RESEARCH COMMUNICATION

Relationship between Obesity and Serum Markers of Oxidative Stress and Inflammation in Japanese

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Abstract

The present study was conducted to assess the relationship between obesity and serum levels of C-reactive protein (CRP), carotenoids, oxidized LDL (oxLDL), oxidized LDL antibodies (oLAB), and leptin in Japanese residents.

The subjects were 158 males and 158 females aged 40-79 years, and living in Hokkaido, Japan, who attended a health examination screening. Serum levels of CRP, oxLDL, oLAB, and leptin were measured by enzyme-linked immunosorbent assay (ELISA) and serum carotenoid levels were measured by high-performance liquid chromatography (HPLC). Body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared and obesity was defined as BMI of 25 or more (kg/m^2).

Serum levels of CRP and leptin were significantly higher in the obese group than in their non-obese counterparts in both genders. Serum levels of β-carotene and β-cryptoxanthin were lower in the obese individuals, especially in females. While values for oxLDL and oLAB did not significantly vary. BMI was positively correlated with log-transformed serum levels of CRP and leptin in both genders (males: $r=0.231$, $p<0.05$; females: $r=0.305$, $p<0.001$). In females, moreover, BMI was negatively correlated with log-transformed serum levels of β-carotene, zeaxanthin/lutein, and β-cryptoxanthin ($r=-0.244$, $p<0.01$; $r=-0.200$, $p<0.05$; $r=-0.207$, $p<0.01$, respectively).

Significantly higher odds ratios (ORs) for high serum levels of CRP (males: OR=2.12; females: OR=3.96) and leptin (males: OR=3.83; females: OR=9.07) were observed in obese versus non-obese men and women, after adjusting for various confounding factors. Significantly lower adjusted odds ratios for high serum levels of α- and β-carotenes (males: OR=0.23, 0.33; females: OR=0.35, 0.39, respectively) were also observed in the obese as compared to the non-obese group.

In conclusion, obesity is highly associated with states of oxidative stress and low-grade inflammation in Japanese residents, suggesting that these latter might play an important role in the association between a high BMI and certain cancers as well as coronary heart disease (CHD).

Key Words: obesity, C-reactive protein, carotenoids, oxidized low-density lipoprotein, leptin, inflammation, oxidative stress, cancer risk

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Introduction

Oxidative stress, a state of imbalance between the production of reactive oxygen species (ROS) and antioxidant defenses, appears to be involved in various ailments, such as development of certain cancers and coronary heart disease (CHD) (Ames et al., 1993; Saintot et al., 1996). In the human body, ROS causes oxidation of lipids, proteins, and DNA (Saintot et al., 1996; Channon, 2002), and a number of enzymatic and non-enzymatic systems, which protect cells against this type of damage, have therefore evolved to compensate .

Smoking is known to generate ROS in vivo, increasing inflammation markers (Das, 1985), such as C-reactive protein (CRP), and decreasing serum levels of carotenoids (Comstock et al., 1988). CRP, an acute-phase protein, has been used clinically for monitoring infections, inflammation, and autoimmune disorders, and development of high-sensitivity methods, such as ELISA, has facilitated its widespread application as a parameter for prediction of future cardiovascular disease in apparently healthy adults (Ridker et al., 1998).

Carotenoids, such as α- and β-carotenes, which are abundant in fruit and vegetables, are known to protect cells from oxidative stress by quenching free radicals (Bendich and Olson, 1989). Several kinds of carotenoids can be detected in human serum, and numerous epidemiologic studies (Bendich, 1990; Comstock et al., 1992; van Poppel and Goldbohm, 1995) have demonstrated that individuals with higher dietary consumption of fruit and vegetables rich in carotenoids, or with high serum level of β-carotene, have lower risks of certain cancers as well as cardiovascular disease.

Oxidized low-density lipoprotein (oxLDL) is an oxidant that is generated by the action of ROS and is believed to play a critical role in the development and progression of atherosclerosis (Witztum and Steinberg, 1991). Macrophages taking up oxLDL and oxLDL antibodies (oLAB) are present both in atherosclerotic lesions and plasma (Witztum, 1994), and serum oxLDL and oLAB levels have been reported to be related to the degree of physical change (Salonen et al., 1992; Maggi et al., 1994). Elevated oxLDL levels have also been detected in the plasma of patients with coronary heart disease (Toshima et al., 2000).

Obesity is reported to be associated with hypertension and elevated serum levels of total- and LDL-cholesterol. It is also a risk factor for diabetes mellitus (Colditz et al., 1990), cardiovascular disease (Manson et al., 1990), and certain neoplasms such as colorectal cancer (Garfinkel, 1985; Murphy et al., 2000). While the exact mechanisms are not well understood, some studies have provided evidence that obesity could contribute to oxidative stress (Keaney et al., 2003) and inflammation (Ford, 1999; Visser et al., 1999), which might partly explain the associations. In the present study, we therefore investigated the relationship between obesity and serum levels of oxLDL, oLAB, carotenoids, and CRP in Japanese subjects.

Subjects and Methods

We selected 158 males and 158 females, aged 40-79 years, matched for sex and age, who attended a health examination for inhabitants living in an area of Hokkaido, Japan, in August 2002. This is one of the study areas of the Japan Collaborative Cohort Study (JACC Study) (Ohno et al., 2001).

Trained nurses administered a questionnaire regarding health and daily lifestyle habits, assessing smoking (current smoker, ex-smoker, or non-smoker), alcohol consumption (regular drinker, ex-drinker, or non-drinker), and history of major illness. Fasting serum samples were taken during the health examination and sera were separated from blood cells within one hour by centrifugation. Serum samples were collected in tubes and stored at -80°C until analyses.

Serum levels of CRP, oxLDL, oLAB, and leptin were measured by ELISA (CRP: High sensitivity C-reactive protein enzyme immunoassay test kit, Diagnostic Automation Inc., USA; oxLDL: Oxidized LDL ELISA kit, Mercodia, Sweden; oLAB: oLAB ELISA kit, Biomedica, Wien, Austria; leptin; Leptin enzyme immunoassay kit, Cayman Chemical Co., USA), following the attached manuals. The measurement times were about 3 or 4 hours. For intra-assay and inter-assay reproducibility, the coefficients of variation (CVs) for CRP, oxLDL, and oLAB (Suzuki et al., 2003) were found to be less than 10%.

Serum levels of α- and β-carotenes, lycopene, β-cryptoxanthin, and zeaxanthin and lutein (zeaxanthin/lutein) were measured separately by high-performance liquid chromatography (Ito et al., 1990). Other biochemical analyses of the sampled sera were performed using an auto-analyzer (JCA-RX20, Nihon Denshi Co., Ltd.) on the health examination day.

Body height and weight were measured and the body mass index (BMI) was calculated as body weight (kg) divided by height (m) squared. We defined obesity as a BMI of 25 or more (kg/m^2), in agreement with the Japan Society for the Study of Obesity (Matsuzawa et al., 2000).

All statistical analyses were conducted using a statistical package (Stat View® ver. 5.0, SAS). We were able to measure 274 samples of oxLDL (137 male and 137 females) and 142 samples of oLAB (71 males and 71 females). The other serum components were measured for all 316 subjects (158 males and 158 females). Since serum levels of CRP, leptin, oLAB, and carotenoids were distributed logarithmically, simple and partial correlation coefficients with BMI were calculated using log-transformed values. The t-test was performed to compare means of log-transformed values between non-obese and obese groups. Partial correlation and logistic regression analyses were performed after adjusting for age, smoking habit, alcohol consumption, systolic blood pressure (SBP), and serum levels of total cholesterol and γ-GTP activity. Classification cut-offs for serum levels of leptin, oLAB, and carotenoids were 75th percentile by gender, and that for serum CRP was 1.1 mg/l. Logistic regression analyses for elevated serum levels of oxLDL and

oLAB among non-obese and obese subjects with or without hypertension were performed after adjusting for gender, age, smoking habit, alcohol consumption, SBP, and serum levels of total cholesterol and γ-GTP activity. The reference group for this analysis was subjects with no history of stroke, myocardial infarction, diabetes mellitus, liver disease, kidney disease, or cancer.

We obtained informed consent from the participants for collection of information and serum for our epidemiological study.

Results

Table 1 summarized data for characteristics of the study subjects. The percentages of current smokers and alcohol drinkers, as well as the levels of serum CRP, triglyceride, SBP, and diastolic blood pressure (DBP) were significantly higher in males than in females. Value for serum carotenoids, total- and HDL-cholesterol, and leptin, in contrast, were significantly higher in females. No significant differences in the levels of serum oxLDL, oLAB, or BMI were observed between males and females.

Table 2 shows the levels of serum CRP, carotenoids, oxLDL, oLAB, and leptin by gender and BMI level. In men and women, serum CRP and leptin levels were significantly higher in the obese group than in non-obese group. Serum levels of β-carotene and β-cryptoxanthin were lower in the obese group, especially in females. No significant differences in serum levels of oxLDL or oLAB were observed between the non-obese and obese groups in either gender.

Table 3 shows the correlation coefficients between BMI and CRP, carotenoids, leptin, oxLDL, and oLAB. In both genders, BMI was positively correlated with log-transformed serum levels of CRP and leptin after adjusting for potential confounding factors. In females, moreover, BMI was negatively correlated with log-transformed serum levels of β-carotene, zeaxanthin/lutein, and β-cryptoxanthin, after adjusting for confounding factors.

Serum CRP levels were significantly and positively correlated with serum leptin levels in both genders (males: r=0.280, P<0.01; females: r=0.338 P<0.001). After adjusting for confounding factors, such as age, smoking, alcohol use, SBP, serum γ-GTP activity, and total cholesterol levels, these results were not changed (males: r=0.301, P<0.001; females: r=0.305, P<0.001). Serum CRP levels were significantly and negatively correlated with serum levels of lycopene and α-

Table 1. Characteristics of the Study Subjects

	Males		Females		p
No.	158	(100.0)	158	(100.0)	
Smoking status					
never smoker	38	(24.1)	135	(85.4)	<0.001[c]
ex-smoker	62	(39.2)	11	(7.0)	
current smoker	58	(36.7)	12	(7.6)	
Alcohol consumption					
non drinker	52	(32.9)	134	(84.8)	<0.001[c]
ex-drinker	9	(5.7)	5	(3.2)	
regular drinker	97	(61.4)	19	(12.0)	
Age[a] (y)	59.0±10.6		58.9±10.6		0.970[d]
CRP[b] (mg/l)	0.53 (0.27-2.20)		0.46 (0.16-0.98)		0.004[d]
Lycopene[b] (μmol/l)	0.348 (0.214-0.611)		0.512 (0.313-0.794)		<0.001[d]
α-Carotene[b] (μmol/l)	0.090 (0.061-0.148)		0.150 (0.109-0.228)		<0.001[d]
β-Carotene[b] (μmol/l)	0.485 (0.294-0.817)		0.988 (0.687-1.605)		<0.001[d]
Zeaxanthin/Lutein[b] (μmol/l)	1.021 (0.768-1.241)		1.224 (0.897-1.553)		0.001[d]
β-Cryptoxanthin[b] (μmol/l)	0.188 (0.125-0.285)		0.325 (0.247-0.428)		<0.001[d]
Leptin[b] (ng/ml)	2.9 (1.2-5.5)		10.2 (5.5-17.6)		<0.001[d]
Oxidized LDL[a] (U/l)	41.6±12.2		42.7±13.9		0.480[d]
Oxidized LDL antibodies[b] (U/l)	170.7 (130.9-301.2)		209.0 (152.6-312.5)		0.128[d]
Body mass index[a] (kg/m^2)	23.9±3.4		23.9±3.3		0.917[d]
Total Cholesterol[a] (mg/dl)	206.1±32.4		217.1±34.9		0.004[d]
Triglyceride[b] (mg/dl)	96.0 (66.0-138.0)		80.5 (59.0-117.0)		0.025[d]
HDL-cholesterol[a] (mg/dl)	53.4±12.5		59.3±12.2		<0.001[d]
Systolic blood pressure[a] (mmHg)	137.4±18.7		132.7±20.0		0.035[d]
Diastolic blood pressure[a] (mmHg)	81.8±12.7		77.5±11.5		0.002[d]

a: mean ± standard deviation. b: median and range of 25-75% in parentheses. c: by chi-square test. d: by t test (males vs females) t tests were conducted using log-transformed values of serum triglyceride, oxidized LDL antibodies, leptin, CRP, and carotenoids.

Table 2. Comparison of Serum CRP, Carotenoids, Oxidized LDL, Oxidized LDL Antibodies, and Leptin Levels between Non-obese and Obese Groups by Gender

	Males			Females		
	Non-obese	Obese	p	Non-obese	Obese	p
N[a]	108	50		106	52	
Age[b] (y)	59.3±10.8	58.3±10.4	0.615	58.7±10.8	59.4±10.2	0.667
BMI[b] (kg/m^2)	22.0±2.0	27.7±2.4	<0.001	22.1±2.0	27.6±1.9	<0.001
CRP[c] (mg/l)	0.41 (0.21-1.98)	0.83 (0.42-2.23)	0.048	0.35 (0.14-0.76)	0.77 (0.38-2.07)	<0.001
Lycopene[c] (μmol/l)	0.36 (0.19-0.61)	0.34 (0.25-0.61)	0.672	0.54 (0.32-0.85)	0.44 (0.27-0.65)	0.077
α-Carotene[c] (μmol/l)	0.10 (0.06-0.15)	0.08 (0.06-0.11)	0.314	0.17 (0.11-0.25)	0.14 (0.09-0.20)	0.057
β-Carotene[c] (μmol/l)	0.53 (0.29-0.85)	0.41 (0.31-0.74)	0.688	1.04 (0.77-1.67)	0.88 (0.53-1.36)	0.019
Zeaxanthin/Lutein[c] (μmol/l)	0.97 (0.76-1.25)	0.94 (0.80-1.23)	0.536	1.18 (0.95-1.62)	1.07 (0.88-1.26)	0.100
β-Cryptoxanthin[c] (μmol/l)	0.20 (0.13-0.29)	0.18 (0.12-0.26)	0.911	0.33 (0.26-0.44)	0.29 (0.21-0.40)	0.025
Leptin[c] (ng/ml)	1.9 (0.5-3.8)	5.1 (3.4-8.3)	<0.001	7.3 (4.6-11.3)	19.2 (11.7-29.6)	<0.001
Oxidized LDL[b,d] (U/l)	41.5±11.8	41.7±12.6	0.831	42.0±13.2	44.6±16.4	0.209
Oxidized LDL antibodies[b,e] (U/l)	169.1 (125.4-268.5)	184.1 (139.1-328.7)	0.779	206.9 (152.6-363.0)	212.4 (153.8-266.5)	0.611

Non-obese group: the subjects with BMI of less than 25 kg/m^2 Obese group: the subjects with BMI of 25 or more kg/m^2

a: The number excluding serum oxidized LDL and oxidized LDL antibodies levels

b: mean ± standard deviation.

c: median and range of 25-75% in parentheses.

d: The numbers of subjects were 137 males (Non-obese; 96, Obese; 41) and 137 females (Non-obese; 94, Obese; 43)

e: The numbers of subjects were 71 males (Non-obese; 44, Obese; 27) and 71 females (Non-obese; 47, Obese; 24)

carotene in males (r=-0.205, -250, P<0.01, respectively) but not in females (r=-0.041, -0.065, respectively). In males, moreover, serum oxLDL levels were significantly and positively correlated with serum levels of α- and β-carotenes, zeaxanthin/lutein, and β-cryptoxanthin. In females, serum leptin levels were significantly and negatively correlated with values for lycopene, α- and β-carotenes and zeaxanthin/lutein, as well as β-cryptoxanthin. However, after adjusting for confounding factors, these relationships were not changed.

Table 4 shows odds ratios and 95% confidence intervals for elevated serum levels of CRP, carotenoids, oxLDL, oLAB, and leptin after adjusting for confounding factors. Significantly higher odds ratios for high serum levels of CRP and leptin, and lower odds ratios for high serum levels of α- and β-carotenes, were observed in the obese group in both genders. In females, moreover, a significantly higher odds ratio for high serum oxLDL levels was observed in the obese group.

Table 5 shows odds ratios and 95% confidence intervals for elevated serum levels of oxLDL and oLAB for subjects with or without obesity and hypertension after adjusting for confounding factors. Significantly higher odds ratios for high serum levels of oxLDL were observed in non-obese and obese subjects with hypertension. The odds ratio for high serum oLAB levels also tended to be higher in obese subjects

Table 3. Correlation between BMI and Serum Levels of CRP, Carotenoids, Leptin, oxidized LDL, and oxidized LDL Antibodies by Gender

	Males (N=158)		Females (N=158)	
	Simple correlation coefficients	Partial correlation coefficients	Simple correlation coefficients	Partial correlation coefficients
CRP	0.231 **	0.284 **	0.305 ***	0.234 **
Lycopene	0.089	-0.032	-0.163 *	-0.153 #
α-Carotene	0.017	-0.092	-0.171 *	-0.140 #
β-Carotene	0.110	-0.022	-0.244 **	-0.234 **
Zeaxanthin/Lutein	0.127	0.014	-0.200*	-0.215 **
β-Cryptoxanthin	0.096	-0.048	-0.207 **	-0.171 *
Leptin	0.536 ***	0.505 ***	0.712 ***	0.684 ***
Oxidized LDL[a]	0.226 #	-0.007	0.216 #	0.086
Oxidized LDL antibodies[b]	0.089	0.055	-0.035	0.105

Partial correlation coefficients were adjusted by age, smoking and alcohol consumption, systolic blood pressure, and serum total cholesterol levels and γ-GTP activity. #: p<0.1, *: p<0.05, **: p<0.01, ***: p<0.001

a: The numbers of subjects were 137 males (Non-obese; 96, Obese; 41) and 137 females (Non-obese; 94, Obese; 43)

b: The numbers of subjects were 71 males (Non-obese; 44, Obese; 27) and 71 females (Non-obese; 47, Obese; 24)

Table 4. Adjusted Odds Aatios [a] and 95% Confidence Intervals for Elevated Levels of Serum CRP, Carotenoids, Leptin, oxidized LDL, and oxidized LDL Antibodies by Gender

	Males		Females	
	Non-obese	Obese	Non-obese	Obese
CRP	1.00	2.12 (1.01-4.72)	1.00	3.95 (1.68-9.32)
Lycopene	1.00	0.66 (0.28-1.55)	1.00	0.43 (0.17-1.07)
α-Carotene	1.00	0.23 (0.08-0.65)	1.00	0.35 (0.14-0.88)
β-Carotene	1.00	0.33 (0.12-0.92)	1.00	0.39 (0.15-0.99)
Zeaxanthin/Lutein	1.00	0.59 (0.23-1.50)	1.00	0.61 (0.25-1.53)
β-Cryptoxanthin	1.00	0.47 (0.18-1.23)	1.00	0.52 (0.21-1.31)
Leptin	1.00	3.83 (1.65-8.89)	1.00	9.07 (3.78-21.74)
Oxidized LDL	1.00	0.91 (0.35-2.35)	1.00	2.62 (1.01-6.84)
Oxidized LDL antibodies	1.00	1.82 (0.44-7.59)	1.00	1.23 (0.23-6.48)

Non-obese group: the subjects with BMI of less than 25 kg/m^2 Obese group: the subjects with BMI of 25 or more kg/m^2
a: Odds ratios and 95% confidence intervals were adjusted for age, smoking and drinking habits, systolic blood pressure, and serum total cholesterol levels and γ-GTP activity.
Classification cut-offs were 75th percentile by gender, excluding CRP. CRP cut-off was 1.1mg/l.

with hypertension compared to non-obese subjects with hypertension.

Discussion

Several studies (Ford, 1999; Visser et al., 1999) have shown that serum CRP levels are increased in obese subjects, a finding that our study confirmed. Inflammatory cytokines, such as interleukin-6 (IL-6) and TNF-α, are released from adipocytes (Hotamisligil et al., 1993; Mohamed-Ali et al., 1997), and their serum levels has been shown to be higher in cancer patients than in healthy individuals (Mantovani et al., 2001). IL-6 has the ability to increase production of CRP in the liver (Heinrich et al., 1990). Therefore, it has been suggested that obese subjects have more IL-6 in serum and consequently higher serum CRP levels compared with non-obese subjects.

In women in the present study, serum levels of carotenoids such as β-carotene were lower in the obese group, in line with previous findings (Wallstrom et al., 2001; Brady et al., 1996). However, in Japanese smokers, there were no significant age-adjusted correlations between BMI and serum levels of carotenoids, excluding lutein (Kitamura et al., 1997). Fat-soluble vitamins such as β-carotene are distributed both plasma and adipose tissue where they are stored (van Vliet, 1996). Accordingly, obese subjects would be expected to have a larger proportion of β-carotene absorbed by adipose tissue compared with their non-obese counterparts.

Recently, it was reported that the urinary levels of 8-epi-PGF$_{2\alpha}$, a marker of oxidative stress, are elevated in obese subjects (Keaney et al., 2003). Obesity is associated with insulin resistance (Baron, 2001) and emerging evidence linking this latter to oxidative stress (Facchini et al., 2000). Moreover, TNF-α is known to induce insulin resistance (Hansen et al., 1999) and impair insulin-receptor signaling in adipose tissue and skeletal muscle, and thereby decreasing insulin-stimulated glucose (Moller, 2000). IL-6 is thought

Table 5. Adjusted Odds Ratios for Elevated Levels of oxidized LDL and oxidized LDL Antibodies by the Subjects with or without Obesity and Hypertension

	Non-Obese		Obese	
Hypertension	NO[a]	YES	NO	YES
Oxidized LDL				
N (Males/Females)	39/48	49/34	12/16	28/26
OR (95%CI)	1.00	4.45 (1.57-12.66)	2.08 (0.87-4.98)	3.51 (1.13-10.91)
Oxidized LDL antibodies				
N (Males/Females)	24/28	17/13	8/10	19/14
OR (95%CI)	1.00	0.80 (0.09-7.24)	0.85 (0.25-2.90)	6.46 (0.97-42.95)

Non-obese group: the subjects with BMI of less than 25 kg/m^2 Obese group: the subjects with BMI of 25 or more kg/m^2
Odds ratios (OR) and 95% confidence intervals (95%CI) were adjusted by gender, age, smoking and drinking habits, and serum total cholesterol levels and γ-GTP activity.
a: The subjects had no medical history of cerebral apoplexy, myocardial infarction, diabetes mellitus, liver disease or kidney disease.

to modify adipocyte glucose and lipid metabolism and impact on body weight (Berg et al., 1994; Greenberg et al., 1992), and administration of human recombinant IL-6 to humans has been shown to induce hyperglycemia and compensatory hyperinsulinemia (Tsigos et al., 1997). Hyperglycemia increases the generation of free radicals by glucose autoxidation and Maillard's reaction (Sakurai and Tsuchiya, 1988; Gilley et al., 1988). Accordingly, serum levels of carotenoids such as β-carotene might be depleted in obese subjects.

Carotenoids, such as β-carotene, protect cells from oxidative stress by quenching free radicals (Bendich and Olson, 1989). Smoking is known to generate ROS in vivo, and it has been reported that serum levels of carotenoids like β-carotene and β-cryptoxanthin are lower in smokers than in non-smokers (Aoki et al., 1987; Ito et al., 1991). In our present study, 36.7% of males were current smokers, a rate 5 times greater than that for females. Since so many men were smokers and smoking has a strong effect on serum carotenoid levels, this might be explain the lack of any significant relationship between obesity and serum carotenoid levels in men in our study. After adjusting for confounding factors, however, the odds ratios for high serum carotenoid levels were significantly lower in the obese compared to the non-obese group in both genders.

No significant differences in serum levels of oxLDL and oLAB were observed between non-obese and obese groups in either gender, although the adjusted odds ratio for high serum oxLDL levels was significantly elevated in the hypertensive individuals and that for high serum oLAB levels tended to be higher in obese subjects who were hypertension. A limitation of this study was that the sample sizes for serum oxLDL and oLAB were relatively small. It has been reported that serum levels of oxLDL and oLAB are higher in patients with CHD, and may be risk factors (Parums et al., 1990). OxLDL is generated by the action of ROS and is believed to play a critical role in the development and progression of atherosclerosis (Witztum and Steinberg, 1991). It is taken up by macrophages and oLAB is present both in atherosclerotic lesions and plasma (Witztum, 1994), where it may control the increase of oxLDL. Actually, serum oLAB levels are reported to be negatively correlated with plasma oxLDL levels in healthy subjects (Shoji et al., 2000) In this study, the odds ratio for elevated serum oLAB levels tended to be higher in obese subjects with hypertension. Therefore, it is thought that serum oxLDL and oLAB levels may be considered as biomarkers for high blood pressure.
Leptin is a hormone that is secreted from adipocytes and is involved in satiety regulation (Zhang et al., 1994; Sarraf et al., 1997). It is well known that serum leptin levels are significantly higher in obese compared with non-obese subjects (Considine et al., 1996), a finding which our study confirmed. Leptin production and secretion are mainly determined by the size of adipose tissue depot.

However, numerous hormones, cytokines, and cytokine-like proteins may also exert an influence (Kristensen et al., 1999; Trayhurn et al., 1999) and TNF-α administration is known to increased plasma leptin levels in mice (Sarraf et al., 1997; Berkowitz et al., 1998). Circulating leptin levels may also rise with inflammation (Bornstein et al., 1998). In our study, serum leptin levels were significantly and positively associated with serum CRP levels in both genders after adjustment for confounding factors.

In conclusion, obesity has found to be highly associated with states of oxidative stress and low-grade inflammation in Japanese subjects. We suggest that these processes may play an important role in the relation between obesity and certain cancers as well as CHD.

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