at least 85 mmHg, or they were using antihypertensive agents. Diabetes: non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication. Hypercholesterolemia: level of total cholesterol was at least 220 mg/dl, or they currently used non-statin lipid-lowering agents. Low HDL cholesterol: level of high density lipoprotein cholesterol below 40 mg/dl.

ate CRP group and the highest CRP group had a two-fold higher OR. The *p*-value for the trend across CRP groups was statistically significant ($p=0.03$). Furthermore, when we repeated the regression by treating the log-transformed CRP value as a continuous variable, a positive trend between log-transformed CRP and low ABI was also observed ($p<0.01$).

The following relationships between other cardiovascular disease risk factors and low ABI were found (Table 3). Current smoking, low HDL cholesterol, and history of hypertension, diabetes and statin use were related significantly to low ABI. Lower BMI as a continuous variable was significantly related to low ABI. A history of cardiovascular diseases tended to be related to lower ABI, although the relationship was only marginally significant. Age, sex, alcohol consumption and history of hypercholesterolemia were not significantly related to low ABI.

When we excluded the subjects who were statin users, a significant positive relationship between log-transformed CRP and low ABI remained ($p<0.01$).

Association of OR of Low ABI with a Combination of Cardiovascular Disease Risk Factors and CRP

Table 4 shows that the OR of low ABI was associated with the combination of a number of cardiovascular disease risk factors and CRP. In this analysis, according to the results of Table 3, we treated hypertension, diabetes, current smoking and low HDL cholesterol as dichotomous cardiovascular disease risk factors. We also treated the subjects with a CRP level higher than 1.0 mg/l as high-CRP subjects, because both CRP groups above 1.0 mg/l showed a similar association with low ABI.

Irrespective of the number of cardiovascular disease risk factors, a higher CRP level was related to a higher risk of low ABI (p for interaction=0.70). Even among the subjects without high CRP levels, the clustering of cardiovascular disease risk factors was related to low ABI. In a multiple logistic regression that included as covariates sex, age, BMI, statin use, and history of cardiovascular disease, the OR for low ABI, compared to 0–1 risk factors, was 5.79 (95% confidence interval [CI]: 2.99–11.20) for 2 risk factors and 17.45 (95% CI: 6.78–49.91) for 3 or more risk factors; the OR for CRP>1.0 mg/l was independently 2.10 (95% CI: 1.13–3.88) compared to the lower CRP values.

Discussion

In this study, we have demonstrated that, in Japan, CRP is related to low ABI independently of other cardiovascular disease atherosclerosis risk factors, and also reconfirmed the impact of the clustering of traditional cardiovascular disease risk factors on low ABI among the Japanese population.

CRP is a circulating acute-phase reactant that is increased many-fold during the inflammatory response to tissue injury or infection. CRP is synthesized primarily in the liver and its release is stimulated by interleukin 6 and other proinflammatory cytokines. This protein has received substantial attention in recent years as a promising biological predictor of atherosclerotic disease (*38*). In Western countries, some prospective studies have investigated the relationship between CRP and cardiovascular diseases, including PAD (*1–14, 21, 22*).

However, no studies have investigated the relationship between CRP and PAD in Japan, and only a few studies have investigated the relationship between PAD and classical factors in a large sample (*23, 24*).

Shinozaki *et al.* reported the relationship between low ABI (ABI<1.0) and cardiovascular disease risk factors among 446 male workers (*23*). Multiple logistic regression analyses for low ABI showed that low BMI, high SBP, and current smoking were related positively to low ABI and current drinking was related negatively to low ABI.

Cui *et al.* reported the relationship between low ABI (ABI<0.9) and cardiovascular disease risk factors among 1,219 elderly men (*24*). They found that low BMI, hyperten-

Table 4. Odds Ratio of Low ABI Associated with a Combination of Number of Cardiovascular Disease Risk Factors and CRP

Numbers of risk factors	CRP (−0.9 mg/l)			CRP (1.0 mg/l−)		
	Odds ratio	95% CI	*p*	Odds ratio	95% CI	*p*
0–1	1.00			1.91	0.74–4.92	0.18
2	5.74	2.39–13.80	<0.01	11.21	4.46–28.20	<0.01
3–	12.46	2.89–53.69	<0.01	42.40	12.72–141.17	<0.01

ABI, ankle brachial systolic blood pressure (BP) index; CRP, C reactive protein; CI, confidence interval. Risk factors: hypertension: home systolic BP was at least 135 mmHg and/or home diastolic BP was at least 85 mmHg, or they were using antihypertensive agents; diabetes: non-fasting blood glucose level was at least 200 mg/dl, or if they currently used antidiabetic medication; current smoking; low high density lipoprotein (HDL) cholesterol: level of HDL cholesterol below 40 mg/dl; adjusted for sex, age, body mass index, statin using and history of cardiovascular diseases.

sion, low HDL cholesterol, history of stroke, major electrocardiogram abnormality, and current smoking were significantly related to low ABI.

Our results were mostly consistent with these reports, but in our study, unlike those of Shinozaki *et al.* (*23*) and Cui *et al.* (*24*), diabetes was related independently and significantly to low ABI.

Because statins affect the CRP level (*34*, *35*), we treated statin use as an independent variable. In this study we also found that statin use was related to low ABI. These relationships might have been observed because the statins were used specifically to treat PAD or because the statin users were those with the highest pre-treatment serum cholesterol.

These risk factors, *i.e.*, low BMI, hypertension, low HDL cholesterol, and current smoking, have also been associated with low ABI among Western subjects (*39–41*). Therefore, in this study, we confirmed that similar correlations of low ABI and cardiovascular disease risk factors exist among Japanese subjects and subjects in Western countries.

The CRP level was related to low ABI independently of these cardiovascular disease risk factors, and the relationship also remained when we excluded the statin users.

Since Albert *et al.* reported that CRP level is related positively to risk clustering (*37*), we attempted to investigate the relationship between ABI associated with a combination of number of cardiovascular disease risk factors and CRP. The results also showed that CRP was related independently to low ABI independent of the number of traditional cardiovascular diseases. Furthermore, the results confirmed the importance of clustering traditional cardiovascular disease risk factors; even those subjects who had multiple risk factors without high CRP levels had a higher OR. Measuring CRP together with traditional cardiovascular disease risk factors may improve our ability to identify individuals with low ABI in the Japanese population.

Our study had some limitations. First, most of the participants were sufficiently active and healthy to participate in the survey; therefore, we have likely underestimated the prevalence of low ABI. Secondly, since this was a cross-sectional study, we cannot conclude that CRP causes PAD or that atherosclerosis leads to higher CRP. Therefore, a prospective study should be undertaken to confirm the relationship between CRP and low ABI in the Japanese population.

In conclusion, we have demonstrated that CRP is related to low ABI. This is the first study to clarify the relationship between CRP and low ABI among Japanese elderly.

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The Relationship between Body Mass Index and a Plasma Lipid Peroxidation Biomarker in an Older, Healthy Asian Community

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PURPOSE: To examine the association between body mass index (BMI) and the plasma level of a lipid peroxidation biomarker in a large sample of elderly healthy Asian population. This cross-sectional study included 1150 community-dwelling Japanese aged 70 years or older in 2002.
METHODS: We measured the lipid peroxidation biomarker 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) using the ELISA method. We also measured the weight and height and calculated the BMI as weight (kg)/height $(m)^2$.
RESULTS: After adjustment for potential confounders, the mean ± SE plasma 8-iso-$PGF_{2\alpha}$ level was significantly higher in subjects with higher BMI: 21.1 ± 0.8 pg/ml in those with BMI of 30.0 or more; 20.5 ± 0.3 pg/ml in those with BMI between 25.0 and 29.9; 20.0 ± 0.2 pg/ml in those with BMI between 18.5 and 24.9; and 19.0 ± 0.7 pg/ml in those with BMI of less than 18.5 (p for trend = 0.011).
CONCLUSIONS: Our results demonstrated that in the healthy Asian population, there was a modest but significant relationship between BMI and the plasma lipid peroxidation level.
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KEY WORDS: Obesity, Body Mass Index, Oxidative Stress, Isoprostanes, Asia, Aged.

INTRODUCTION

Although obesity is an established risk factor for atherosclerotic cardiovascular diseases (1–3), its pathomechanism has been unclear (4). On the other hand, there has been considerable progress in understanding the role of lipid peroxidation in the formation and progress of atherosclerosis. Recent studies have identified isoprostane compounds as a biomarker of lipid peroxidation, and examined the association between atherosclerotic cardiovascular diseases and oxidized lipids. An association between obesity and high oxidative stress has been demonstrated by two observational epidemiologic studies of large sample populations of healthy humans in the United States (5, 6). Since ethnic variability in the level of oxidative stress was suggested (6), this finding needs to be confirmed for other ethnicities such as Asians. These previous studies dealt mainly with Caucasian populations. Given the possible ethnic variability in such factors as genetic variability and nutritional status, it is necessary to determine whether obesity is a risk factor for oxidative stress among Asian populations.

The aim of the present study was to test the hypothesis that obesity is associated with increased oxidative stress in a healthy Asian population. To estimate the oxidative stress status, we used a lipid peroxidation biomarker, 8-iso-prostaglandin F_2-α (8-iso-$PGF_{2\alpha}$), because it is one of the most reliable indices for assessing oxidative stress status *in vivo* (7). 8-iso-$PGF_{2\alpha}$ is one of the four known classes of F_2-isoprostanes, which are lipid peroxidation products of arachidonic acid (8).

METHODS

Study Population

The Tsurugaya Project was a community-based Comprehensive Geriatric Assessment (CGA) (9, 10) of elderly Japanese individuals living in Tsurugaya district, a suburban area of Sendai City in northern Japan, between July and October 2002. At this time, there were 2730 people aged 70

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years or older living in Tsurugaya. We invited all of these individuals to participate, and 1179 (43.2%) of them did so, and gave their written informed consent for analysis of the data. The subjects also responded to interviews on the questionnaire included in the CGA. The protocol of this study was approved by the Institutional Review Board of Tohoku University Graduate School of Medicine.

Weight and height of the subjects were measured at the baseline survey. Body mass index (BMI) was calculated as the weight (kg)/height $(m)^2$ and then classified into four categories: less than 18.5 kg/m^2, between 18.5 kg/m^2 and 24.9 kg/m^2, between 25.0 kg/m^2 and 29.9 kg/m^2, and 30.0 kg/m^2 or more. Smoking and drinking status were classified into three groups: current smokers/drinkers, past smokers/drinkers, or never smokers/drinkers. Definition for hypertension included a self-reported history of hypertension or use of oral hypotensive drugs, and that for hyperlipidemia included a casual serum total cholesterol level greater than or equal to 220 mg/dl or casual serum triglyceride level greater than or equal to 150 mg/dl, or use of hypolipidemic drugs, or a self-reported history of hyperlipidemia, and that for diabetes included a casual plasma glucose level greater than or equal to 200 mg/dl, or use of oral hypoglycemic drugs or insulin, or a self-reported history of diabetes.

Plasma 8-iso-prostaglandin $F_{2\alpha}$ Measurements

Among the 1179 subjects, plasma 8-iso-$PGF_{2\alpha}$ data were obtained from 1150 (mean age, 75.7 ± 4.8 years; men, 41.3%). For 8-iso-$PGF_{2\alpha}$ measurement, peripheral venous blood was collected in EDTA2Na (Ethylenediaminetera-acetic acid 2Na)- and EDTA4Na-coated cold polyethylene tubes containing 1 mmol indomethacin, an inhibitor of cycloxygenese, and aprotinin, an inhibitor of kellikreins, to prevent any *in vitro* formation of 8-iso-$PGF_{2\alpha}$. After collection, blood samples were cooled immediately at 4 °C and transferred to the laboratory within 4 hours. In the laboratory, the samples were centrifuged at 3000 × g at 4 °C for 10 minutes. The plasma fraction was removed and stored at −80 °C for later 8-iso-$PGF_{2\alpha}$ assay. A specific enzyme immunoassay kit (Cayman Chemical, Ann Arbor, MI) (11) was used to measure the 8-iso-$PGF_{2\alpha}$ concentration in plasma samples. The assay was validated directly by gas chromatography/mass spectrometry. The antiserum used in this assay has 100% cross-reactivity with 8-iso-$PGF_{2\alpha}$, 0.2% with prostaglandin (PG) F_2-α, PGF_3-α, PGFI, and PGF_2, and 0.1% with 6-keto PGF_2-α1. The intra-assay and interassay variabilities were within 6% for both. Data obtained in this manner correlate well with those obtained using electrospray-negative ionization gas chromatography–mass spectroscopy (GC/MS) (12). The detection limit of the assay was 4 pg/ml.

Statistical Analysis

The association between plasma 8-iso-$PGF_{2\alpha}$ levels and baseline characteristics was examined and the standard error (SE) of plasma 8-iso-$PGF_{2\alpha}$ level was estimated using *t* test or ANOVA, as appropriate. Then plasma 8-iso-$PGF_{2\alpha}$ levels were compared with BMI categories, adjusting for potential confounders using ANCOVA and trend tests were performed by including the ordinal variable in a linear regression analysis. Since previous studies have shown that F_2-isoprostane levels might be elevated under conditions such as the use of multivitamin/vitamin C/vitamin E supplements (13, 14), non-steroidal anti-inflammatory drugs (NSAIDs) (14), smoking (5, 6, 15), hyperlipidemia (5, 16), and diabetes (5, 17), we used the following confounders as covariates in these analyses. First, we regarded the following data as covariates: sex, age (continuous variable), physical function status (being able to perform vigorous or moderate activities, being independent in activities of daily living, or being dependent in activities of daily living), consumption frequencies of soy beans products such as *tohu* (daily, 1–6 times per week, or less than 1 time per week) and Japanese green tea (more than 4 cups per day, 1–3 cups per day, or less than 1 cup per day), use of multivitamin/vitamin C/vitamin E supplements, use of NSAIDs, and smoking (never, former, current smoking), and alcohol drinking (never, former, current drinking). Second, we adjusted for the obesity-related comorbid conditions; hypertension, hyperlipidemia, and diabetes.

All statistical analyses were performed using SAS software, version 8.02 (18). We used approximate variance formulae to calculate the 95% confidence intervals (CI). All the statistical tests reported here were two-sided. Differences at $p < 0.05$ were accepted as statistically significant.

RESULTS

Table 1 shows the baseline characteristics and plasma 8-iso-$PGF_{2\alpha}$ levels of the study subjects. The mean age of the subjects was 75.7 years (standard deviation [SD] 4.8), and 20.6% were aged 80 years or older. Sex and BMI were significantly associated with the plasma 8-iso-$PGF_{2\alpha}$ level ($p = 0.0158$ and 0.0173, respectively). The plasma 8-iso-$PGF_{2\alpha}$ levels were higher among past/current smokers than never smokers, although not statistically significant.

Table 2 shows the association between BMI and plasma 8-iso-$PGF_{2\alpha}$. After adjustment for sex, age, physical function status, use of multivitamin/vitamin C/vitamin E supplements, use of NSAIDs, consumption frequencies of soy beans products and Japanese green tea, smoking, and alcohol drinking, significant dose–response relationships between BMI and the plasma 8-iso-$PGF_{2\alpha}$ level were observed (Model 1: p for trend = 0.0082). Even after

TABLE 1. Characteristics of the subjects and 8-iso-$PGF_{2\alpha}$ levels

	8-iso-$PGF_{2\alpha}$			
	N	Mean	SE	p-value
BMI				
<18.5	63	18.94	0.68	0.016
18.5–24.9	684	19.96	0.21	
25.0–29.9	354	20.46	0.29	
30.0<	49	20.98	0.77	
Sex				
Male	475	20.55	0.25	0.017
Female	675	19.79	0.21	
Age (years)				
70–74	563	20.18	0.23	0.86
75–79	350	19.80	0.29	
80+	237	20.38	0.35	
Smoking				
Current smoking	144	20.21	0.44	0.28
Past smoking	338	20.43	0.29	
Never smoking	646	19.87	0.21	
Drinking				
Current drinking	441	20.40	0.25	0.32
Past drinking	144	20.38	0.45	
Never drinking	510	19.91	0.24	
Consumption frequencies of soy beans products				
Daily	587	20.07	0.22	0.99
1–6 times per week	511	20.06	0.24	
Less than 1 time per week	34	19.92	0.92	
Consumption frequencies of Japanese green tea				
More than 4 cups per day	522	19.75	0.24	0.16
1–3 cups per day	377	20.45	0.28	
Less than 1 cup per day	231	20.11	0.35	
Use of vitamin supplement*				
Yes	155	19.87	0.43	0.56
No	995	20.14	0.17	
Use of NSAIDs†				
Yes	250	20.35	0.34	0.42
No	900	20.04	0.18	

*Multivitamin/vitamin C/vitamin E.
†Non-steroidal anti-inflammatory drug.

adjustment for obesity-related confounding factors such as hypertension, hyperlipidemia, and diabetes there was no change in the linear relationship between plasma 8-iso-$PGF_{2\alpha}$ level and BMI. The mean ± SE plasma 8-iso-$PGF_{2\alpha}$ level was significantly higher in subjects with higher BMI: 21.1 ± 0.8 pg/ml in those with BMI of 30.0 or more; 20.5 ± 0.3 pg/ml in those with BMI between 25.0 and 29.9; 20.0 ± 0.2 pg/ml in those with BMI between 18.5 and 24.9; and 19.0 ± 0.7 pg/ml in those with BMI of less than 18.5 (Model 2: p for trend = 0.011). The gender difference that was significant in the unadjusted analysis was no longer so after adjustment (data not shown).

Furthermore, stratified analyses of obesity-related comorbid states such as hypertension, hyperlipidemia, and diabetes did not change the main findings (data not shown). The most significant linear relationship between plasma 8-iso-$PGF_{2\alpha}$ level and BMI was observed among the subjects with hyperlipidemia.

DISCUSSION

In this population of elderly Japanese individuals, we observed a modest but significant dose–response relationship between a higher BMI and a higher plasma 8-iso-$PGF_{2\alpha}$ level, after adjustment for a variety of potential confounders. To our knowledge, this is the first study to examine the association between BMI and oxidative stress in an Asian population.

The present study has a number of strengths. First, our sample size was large enough (N = 1150) to detect a positive, negative or null association. Second, we adjusted for a variety of possible confounders that would affect the 8-iso-$PGF_{2\alpha}$ level or BMI: age, sex, use of vitamin A/vitamin C/vitamin E supplements, use of NSAIDs, consumption frequencies of soy beans products and Japanese green tea, smoking, drinking, and physical function. Furthermore, even when we stratified the subjects according to the complications of diabetes, hypercholesterolemia, and hypertension, the finding of a positive association between obesity and the 8-iso-$PGF_{2\alpha}$ level was unchanged.

The present results indicated that the 8-iso-$PGF_{2\alpha}$ level was significantly associated with a higher BMI. Our results are consistent with previous studies of a USA population (5, 6) and a small intervention study of obesity (19) in the USA. Keaney et al. examined 2828 subjects aged 33 to 88 years from the Framingham Heart Study and measured

TABLE 2. The relationship between 8-iso-$PGF_{2\alpha}$ and body mass index

	BMI [weight (kg)/height $(m)^2$]				
8-isoprostane (± SE)	<18.5	18.5–25.0	25.0–30.0	>30.0	p for trend
Model 1	19.04 ± 0.69	19.94 ± 0.21	20.56 ± 0.29	21.16 ± 0.77	0.0082
Model 2	19.01 ± 0.70	19.95 ± 0.21	20.54 ± 0.29	21.14 ± 0.77	0.011

Model 1: Adjusted for sex, age, multivitamin/vitamin C/vitamin E supplement use, non-steroid anti-inflammatory drug use, physical functioning status, smoking status (current-smoking, ex-smoking, and never smoking), drinking status (current-drinking, ex-drinking, and never drinking), consumption frequencies of soy bean products (daily, 1–6 times per week, or less than 1 time per week), and consumption frequencies of Japanese green tea (more than 4 cups per day, 1–3 cups per day, or less than 1 cup per day).
Model 2: Adjusted for variables above and history of hypertension, diabetes mellitus, and hyperlipidemia.

urinary creatinine-indexed 8-epi-$PGF_{2\alpha}$ as a marker of systemic oxidative stress (5). Block et al. measured urinary plasma 8-epi-$PGF_{2\alpha}$ among 298 subjects aged 19 to 78 years (6). Those two studies of healthy populations indicated that BMI was associated with a higher plasma level of 8-epi-$PGF_{2\alpha}$. Davi et al. conducted an intervention study of obese women aged 24 to 63 years and demonstrated the possibility that successful weight loss may be adequate for minimizing oxidative stress in obese subjects with a BMI of 28 or more (19). Our study confirmed the positive association between BMI and plasma 8-epi-$PGF_{2\alpha}$ in this Asian population, which is largely different from Caucasian in terms of genetic background and nutritional intake. The role of lipid peroxidation in the formation and progress of atherosclerosis has been well understood. The present results support the hypothesis that oxidative stress is one of the mechanisms responsible for atherosclerosis in obesity.

Several hypotheses for the association between oxidative stress and obesity have been proposed. Obesity is associated with insulin resistance and several mechanisms have been suggested to explain the association between oxidative stress and insulin resistance (5). For example, insulin itself promotes hydrogen peroxide formation in human fat cells (20). Nutritional intake is also suggested to explain the association between obesity and oxidative stress. Glucose intake increases more reactive oxygen species generation from leukocytes in obese subjects than in normal subjects (21). The results of the present study support these basic researches.

Previous studies have suggested a relationship between isoprostanes level and smoking (5, 6, 15). In this study, we confirmed the relationship between the plasma 8-iso-$PGF_{2\alpha}$ level and smoking, although not statistically significant.

Our study also had some limitations. The study population aged 70 years or older might represent healthy aging resistance to oxidative stress. Most of the elderly participants were active and healthy enough to participate in the survey, and this might have led to small inter-individual differences in the study data. However, despite this limitation, we detected a modest but significant dose–response relationship among the population. We used ELISA rather than GC/MS because we had to process large numbers of samples in a timely manner. To minimize autoxidation, care was taken with plasma sample preparation and also to avoid artificial autoxidation.

Our study focusing on elderly Asian individuals demonstrated a statistically significant dose–response relationship between BMI and a lower plasma level of 8-iso-$PGF_{2\alpha}$. The impact of obesity upon the risk of atherosclerotic cardiovascular diseases (22–24) and medical care costs (25) in Asia are as large as those in Western countries. Obesity has been increasing rapidly in Asia (26, 27); the prevalence of obesity in Japanese men doubled between 1976 and 1995 (27). Thus, obesity is an urgent issue not only in Western but also in Asian countries. The present results confirm the hypothesis that oxidative stress is one of the pathomechanisms responsible for the association between obesity and atherosclerosis in Asians.

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Modifiable Factors for the Length of Life with Disability before Death: Mortality Retrospective Study in Japan

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Key Words
Disability · Lifestyles · Compression of morbidity · Elderly

Abstract

Background: Past studies have measured and described the length of life with disability before death, but there has been no study of the relationship between modifiable lifestyle factors and duration of disability. ***Objective:*** To examine whether there are modifiable factors influencing the length of life with disability before death. ***Methods:*** The study was designed as a retrospective observation of the deceased who had earlier been enrolled in a prospective cohort study. During the follow-up period (1996–1999), we documented 781 deaths among those who were 70–79 years of age at the baseline survey in 1994 (n = 10,216). In 2000, we interviewed family members of the deceased about the duration of the subjects' disability before death (n = 655). ***Results:*** The median duration of disability before death was approximately 6 months. Both higher Body Mass Index (BMI) and shorter time spent walking were significantly associated with an increased risk of long-term disability (more than 6 months). The odds ratios of long-term disability were 1.3 in those with BMI 20–25 and 2.1 in those with BMI >25, compared with BMI <20. The odds ratios of long-term disability were 1.3 in those walking for 0.5–0.9 h/day and 1.7 in those walking for <0.5 h/day, compared with those walking for >1.0 h/day. These relationships were unchanged after stratification for causes of death. ***Conclusion:*** Weight control and walking in later life may shorten the length of life with disability before death.

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Introduction

In an era when human life expectancy is approaching its biological limits [1], increasing attention is being paid to the quality of the last months of life [2]. Fear of death is often joined by fears of disability or institutionalization [3]. We would all like to remain independent until the very last days of our lives, and thus decrease the length of life with disability.

To provide strategies for disability prevention among the elderly, past epidemiological studies have identified a number of risk factors for the incidence of disability in later life [4–10]. Although a lower incidence of disability may imply postponement of its onset [11], it has not been proven whether lowering the incidence of disability leads to a shortening of the period of disability.

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