European Journal of Endocrinology (2003) **148** 657–662 ISSN 0804-4643

CLINICAL STUDY

Decreased plasma adiponectin concentrations in women with low-grade C-reactive protein elevation

Miyao Matsubara, Katsuhiko Namioka and Shinji Katayose[1]

Division of Endocrinology and Metabolism, Otaru City General Hospital, Otaru 047-8550 and [1]Otsuka Assay Institute, Sapporo 060-0061, Japan

(Correspondence should be addressed to M Matsubara; Email: miyamatsuba@proof.ocn.ne.jp)

Abstract

Objective: Inflammation has been suggested as a risk factor for the development of atherosclerosis, while some components of metabolic syndrome X have been related to inflammatory markers. We hypothesized that adipocyte secreting protein, adiponectin and leptin, for which have been demonstrated an association with metabolic syndrome X and coronary artery disease, may be associated with inflammatory markers in nondiabetic humans.

Design and methods: We measured high-sensitivity C-reactive protein (hs-CRP), as an inflammatory marker, and adiponectin and leptin concentrations in 384 nondiabetic Japanese women (mean± S.E.M. age 53.6±0.8 years, body mass index (BMI) 23.0±0.2 kg/m^2) undergoing measurement of markers of metabolic syndrome X.

Results: The women who had a low-grade hs-CRP elevation (> 2.0 mg/l) were significantly older and had higher BMI, body fat mass (BFM), total cholesterol (TC), triglyceride (TG), atherogenic index (AI = (TC − HDLC)/HDLC), where HDLC is high-density lipoproten-cholesterol), fasting blood glucose and leptin concentrations before and after adjustment for BMI or BFM, while lower HDLC and adiponectin concentrations before and after adjustment compared with women with normal CRP levels (< 0.5 mg/l). BMI, BFM, TG, AI and leptin before and after adjustment were found to be correlated with hs-CRP levels, while HDLC and adiponectin before and after adjustment were inversely correlated (all $P < 0.0001$). hs-CRP was independently associated with white blood cell count, blood urea nitrogen and AI and inversely with adiponectin/BFM in the stepwise regression analysis model.

Conclusions: These data demonstrate a significant decrease in plasma adiponectin in low-grade chronic inflammation, and suggest that there is an important linkage between inflammation/adipose tissue/atherosclerosis.

European Journal of Endocrinology **148** 657–662

Introduction

Adiponectin is a product of the adipose most-abundant gene transcript 1 gene, which is specifically and highly expressed in human adipose tissue, and belongs to the soluble defense collagen superfamily (1). Experimental data indicate that adiponectin reduces tumor necrosis factor (TNF-α) effects in macrophages and endothelial tissue, suppressing the expression of nuclear transcription factor-κB mRNA, inhibiting the expression of adhesion molecules critical for monocyte attachment and adhesion to the endothelial wall (2–5). Therefore, it has been suggested that adiponectin possesses anti-atherogenic and anti-inflammatory properties (2–5). Plasma adiponectin concentrations have been reported to be decreased in obesity (6, 7), type 2 diabetes (8), insulin resistance (9, 10), dyslipidemia (11) and coronary artery disease (CAD) (3). Recent data suggest that adiponectin may play a role in the development of metabolic syndrome X, and hypoadiponectinemia can be considered a risk factor for CAD (3–6, 8–11). However, clinical evidence regarding a potential anti-inflammatory effect of this protein has not been found. Leptin, the *obese* gene product, is a signal to the central nervous system of energy stores in the adipose tissue and a regulatory signal for a variety of other physiological processes in addition to body weight maintenance (12, 13). Leptin plays a role in fat metabolism and correlates with insulin resistance and other markers of metabolic syndrome X independently of total adiposity (12–14).

While inflammation plays a major role in determining atherosclerotic plaque vulnerability, low-grade chronic inflammation is associated with an increased risk of atherosclerotic cardiovascular disease (15, 16). Endothelial cell activation is an early event in atherogenesis, and previous studies have reported correlations between indirect markers of endothelial cell activation

and C-reactive protein (CRP) concentration, a sensitive marker of inflammation. A relationship between plasma high-sensitivity CRP (hs-CRP) levels and the development of atherosclerotic disease has been observed in experimental and epidemiological studies (15–18). Recent evidence suggests that CRP correlates with adiposity and insulin resistance independently of body mass index (BMI), and that the inflammatory marker predicts risk of diabetes (17, 18). However, the nature of the association of CRP with metabolic syndrome X is poorly understood.

We hypothesized that circulating CRP levels may be associated with adipocyte secreting protein, adiponectin and leptin concentrations; such an association would potentially provide insights into the role of CRP in atherosclerotic disease and further clarify the association of inflammation/adipose tissue/atherosclerosis linkage *in vivo*. Therefore, we cross-sectionally examined associations of serum hs-CRP, adiponectin, leptin concentrations and several parameters of metabolic syndrome X in nondiabetic subjects. Because sex differences have been reported in plasma adiponectin (6), leptin (13), triglyceride (TG), high-density lipoprotein-cholesterol (HDLC), uric acid (UA) and percent body fat mass (BFM) (11), we chose to study women only.

Subjects and methods

Participants

The original design of this cross-sectional study had been described previously (7, 11). Briefly, 384 Japanese women residing in Hokkaido, Japan, aged 16–86 years (mean ± S.E.M 53.6±0.8 years) were included in this cross-sectional study. Women taking the birth control pill and postmenopausal hormone replacement therapy, and any with diabetes mellitus, renal failure, untreated endocrine diseases or clinically significant infectious diseases were excluded. Systolic (≧160 mm Hg) and diastolic hypertension (≧90 mm Hg) were observed in 29.6 and 20.7% respectively, while 54 were receiving calcium channel blockers, angiotensin converting enzyme inhibitors, or both. Approximately 34.7 and 12.0% of females had high serum total cholesterol (TC) (≧5.69 mmol/l) and TG (≧1.69 mmol/l) respectively. Overweight (BMI ≧ 25.0 kg/m^2) and insulin resistance (homeostasis model assessment (HOMA) ≧3.0) were observed in 24.9 and 11.5% respectively. Percent BFM was determined by bioelectrical impedance analysis (7, 11). All subjects reported that their body weight had been stable (± 2 kg) for at least 3 months before the study, and they provided informed consent.

Biochemical analyses

Blood samples after overnight fasting were collected for various biochemical analyses using commercially available kits. CRP levels were determined with a clinically validated high-sensitivity assay with use of latex-photometric immunoassay on an automated autoanalyzer (TBA-200FR; Toshiba, Tokyo, Japan). Atherogenic index (AI) was calculated by the formula AI = (TC − HDLC)/HDLC, and HOMA by using fasting blood glucose (FBG) and insulin concentrations (7, 19). Assuming that normal-weight normal subjects < 35 years of age have an insulin resistance of 1, the value for insulin resistance can be assessed by the formula: FBG (mmol/l) × fasting insulin (μU/ml)/22.5. The results of the HOMA ratio correlated well with the measurements obtained by means of the euglycemic clamp technique, as was shown in the HOMA method validation study (7, 19). Blood samples for measurement of fasting plasma adiponectin concentrations were drawn with 1/10 volume EDTA-aprotinin tubes, and immediately placed on ice. All tubes were centrifuged at 4 °C for collection of plasma and stored at − 80 °C until analyses at Otsuka Assay Institute, Tokushima, Japan. Adiponectin was determined using a validated sandwich ELISA employing an adiponectin-specific monoclonal and polyclonal antibody, which has been previously described (6, 7, 11).

Statistical analyses

We assessed associations among variables with use of Pearson's correlation coefficient. Serum hs-CRP, TG, AI, insulin, HOMA ratio, leptin and adiponectin values were log-transformed to correct their skewed distributions. After dividing subjects into tertiles based on the distribution of control values for hs-CRP (~< 0.5 mg/l, 0.5 ≦~< 2.0, 2.0 ≦~) or mean ± S.D. values (8.4±2.8 μg/ml) for adiponectin (~< 6.0 μg/ml, 6.0 ≦~< 11.0, 11.0 ≦~), the differences across tertiles of various continuous parameters were tested with ANOVA. Stepwise linear regression models were fitted for log CRP, adiponectin/BFM or leptin/BFM as a dependent variable, including all variables of interest at the same time as independent variables to demonstrate the relative contribution of each of these variables to the outcome variable. The following independent variables were considered for the model: age, white blood cell count (WBC), blood urea nitrogen (BUN), diastolic blood pressure (BP), BMI, log-transformed AI, HOMA ratio, and/or CRP, and/or adiponectin/BFM, and/or leptin/BFM. All data are expressed as the mean ± S.E.M. $P < 0.05$ was considered statistically significant.

Results

WBC, BMI, BFM, TG, AI and leptin before and after adjustment for BMI or BFM were found to be correlated with serum hs-CRP levels (Table 1), while HDLC and adiponectin before and after adjustment for BMI or

Table 1 Correlations between serum hs-CRP, adiponectin, adiponectin/BFM(%) or leptin and various related parameters in 384 women.

	hs-CRP[#]	Adiponectin[#]	Adiponectin/BFM[#]	Leptin[#]
Age	0.175[†]	0.191[†]	0.058	0.061
WBC	0.229[‡]	−0.227[‡]	−0.212[†]	0.152[**]
Serum TP	0.145[**]	−0.128[*]	−0.188[†]	0.162[***]
Albumin	−0.066	−0.108	−0.093	−0.040
BUN	0.159[**]	0.231[†]	0.174[**]	−0.014
Creatinine	0.140[*]	0.213[†]	0.160[*]	0.124[*]
Uric acid	0.183[†]	−0.051	−0.099	0.190[†]
Systolic BP	0.183[†]	0.022	−0.054	0.098
Diastolic BP	0.101	−0.067	−0.160[**]	0.245[‡]
BMI	0.254[‡]	−0.253[‡]	−0.556[‡]	0.735[‡]
BFM(%)	0.240[‡]	−0.216[‡]	−0.489[‡]	0.744[‡]
Serum TC	0.145[**]	0.065	−0.090	0.218[‡]
TG[#]	0.251[‡]	−0.306[‡]	−0.398[‡]	0.295[‡]
HDLC	−0.226[‡]	0.352[‡]	0.370[‡]	−0.221[‡]
AI[#]	0.310[‡]	−0.281[‡]	−0.410[‡]	0.365[‡]
FBG	0.150[***]	−0.132[*]	−0.178[***]	0.110[*]
Fasting insulin[#]	0.101	−0.377[‡]	−0.470[‡]	0.509[‡]
HOMA ratio[#]	0.120[*]	−0.364[‡]	−0.459[‡]	0.493[‡]
Leptin[#]	0.248[‡]	−0.346[‡]	−0.567[‡]	—
Leptin/BMI[#]	0.216[‡]	−0.337[‡]	−0.509[‡]	0.978[‡]
Leptin/BFM[#]	0.215[‡]	−0.332[‡]	−0.475[‡]	0.955[‡]
Adiponectin[#]	−0.248[‡]	—	0.925[‡]	−0.346[‡]
Adiponectin/BMI[#]	−0.296[‡]	0.957[‡]	0.984[‡]	−0.525[‡]
Adiponectin/BFM[#]	−0.313[‡]	0.925[‡]	—	−0.567[‡]

[*]$P < 0.05$, [**]$P < 0.01$, [***]$P < 0.005$, [†]$P < 0.001$, [‡]$P < 0.0001$. [#]Log-transformed statistics.

BFM were inversely correlated (all $P < 0.0001$). Apparent associations (correlation coefficients >0.3) were found between CRP and AI (positively), and adiponectin/BFM (inversely). Plasma adiponectin levels correlated inversely with WBC, BMI, BFM, TG, AI, insulin, HOMA ratio and leptin before and after adjustment (all $P < 0.0001$), while positively with serum creatinine (Cr), BUN and HDLC (all $P < 0.001$). These inverse associations became stronger after adjustment for BFM (all $P < 0.0001$) (Table 1). Serum leptin levels correlated positively with diastolic BP, BMI, BFM, TC, TG, AI, insulin and HOMA ratio (all $P < 0.0001$), while inversely with HDLC and adiponectin before and after adjustment (all $P < 0.0001$) (Table 1).

Table 2 shows the ANOVA data according to the tertile of hs-CRP or adiponectin levels in plasma. The women who had a low-grade CRP elevation (tertile 3) were significantly older, with increased WBC, and had significantly higher serum total protein (TP), BUN, Cr, UA, BMI, BFM, TC, TG, AI, FBG and leptin concentrations before and after adjustment, while lower HDLC and adiponectin concentrations before and after adjustment compared with the values of the tertile 1. Women who had high plasma adiponectin levels (tertile 3) were significantly older, and had significantly lower WBC, CRP, BMI, BFM, TG, AI, FBG, insulin, HOMA ratio and leptin concentrations before and after adjustment, while higher BUN, Cr and HDLC levels compared with the values of the tertile 1 (Table 2).

As shown in Table 3, log-transformed hs-CRP was independently associated with WBC, BUN and AI and inversely with adiponectin/BFM in women in the stepwise regression analysis model. In contrast, age, diastolic BP, BMI, HOMA ratio and leptin/BFM were not related to the hs-CRP concentrations. Log-transformed leptin/BFM was independently associated with BMI and HOMA ratio and inversely with adiponectin/BFM (Table 3). In contrast, age, WBC, CRP, BUN, diastolic BP and AI were not independently related to the leptin/BFM values. Moreover, log-transformed adiponectin/BFM was independently associated with age and BUN, and inversely with WBC, CRP, BMI, AI, HOMA ratio and leptin/BFM in women in the stepwise regression analysis model (Table 3).

Discussion

In the present study, we have confirmed that CRP, a sensitive marker of inflammation that has previously been associated with CAD, was independently related to serum leptin and various parameters of metabolic syndrome X in nondiabetic women (16–18). Our principal finding was that plasma adiponectin before and after adjustment for BMI or BFM had a significantly negative association with CRP and WBC levels. Moreover, the association of low adiponectin with elevated CRP levels found in the present study could potentially explain the anti-inflammatory effect of adiponectin *in vivo*. CRP and WBC levels are considered to be influenced not only by chronic inflammation but also potentially by the presence of obesity and metabolic

Table 2 Relationship between stratified serum hs-CRP or adiponectin and the various related parameters. Data are means ± S.E.M. Significance of tertile 2 or 3 is the comparison with tertile 1.

	hs-CRP (mg/l)			**Plasma adiponectin** (μg/ml)		
Variables	Tertile 1 (~ < 0.5)	2 (0.5 ≦ ~ < 2.0)	3 (2.0 ≦ ~)	Tertile 1 (~ < 6.0)	2 (6.0 ≦ ~ < 11.0)	3 (11.0 ≦ ~)
n (%)	221 (57.6)	112 (29.2)	51 (13.3)	103 (26.8)	206 (53.6)	75 (19.5)
Age (years)	50.8 ± 1.2	57.4 ± 1.4†	57.5 ± 2.1**	50.9 ± 1.8	53.1 ± 1.2***	59.6 ± 2.1***
WBC (× 10^9/l)	5.19 ± 0.09	5.63 ± 0.16*	6.10 ± 0.25†	5.80 ± 0.16	5.22 ± 0.11*	5.25 ± 0.19*
hs-CRP# (mg/l)	0.24 ± 0.01	1.07 ± 0.04‡	7.25 ± 0.75‡	2.2 ± 0.4	1.2 ± 0.2†	0.9 ± 0.3†
Serum TP (g/l)	74.2 ± 0.3	73.7 ± 0.5	77.5 ± 0.8‡	74.8 ± 0.6	74.4 ± 0.4	73.2 ± 0.7
Albumin (g/l)	47.4 ± 0.2	46.6 ± 0.3	47.3 ± 0.5	47.3 ± 0.4	47.4 ± 0.2	46.0 ± 0.4*
BUN (mmol/l)	4.9 ± 0.1	5.3 ± 0.2	5.9 ± 0.6**	4.8 ± 0.1	5.0 ± 0.1	6.0 ± 0.5**
Creatinine (μmol/l)	52 ± 1	55 ± 2	65 ± 9***	50 ± 1	53 ± 2	67 ± 5‡
Uric acid (μmol/l)	262 ± 6	286 ± 6**	303 ± 12†	286 ± 6	262 ± 6*	280 ± 12
Systolic BP (mmHg)	141.2 ± 1.3	150.3 ± 1.9‡	146.4 ± 2.6	144.8 ± 2.1	144.4 ± 1.5	146.1 ± 2.6
Diastolic BP (mmHg)	79.9 ± 0.8	81.9 ± 0.9	82.9 ± 1.5	81.1 ± 1.0	81.2 ± 0.8	78.4 ± 1.3
BMI (kg/m^2)	21.9 ± 0.2	24.5 ± 0.3‡	23.7 ± 0.6†	24.0 ± 0.4	22.6 ± 0.2***	22.0 ± 0.4†
BFM (%)	28.6 ± 0.4	32.3 ± 0.5‡	31.7 ± 0.9†	31.8 ± 0.6	29.6 ± 0.4***	28.9 ± 0.7***
Serum TC (mmol/l)	5.18 ± 0.07	5.39 ± 0.09	5.54 ± 0.14*	5.26 ± 0.10	5.29 ± 0.07	5.41 ± 0.12
TG# (mmol/l)	0.95 ± 0.03	1.13 ± 0.06*	1.33 ± 0.09‡	1.32 ± 0.07	0.97 ± 0.04‡	0.85 ± 0.04‡
HDLC (mmol/l)	1.75 ± 0.03	1.61 ± 0.04***	1.47 ± 0.05‡	1.47 ± 0.04	1.73 ± 0.03‡	1.83 ± 0.05‡
AI#	2.1 ± 0.1	2.6 ± 0.1‡	3.0 ± 0.2‡	2.8 ± 0.1	2.2 ± 0.1‡	2.0 ± 0.1‡
FBG (mmol/l)	5.2 ± 0.1	5.5 ± 0.1**	5.4 ± 0.1*	5.5 ± 0.1	5.3 ± 0.1*	5.2 ± 0.1*
Fasting insulin# (μU/ml)	6.6 ± 0.3	8.1 ± 0.5†	7.6 ± 0.7	9.5 ± 0.6	6.6 ± 0.3‡	5.7 ± 0.5‡
HOMA ratio#	1.5 ± 0.1	2.0 ± 0.1†	1.9 ± 0.2	2.3 ± 0.2	1.6 ± 0.1‡	1.3 ± 0.1‡
Leptin# (ng/ml)	6.8 ± 0.3	9.4 ± 0.5‡	9.7 ± 0.9†	9.3 ± 0.5	7.2 ± 0.4‡	6.6 ± 0.7‡
Leptin/BMI#	0.29 ± 0.01	0.37 ± 0.02‡	0.38 ± 0.03†	0.38 ± 0.02	0.31 ± 0.01‡	0.28 ± 0.03‡
Leptin/BFM#	0.22 ± 0.01	0.28 ± 0.01‡	0.29 ± 0.02***	0.29 ± 0.01	0.23 ± 0.01‡	0.22 ± 0.02‡
Adiponectin# (μg/ml)	9.1 ± 0.3	7.8 ± 0.4†	7.4 ± 0.5***	4.6 ± 0.1	8.4 ± 0.1‡	13.8 ± 0.4‡
Adiponectin/BMI#	0.43 ± 0.01	0.33 ± 0.02‡	0.33 ± 0.03†	0.20 ± 0.01	0.38 ± 0.01‡	0.65 ± 0.03‡
Adiponectin/BFM#	0.33 ± 0.01	0.25 ± 0.02‡	0.26 ± 0.04‡	0.15 ± 0.01	0.29 ± 0.01‡	0.50 ± 0.03‡

Log-transformed statistics.
*$P < 0.05$, **$P < 0.01$, ***$P < 0.005$, $^{\dagger}P < 0.001$, $^{\ddagger}P < 0.0001$.

syndrome X (15–18). Hypoadiponectinemia may contribute to serum CRP elevation in obesity and metabolic syndrome X. Future trials are needed to test the changes of plasma adiponectin in young patients with acute and chronic infection during and after treatment. The tendency for plasma adiponectin elevation in aged women may suggest the possibility that the prevalence of the accumulation of adiponectin to the injured endothelial barrier, accompanied with serum CRP elevation and the possible adiponectin production, increase with age. However, since adiponectin is presumed to form a homotrimeric subunit with a collagen-like triple-helical structure and circulates through the body as a multimer of trimers (4, 6), possible impaired adiponectin degradation in the aging may lead to an increase in plasma adiponectin concentration.

Table 3 Stepwise regression analyses of all variables of interest on hs-CRP or adiponectin/BFM or leptin/BFM. The *F* value to enter was set at 4.0 at each step.

	hs-CRP#			**Adiponectin/BFM#**			**Leptin/BFM#**		
Independent variable	r^2	β	*F*	r^2	β	*F*	r^2	β	*F*
—	0.254	—	—	0.493	—	—	0.386	—	—
Age	—	—	1.509	—	0.180	10.052	—	—	3.803
WBC	—	0.228	14.973	—	−0.111	4.872	—	—	0.235
hs-CRP#	—	—	—	—	−0.132	5.748	—	—	2.114
BUN	—	0.197	11.059	—	0.146	7.726	—	—	1.738
Diastolic BP	—	—	0.292	—	—	0.240	—	—	0.020
BMI	—	—	1.155	—	−0.327	27.163	—	0.374	31.428
AI#	—	0.254	16.651	—	−0.191	11.237	—	—	0.013
HOMA ratio#	—	—	0.606	—	−0.172	9.465	—	0.228	14.427
Leptin/BFM#	—	—	1.112	—	−0.122	4.050	—	—	—
Adiponectin/BFM#	—	−0.204	10.018	—	—	—	—	−0.155	5.494

Log-transformed statistics.

TNF-α has been suggested to play a role in the pathogenesis of metabolic syndrome X, and TNF-α mRNA is significantly elevated in adiposity and insulin resistance (20, 21). Crystal structure analysis revealed topological homology among the mouse adiponectin homolog, ACRP 30 and TNF-α, which have an evolutionary link (22). Ouchi *et al.* (3) have shown that adiponectin has an inhibitory effect on the expression of TNF-α and adhesion molecules *in vitro*. We suggest that the hypoadiponectinemia associated with the components of metabolic syndrome X (6, 8–11) cannot reduce increased TNF-α action in the chronic inflammatory state, thus cannot suppress the elevation of serum CRP levels. Furthermore, we have to consider the possibility that the increased TNF-α in the inflammatory state may lead to decreased concentration of adiponectin. Indeed, a previous report showed that TNF-α inhibited adipose most-abundant gene transcript 1 secretion in an adipose cell line (23). This induced hypoadiponectinemia may accelerate the atherogenic reaction in subjects with an inflammatory state. Moreover, since recombinant adiponectin administration has been reported to inhibit lipopolysaccharide-induced TNF-α production and TNF-α mRNA expression in macrophages (5), it may have the possibility of therapeutic applications in diseases caused by systemic severe inflammatory responses such as septic shock and/or multiple organ failure.

Leptin correlates with markers of metabolic syndrome X, such as obesity, insulin resistance, hypertension and dyslipidemia (12–14). Soderberg *et al.* (24, 25) reported that plasma leptin was an independent risk factor for acute myocardial infarction and hemorrhagic stroke. Further, Wallance *et al.* (26) reported that leptin linked to CRP levels, and was a robust predictor of risk for CAD in men. Our results show the correlation between serum CRP and leptin, and the parameters of metabolic syndrome X may also provide further support for a link between adipocyte function and CAD. Kissebah *et al.* (27) have demonstrated two quantitative trait loci that influence the phenotypes of the insulin resistance-metabolic syndrome; one is located on chromosome 3q27 where the adiponectin gene is encoded (28), and the other is on 17p12 that is strongly linked to serum leptin.

Several experimental studies suggest a direct role of CRP in the initiation and progression of atherosclerotic lesions (15–17). CRP, a liver-derived protein, is regulated by interleukin-6 (IL-6), which is produced by inflammatory cells. Adding the production of IL-6 and TNF-α in adipocytes, our observations strongly suggest the possibility that adipose tissue may contribute to the inflammation. Because both adiponectin and leptin were reported to be involved in the pathophysiology of metabolic syndrome X and CAD, the existence of a linkage between inflammation/adipose tissue/atherosclerosis can be suggested.

Conclusions

We found significant reduction of plasma adiponectin in women with low-grade CRP elevation, and these two proteins were inversely correlated before and after adjustment for body composition. Adding the associations with leptin, these factors may contribute to the well-known relationship between inflammation and atherosclerosis risk, suggesting the existence of the linkage of inflammation/adipose tissue/atherosclerosis.

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Received 5 November 2002
Accepted 10 March 2003