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G. 知的財産権の出願・登録状況
（予定を含む。）

1. 特許取得
該当なし。

2. 実用新案登録
該当なし。

3. その他
なし。

Ⅱ．研究成果の刊行に関する一覧表

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ORIGINAL ARTICLE

C allele of angiotensin II type 1 receptor gene A1166C polymorphism affects plasma adiponectin concentrations in healthy young Japanese women

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Angiotensin II and its type 1 receptor (AT1R) are both expressed in the adipose tissue and involved in the genesis of atherosclerosis as well as hypertension. However, the influence of the AT1R gene A1166C polymorphism on atherosclerosis risk factors and on the development of early atherosclerosis is not clear. We evaluated 416 healthy young women to investigate the effects of this genotype on atherosclerosis risk factors and on carotid intima-media thickness as a validated marker of early atherosclerosis. After adjusting for confounding factors including body mass index, homeostasis model assessment of insulin resistance and plasma high-density lipoprotein (HDL)-cholesterol levels, plasma adiponectin concentrations were significantly lower in carriers of the C allele compared with non-carriers. Moreover, multiple logistic regression analysis showed that the C allele was the strongest and most independent determinant of lower plasma adiponectin concentrations. It is noted that the participants with the lowest quartile of plasma adiponectin concentrations had thicker levels of carotid intima-media thickness, lower plasma HDL-cholesterol and lipoprotein lipase levels, as well as higher trunk fat mass compared with the highest quartile. In addition, a weak but significant positive correlation was observed between percentages of fat in the diet and plasma adiponectin concentrations in non-carriers of the C allele. In conclusion, *AT1R* A1166C was associated with plasma adiponectin concentrations and influenced the correlations between dietary fat intake and plasma concentrations of adiponectin. These findings may help to identify vulnerable populations that are susceptible to the development of atherosclerosis and require early dietary recommendations for young women.
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Keywords: angiotensin II type 1 receptor; polymorphism; adiponectin; dietary fat intake

INTRODUCTION

Accumulating evidence shows that angiotensin II (AII), a major effector peptide of the renin–angiotensin system (RAS), contributes to the pathogenesis of the metabolic syndrome and atherosclerosis.[1–3] It is noted that human adipose tissue possesses all of the components necessary for production of AII and AII type 1 receptor (AT1R). The adipose tissue RAS has a role in the process of adipogenic differentiation and in the regulation of body weight.[3] Most physiological responses triggered by AII occur through activation of the G-protein-coupled AT1R. A common polymorphism in the *AT1R* (A1166C) has been linked to enhanced physiological responses to AII.[4] In addition, this polymorphism in the human *AT1R* has been associated with phenotypic effects including insulin sensitivity and metabolic syndrome traits as well as high blood pressure.[5,6] Although this polymorphism is located in the 3′-untranslated region of the human *AT1R*, recent evidence shows that the polymorphism can lead to increased AT1R densities through inhibition of the ability of miR-155 to attenuate translation of AT1R mRNA.[7]

Adipose tissue is a highly active metabolic and endocrine organ that secretes many biologically active substances, collectively known as adipocytokines.[8] Adiponectin is an anti-atherogenic and insulin-sensitizing adipocytokine that is stably present in the plasma at very high concentrations. Human studies showed that adiponectin is downregulated in patients with obesity-related diseases, including type 2 diabetes, metabolic syndrome and hypertension.[9] Importantly, AII infusion decreases plasma adiponectin levels,[10] and RAS blockade decreases adipocyte size with improvement in insulin sensitivity in rats.[11] In addition, blockade of the RAS increases plasma adiponectin concentrations in patients with essential hypertension.[12] However, it remains to be determined whether *AT1R* A1166C affects plasma adiponectin concentrations in humans. Furthermore, plasma adiponectin concentrations were lower in mice fed a high-fat diet compared

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with control mice.[13] Another study reported that a high-fat meal did not elicit changes in serum adiponectin compared with fasting baseline levels in healthy male subjects.[14] Thus, the effects of dietary fat intake on plasma adiponectin concentrations are unclear at present.

It is well established that atherosclerosis is a progressive multifactorial process that begins in early life.[15–17] However, few studies have examined the risk factors of atherosclerosis development in young women. In particular, the interaction between genes and environmental factors in the development of early atherosclerosis in young female populations is not clear. Thus, this study was designed to investigate the association between *AT1R* A1166C and plasma adiponectin concentrations in young female subjects. We also investigated the influence of *AT1R* A1166C on the correlation between dietary fat intake and plasma adiponectin concentrations in these subjects.

METHODS

Participants

Between July 2004 and December 2007, 416 students from 18 to 23 years of age were recruited from Mukogawa Women's University. We received approval from the Institutional Review Board and written informed consent was obtained from all participants in this study.

Body composition and biochemical measurements

Blood samples were taken from each of the participants in the morning following overnight fasting. We measured the fasting plasma glucose, insulin, hemoglobin A1c (HbA1c), lipoprotein lipase (LPL), high-sensitivity C-reactive protein (hs-CRP), free fatty acid (FFA) and serum lipid concentrations including triglycerides (TG), high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol by standard laboratory techniques. Plasma levels of adiponectin and plasminogen-activator inhibitor 1 (PAI-1) were measured with commercial kits. Body composition was determined by dual-energy X-ray absorptiometry. Blood pressure was measured between 0900 and 1200 h (noon), with participants resting in the sitting position. Intima-media thickness (IMT) in the carotid artery was measured with the participants in a supine position after a few minutes of rest. Indices of obesity and insulin resistance were derived from body mass index (BMI) and a homeostasis model assessment of insulin resistance (HOMA-IR), respectively.

Estimation of habitual food intake

Percentages of protein, fat and carbohydrate in the diet were estimated by using the responses to a self-administered diet history questionnaire, developed for use in the evaluation of nutrient intake levels and health education among both healthy individuals and high-risk populations. The diet history questionnaire was designed to obtain information about dietary habits for the previous month with regard to total energy and 17 nutrients.[18]

Determination of AT1R A1166C polymorphism genotypes

Genomic DNA was extracted from 200 μl of whole blood, following the blood spin protocol recommended by the manufacturer for use of the QIAamp DNA Blood Kit (Qiagen Inc., Valencia, CA, USA). *AT1R* A1166C polymorphism genotypes were determined by the TaqMan polymerase chain reaction method. The primers and probes for genotype determinations were as follows: forward primer 5′-CATTCCTCTGCAGCACTTCACT-3′, reverse primer 5′-CGGTTC AGTCCACATAATGCAT-3′, probe for A (1166) 5′-FAM-CAAATGAGCAT TAGCTACMGB-3′, probe for C (1166) 5′-VIC-CAAATGAGCCTTAGCTACT-MGB-3′. Each reaction included 1 μl of the DNA sample including 30 ng of genetic DNA, 0.3 μl of each primer, 0.1 μl of each probe, 5 μl of the TaqMan Universal Master Mix (Applied Biosystems, Foster City, CA, USA) and 3.2 μl of sterile distilled water. Polymerase chain reaction cycling conditions were 1 cycle at 95 °C for 10 min, 45 cycles at 92 °C for 15 s and 60 °C for 1 min. Polymerase chain reaction and allelic detection were carried out using an ABI Sequence Detection System 7500 and allelic discrimination software, both from Applied Biosystems.

Ultrasound studies

IMT was measured by ultrasonic diagnosis equipment (Shimazu SDU-2200, Shimazu, Tokyo, Japan) that was programmed with IMT software (Intimascope, Media Cross Co. Ltd., Tokyo, Japan) as described.[19] This software makes it possible to automatically recognize the edges of the internal and the external membranes of the blood vessels and to automatically measure the distance at a sub-pixel level (estimated to be 0.01 mm), using a three-dimensional polynomial measurement formula.

Carotid artery ultrasonography was performed using a 10-MHz scanning frequency in B mode. One skilled observer, blinded to the subjective data, scanned the vessel in transverse planes. Subjects were examined in a supine position. Images were obtained in the 20 mm proximal to the origin of the bulb at the far wall of the right common carotid artery. In all subjects examined in this study, no plaque was observed in this segment. Average IMT was the average value of 250 computer-based points in the region.

Statistical analysis

Agreement with the Hardy–Weinberg equilibrium was tested by comparing the observed and expected genotype frequencies of the participants using the χ^2-test for good fit with Fisher's exact tests. On account of the very low frequency of the 1166C allele, participants who were homozygous for CC were combined in the analysis with those who were heterozygous AC to increase the statistical power. Normality of variable distribution was tested by the Kolmogorov–Smirnov test.

Quantitative data with a normal distribution were presented as the mean ± s.d., and data with a skewed distribution were presented as the median (interquartile range). Comparisons between carriers of the C allele and non-carriers were made using unpaired *t*-tests for continuous variables with normal distribution and with the nonparametric Mann–Whitney *U*-test for continuous variables with a skewed distribution. Pearson's and Spearman's coefficients of correlation were used as appropriate. A univariate generalized linear model was used to test for the heterogeneity of regression. To examine the independent contribution of the *AT1R* A1166C polymorphism to plasma adiponectin levels when adjusting for the effects of other clinical characteristics, logistic regression analysis with forward stepwise selection was used. For this analysis, participants were divided into two groups at the median of plasma adiponectin concentrations. We adjusted for confounders with the use of analysis of covariance (ANCOVA). To normalize variables with skewed distributions, logarithm, square root and inverse were used for data transformations as appropriate. Data were analyzed with SPSS (release 16.0J; SPSS Japan, Tokyo, Japan) and differences were considered significant with a *P*-value of $\leqslant 0.05$.

RESULTS

Genotype and participant characteristics

We examined the influence of *AT1R* A1166C on anthropometric features. The distributions of *AT1R* A1166C genotypes were as follows: *AT1R* A1166C AA, 83.2% (n=346); AC, 15.9% (n=66); and CC, 0.9% (n=4). The observed genotype frequencies in this study were in the Hardy–Weinberg equilibrium (χ^2=0.185, P=0.912) and were similar to results from previous studies of Japanese populations.[20] There were no significant differences between carriers of the C allele and non-carriers in terms of age, height, weight, BMI, SBP, DBP, pulse rate, trunk fat mass, plasma concentrations of lipoproteins, plasma fasting glucose levels, HOMA-IR, HbA1c or IMT (Table 1). However, plasma adiponectin concentrations were significantly lower in carriers of the C allele compared with non-carriers. For comparison of plasma adiponectin concentrations between genotype groups, we used ANCOVA with BMI, HDL-Ch and HOMA-IR as covariates. The results of the evaluation of the assumptions of normality for sampling distributions and the homogeneity of variance were satisfactory. After adjustment by covariates, plasma adiponectin levels were significantly lower in carriers of the C allele compared with non-carriers (P=0.043) (Table 2). As shown in Table 3, multiple logistic regression analysis with forward stepwise selection, after controlling for age, BMI,

Table 1 Characteristics and plasma adipocytokine concentrations of carriers and non-carriers of the C allele of the *AT1R* A1166C polymorphism

	n	*AA*	n	*AC+CC*	*P-value*
Age (years)	346	20.0 (20.0–21.0)	70	20.0 (19.0–21.0)	0.050
Height (cm)	346	160.4 (157.0–164.2)	70	162.4 (158.3–166.0)	0.053
Weight (kg)	346	53.2 (49.3–58.8)	70	54.7 (50.3–60.4)	0.215
BMI ($kg\,m^{-2}$)	346	20.6 (19.4–22.1)	70	20.6 (19.4–22.0)	0.878
TG ($mg\,dl^{-1}$)	346	52.0 (41.0–68.3)	70	45.5 (38.8–67.3)	0.149
HDL-Ch ($mg\,dl^{-1}$)	346	74.0 (67.0–84.0)	70	74.0 (63.8–82.3)	0.474
LDL-Ch ($mg\,dl^{-1}$)	346	93.4 (78.8–109.7)	70	90.2 (77.0–105.9)	0.242
Glucose ($mg\,dl^{-1}$)	346	83.0 (79.0–88.0)	70	83.0 (80.8–89.0)	0.440
HbA1c (%)	346	4.8 (4.6–5.0)	70	4.7 (4.6–4.9)	0.145
HOMA-IR	342	1.1 (0.7–1.5)	69	1.0 (0.7–1.6)	0.792
LPL ($ng\,dl^{-1}$)	220	72.2 (60.2–85.3)	40	79.5 (65.0–96.8)	0.088
SBP (mm Hg)	346	106.5 (100.0–112.6)	70	106.0 (99.0–113.1)	0.699
DBP (mm Hg)	346	60.0 (55.5–66.1)	70	60.3 (56.0–66.8)	0.892
Pulse rate (beats/min)	344	60.0 (55.0–66.0)	70	60.5 (53.0–69.0)	0.781
Trunk fat mass (kg)	343	6.5 (5.3–8.1)	69	6.6 (5.2–7.7)	0.791
IMT (mm)	122	0.41 (0.37–0.45)	18	0.44 (0.40–0.47)	0.054
Adiponectin ($\mu g\,ml^{-1}$)	346	11.1 (8.4–14.2)	70	10.2 (7.6–13.2)	0.021*
PAI-1 ($ng\,ml^{-1}$)	345	19.0 (13.0–26.0)	69	19.0 (13.0–25.5)	0.785

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HDL, high-density lipoprotein, HOMA, homeostasis model assessment; IMT, Intima-media thickness; LDL, low-density lipoprotein; PAI-1, plasminogen-activator inhibitor 1; SBP, systolic blood pressure. Values are expressed as median (interquartile range). *$P<0.05$.

Table 2 Analysis of covariance of genotype groups of *AT1R* A1166C toward plasma adiponectin concentration, with BMI, HDL-Ch and HOMA-IR as the covariates

Source of variance	*Adjusted sum of square*	*d.f.*	F	B	*P-value*
BMI	3.184	1	8.567	17.187	0.004**
HDL-Ch	13.164	1	35.459	0.229	<0.001**
HOMAIR	0.088	1	0.264	−0.061	0.608
Genotype	1.531	1	4.123	−0.164	0.043*

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HOMA, homeostasis model assessment.
Data transformation: BMI; Inverse, HDL-Ch; Square root, HOMA-IR; Logarithm. d.f.: degree of freedom, F:F value, *B*: standardized partial regression coefficient. *$P<0.05$, **$P<0.01$. Values are expressed as median (interquartile range).

Table 3 Stepwise logistic regression analysis with above and below the median of plasma adiponectin concentrations as the dependent variable and selected variables as the independent variable

					95% Confidence interval for odds ratio	
Variables	B	*s.e.*	*P-value*	*Odds ratio*	*Lower*	*Upper*
C allele	0.720	0.291	0.010	2.055	1.184	3.565
BMI	0.104	0.045	0.022	1.110	1.015	1.213
HDL-Ch	−0.036	0.008	<0.001	0.965	0.950	0.980

Abbreviations: BMI, body mass index; HDL, high density lipoprotein; TG, triglycerides.
B: partial regression coefficient. Not accepted variables were age, TG, HOMA-IR.

HDL-Ch, triglycerides and HOMA-IR, showed that the genotype with the C allele of the *AT1R* A1166C polymorphism was the strongest and the most independent determinant of lower plasma adiponectin concentrations (odds ratio: 2.055, 95% CI: 1.184–3.565, $P=0.010$), followed by BMI (odds ratio: 1.110, 95% CI: 1.015–1.213, $P=0.022$) and HDL-Ch (odds ratio: 0.965, 95% CI: 0.950–0.980, $P<0.001$). There were no significant differences, however, in plasma PAI-1 concentrations between these two groups.

Next, we examined whether clinical parameters differed between the participants in the lowest quartile of plasma adiponectin concentrations and those in the highest quartile. The participants in the lowest quartile of plasma adiponectin concentration showed significantly lower HDL-Ch and LPL levels and higher BMI and trunk fat mass when compared with participants in the highest quartile. Importantly, carotid IMT levels were significantly higher in the lowest quartile of plasma adiponectin concentrations than those in the highest quartile. No significant differences in low-density lipoprotein cholesterol, triglycerides, HOMA-IR and blood pressure, however, were observed between these groups (Table 4).

Correlations between percentage of fat in the diet and plasma adiponectin concentrations in the genotype groups

Next, we examined the effects of dietary fat intake on plasma adiponectin concentrations in both genotypes. There were no significant differences in the mean or median intake of protein, fat and carbohydrate in the diet between carriers of the C allele and non-carriers (Table 5). Unexpectedly, a weak but significant positive correlation was found between the estimated percentages of fat in the diet and plasma adiponectin concentrations in non-carriers of the C allele ($r=0.161$, $P=0.004$) but not in carriers ($r=0.148$, $P=0.263$). There was no significant difference between the slopes of regression for carriers and non-carriers of the C allele ($P=0.731$) (Figure 1).

DISCUSSION

In this study, we found that plasma adiponectin concentrations were significantly lower in carriers of the C allele of the *AT1R* A1166C gene polymorphism compared with non-carriers among a population of young Japanese women. To our knowledge, this report is the first to

Table 4 Characteristics of the participants in the lowest or highest quartiles of plasma adiponectin concentrations

	Plasma adiponectin concentrations				
	n	*The lowest quartile <8.3*	n	*The highest quartile 13.9≤*	P-*value*
BMI ($kg\,m^{-2}$)	104	21.0 (19.7–22.4)	105	20.4 (19.2–22.0)	0.016*
Trunk fat mass (kg)	104	7.1 (5.7–9.4)	104	6.5 (5.3–7.4)	0.003**
HDL-ch ($mg\,dl^{-1}$)	104	69.0 (61.0–78.0)	105	78.0 (68.0–90.0)	<0.001**
LDL-ch ($mg\,dl^{-1}$)	104	93.5±22.4	105	93.0±23.1	0.869
TG ($mg\,dl^{-1}$)	104	60.5 (42.0–75.5)	105	52.0 (38.5–65.5)	0.060
LPL ($ng\,ml^{-1}$)	58	63.9 (55.1–76.1)	79	79.4 (69.0–96.2)	<0.001**
HOMA-IR	102	1.06 (0.74–1.67)	104	1.09 (0.73–1.55)	0.730
Glucose ($mg\,dl^{-1}$)	104	83.7±6.5	105	83.3±7.8	0.747
HbA1c (%)	104	4.8 (4.6–5.0)	105	4.7 (4.6–4.9)	0.390
Leptin ($ng\,ml^{-1}$)	104	8.1 (5.3–10.9)	105	6.9 (5.2–9.5)	0.049*
SBP (mm Hg)	104	106.0 (99.6–114.8)	105	108.0 (102.5–113.0)	0.409
DBP (mm Hg)	104	61.8 (55.1–67.4)	105	62.5 (57.0–68.0)	0.260
Pulse rate (beats/min)	104	62.0 (55.3–67.8)	105	58.0 (53.0–67.0)	0.124
IMT (mm)	40	0.43±0.06	45	0.39±0.06	0.003**

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL, high-density lipoprotein, HOMA, homeostasis model assessment; IMT, Intima-media thickness; LDL, low-density lipoprotein; LPL, lipoprotein lipase; SBP, systolic blood pressure; TG, triglycerides.
Values are expressed as median (interquartile range) or mean±s.d. *$P<0.05$, **$P<0.01$.

Table 5 Estimated habitual food intakes in carriers and non-carriers of the C allele of the *AT1R* A1166C polymorphism

	n	*AA*	n	*AC+CC*	P-*value*
Fat (percentage of energy)	309	30.1 (26.0–33.2)	59	30.4 (27.0–33.6)	0.852
Carbohydrate (percentage of energy)	309	54.8 (51.0–58.9)	59	55.5 (50.7–58.9)	0.996
Protein (percentage of energy)	309	13.3±2.0	59	13.2±2.3	0.803

Values are expressed as median (interquartile range) or mean±s.d. *$P<0.05$.

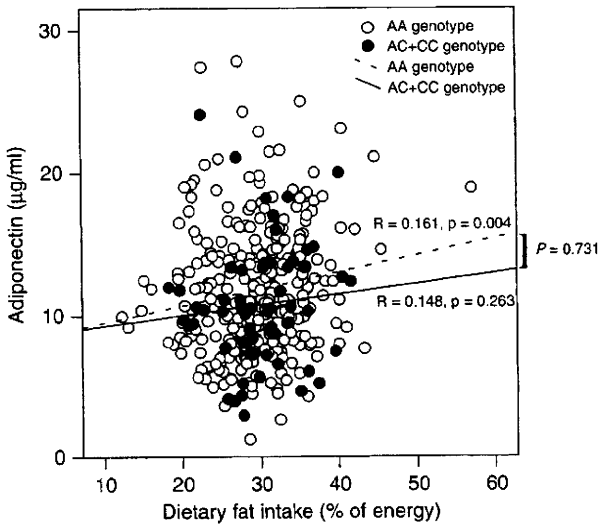

Figure 1 Correlations between dietary fat intake (percentage of energy) and plasma concentrations of adiponectin.

show that the *AT1R* A1166C polymorphism may influence changes in plasma adiponectin concentrations in humans. Adiponectin is a unique and essential adipocytokine that is produced very abundantly from adipocytes and is stably present in the plasma at very high concentrations. Recent studies emphasize the part played by adiponectin in the homeostasis of adipose tissue and in the pathogenesis of the metabolic syndrome and atherosclerosis.[21] Adiponectin levels are positively correlated with HDL-cholesterol but inversely with insulin; the levels are reduced in obesity and type II diabetes[9] and lower in hypertensive patients compared with normotensive patients.[22] Plasma concentrations of adiponectin are, however, stable throughout the menstrual cycle[23] and also not affected by menopause in healthy women.[24]

Interestingly, participants in the lowest quartile of plasma adiponectin concentration had lower HDL-Ch and LPL levels and higher trunk fat mass compared with those in the highest quartile. In addition, the participants in the lowest quartile had thicker carotid IMT levels compared with those in the highest quartile. These results suggest that carriers of the C allele with lower adiponectin concentrations may be more susceptible to the development of atherosclerosis.

Although the mechanism underlying lower adiponectin concentrations in carriers of the C allele of the AT1R A1166C gene polymorphism is not clear at present, a silent polymorphism, A1166C, occurs in the 3′-untranslated region of the human *AT1R* gene that can lead to increased AT1R densities.[7] This suggests that the effect of AII may be enhanced in carriers of the C allele of the *AT1R* A1166C polymorphism.[4,25–27] It is noted that AII infusion decreases plasma adiponectin levels through its type 1 receptor in rats,[10] and treatment with an AII type 1 receptor antagonist increases plasma adiponectin levels in hypertensive patients.[12] These results suggest that a difference in activation of the local RAS may be directly involved in the variation between genotypes with regard to plasma adiponectin concentrations. However, further investigation is required to confirm this hypothesis.

In this study, we also found a genotype-dependent correlation between the percentage of fat in the diet and plasma adiponectin concentrations. Unexpectedly, there was a weak but significant positive correlation between plasma adiponectin concentrations and percentage of fat in the diet in non-carriers of the C allele, but not in carriers. Although the mechanism of this result is not clear, it was reported earlier that no correlation was found between dietary fat intake and plasma adiponectin concentration in humans,[14] suggesting that this relation may be specific for this genotype. Follow-up studies are necessary to clarify these points.

In conclusion, we showed that plasma adiponectin concentrations were associated with the C allele of the *AT1R* gene in young healthy women and that the *AT1R* genotype might affect plasma levels of adiponectin when these young women consume a high-fat diet. These results suggest that genotyping of the *AT1R* A1166C polymorphism may help to prevent the development of metabolic syndrome and atherosclerosis in young women.

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Relationships of Systemic Oxidative Stress to Body Fat Distribution, Adipokines and Inflammatory Markers in Healthy Middle-aged Women

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Abstract. Obesity and systemic oxidative stress are closely related. However data concerning the relationships between oxidative stress and body fat mass distribution are sparse. Anthropometric and metabolic profile was evaluated in 148 clinically healthy middle-aged women to assess the correlations between oxidative stress, fat mass distribution, adipokines, and inflammatory markers. Systemic oxidative stress was assessed by urinary creatinine-indexed 8-epi-prostaglandin $F_{2\alpha}$ (8-epi-$PGF_{2\alpha}$). Body fat mass distribution was examined by dual-energy X-ray absorptiometry (DXA). Lipid profile, adipokines and inflammatory markers including leptin, adiponectin, high sensitive C-reactive protein (hsCRP), plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor-α (TNF-α) were determined. We found body mass index (BMI), waist circumference (WC), both central and peripheral DXA-derived regional fat mass (FM) accumulations were positively correlated with 8-epi-$PGF_{2\alpha}$. Leptin, hsCRP and PAI-1also positively associated with 8-epi-$PGF_{2\alpha}$. After adjustment for BMI and WC, lower-body FM, total FM and PAI-1 retained significant association with 8-epi-$PGF_{2\alpha}$. Mutliple linear regression analyses indicated lower-body FM and PAI-1 were the two important predicators of 8-epi-$PGF_{2\alpha}$. These results suggest that DXA-derived regional FM indices, especially low extremity adiposity, are more closely associated with systemic oxidative stress than indirect anthropometric indices. Positive associations between 8-epi-$PGF_{2\alpha}$ and PAI-1, hsCRP, leptin support the notion that oxidative-stress-induced dysregulation of inflammation and adipokines may mediate the obesity-related metabolic derangement.

Key words: Oxidative stress, Body fat distribution, Adipokines

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OBESITY is the principle causative factor and main component of metabolic syndrome (MetS) [1]. MetS is associated with high risk for the development of diabetes and cardiovascular diseases (CVD)[2]. However, the underlying mechanisms linking obesity with MetS have not been fully elucidated. It is well known that overproduction of some adipokines, including TNF-α [3] and PAI-1 [4] in adipose tissue may lead to the development of insulin resistance and atherosclerosis. But the factors regulating the production and secretion of such adipokines in adipose tissue have not been clearly understood.

Oxidative stress is one of the important pathways that involves in atherosclerosis [5, 6], endothelial dysfunction [7] and diabetes [8]. Recently it is reported that in cultured adipocytes, increased oxidative stress may cause deregulated production of adipokines, including leptin, adiponectin, PAI-1 and monocyte chemotactic protein-1 (MCP-1) thus lead to metabolic derangements [9]. Various cross-sectional studies implicated a significant positive relationship of systemic oxidative stress with obesity–related indices such as BMI and WC [9-12]. Obesity is regarded as a hyper-oxida-

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