ORIGINAL ARTICLE

Visceral adiposity and leptin are independently associated with C-reactive protein in Korean type 2 diabetic patients

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Abstract The inflammatory marker, C-reactive protein (CRP) is associated with long-term cardiovascular events. The aim of the study was to investigate the factors contributing to serum CRP, assess the relationship between CRP level and the parameters of visceral obesity, and examine the association between leptin and CRP level in type 2 diabetic patients. 150 patients with type 2 diabetes were enrolled. These patients were recently diagnosed ($\leq$3 years) with type 2 diabetes and were drug naive or taking sulfonylureas only. BMI, WC, and serum concentration of CRP, glycosylated hemoglobin (HbA1c), glucose, lipids, plasminogen activator-1 (PAI-1) and leptin were measured. Insulin resistance was estimated by the insulin resistance index of homeostasis model assessment (HOMA-IR). We measured the carotid intima-media thickness (IMT). Fat mass assessed by dual-energy X-ray absorptionmetry and abdominal fat distribution was determined by CT scan. Serum concentration of CRP was significantly correlated with BMI ($\gamma = 0.257$, $P < 0.01$), WC ($\gamma = 0.293$, $P < 0.01$), fat mass ($\gamma = 0.213$, $P < 0.01$), total adipose tissue ($\gamma = 0.263$, $P < 0.01$), visceral adipose tissue ($\gamma = 0.296$, $P < 0.01$), insulin ($\gamma = 0.189$, $P = 0.047$), PAI-1 ($\gamma = 0.206$, $P < 0.01$), leptin ($\gamma = 0.322$, $P < 0.01$), mean IMT ($\gamma = 0.132$, $P = 0.042$), and HOMA-IR ($\gamma = 0.172$, $P = 0.045$). After adjustment for age and gender, multiple regression analysis showed that serum CRP was significantly associated with leptin ($\beta = 0.326$, $P = 0.01$) and visceral adipose tissue ($\beta = 0.265$, $P = 0.035$). In conclusion, serum CRP level is significantly associated with obesity, especially the visceral adipose tissue, and serum leptin is another important independent factor associated with CRP in Korean type 2 diabetic patients.

Keywords CRP · Leptin · Visceral adipose tissue · Type 2 diabetes

Introduction

Inflammation is a major factor in atherosclerotic disease [1, 2]. C-reactive protein (CRP), a marker of inflammation and indicator of cardiovascular risk [3–7] and is associated with future cardiovascular events in patients with acute coronary artery disease and type 2 diabetes [8, 9].

Obesity has been associated with the increased risk of cardiovascular disease [10–14]. Although the mechanisms linking obesity with cardiovascular disease are not completely understood, inflammation might play an important role. In the nondiabetic population, obesity is an important determinant of the CRP level [15, 16]. It has been reported that the CRP level is associated with obesity, especially visceral obesity [17, 18]. Waist circumference and waist hip ratio are crude indices of visceral obesity, but there are few reports on the relationship between CRP and visceral adipose tissue measured directly with computed tomography (CT), especially in type 2 diabetic patients.

Leptin, the adipocyte derived protein product of the ob gene [19], is an independent risk factor for coronary heart

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disease in humans [20]. The association between leptin and cardiovascular events may be mediated by inflammatory mechanisms, as several studies have demonstrated a correlation between plasma leptin and CRP levels [21–23]. However, inconsistent results have been observed after adjustment for other markers of obesity and there is little information on the relationship between plasma leptin and CRP levels, particularly in type 2 diabetic patients.

Therefore, we explored the factors contributing to serum C-reactive protein and the relationships between visceral adipose tissue accumulation measured by CT and the CRP level, and examined the association between leptin and CRP level in type 2 diabetic patients.

Subjects and methods

Subjects

About 150 Korean type 2 diabetic patients who visited Yonsei University College of Medicine were enrolled for the present study. The diagnosis of type 2 diabetes was based on a previous history of diabetes or the criteria by the American Diabetes Association's diagnostic guidelines. They had no evidence of current acute illness including clinically significant infectious disease. Therefore, to minimize the possible confounding effects of glucose-lowering pharmacological treatment, these patients were recently diagnosed with type 2 diabetes (within 3 years) and were drug naïve or taking sulfonylureas. No patients have received insulin therapy, thus allowing us to compare the effects of obesity, insulin resistance, and glycemia without the possible confounding effects of diabetes treatment. The Institutional Review Board of Yonsei University College of Medicine approved the study protocol, and all the subjects provided informed consent prior to the start of this study.

Body composition and fat distribution

Body weight and height were measured in the morning with participants wearing light clothing. BMI was calculated as weight (kg)/height (m^2). Waist circumference was measured by at the mid point between the lower border of the rib cage and the iliac crest. Body fat percentage was determined by dual-energy X-ray absorptiometry (Hologic QDR 1500; Delphi, Waltham, MA, USA). Computed-tomography scan (Philips, Tomoscan 350, Mahway, NJ, USA) of the abdomen was performed as described previously [24]. With the participant in a supine position, a 10 mm CT slice scan was acquired at the L4 to L5 levels to measure the total abdominal and visceral fat area. Area of total adipose tissue (TAT) was measured by delineation

with a graph pen, followed by computing the adipose tissue area with an attenuation range of −150 to −50 Hounsfield units. Area of abdominal visceral adipose tissue (VAT) was measured by drawing a line within the muscle wall surrounding the abdominal cavity, and area of subcutaneous adipose tissue (SAT) was calculated by subtracting the VAT area from the TAT area.

Biochemical profiles

All measurements were obtained in the morning, after the patient fasted from midnight on. Blood samples were immediately centrifuged, and plasma and serum samples were kept at −70°C until laboratory testing. Glucose was measured with a standard glucose oxidase reference method (747 automatic analyzer, Hitachi, Tokyo, Japan). Total cholesterol (TC), HDL cholesterol (HDL-C) and triglycerides (TG) were measured with an enzymatic color test (Daiichi, Hitachi 747, Japan). LDL cholesterol (LDL-C) was calculated according to the Friedewald formula [25]. HemoglobinA1c (HbAIc) was determined by means of high performance liquid chromatography (Variant II, Bio-Rad, Hercules, CA, USA). Fasting serum insulin was determined by means of chemiluminescence (RIA kit, Daiichi, Japan). Insulin resistance was estimated using a Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) index [26], calculated from the following formula: HOMA-IR = fasting insulin (μU/mL) × fasting plasma glucose (mmol/L)/22.5. CRP levels were measured by nephelometry, a latex particle-enhanced immunoassay (N Latex CRP II, Dade Behring, Tokyo, Japan) and Serum leptin concentration was measured with a radioimmunoassay kit (Linco Research, St. Charles, MO, USA). PAI-1 antigen was quantified using an enzyme immunoassay (Biopool TintElize; Trinity Biotech, Carlsbad, CA, USA).

Carotid artery intima-media thickness

Carotid intima-media thickness (IMT) was evaluated by a single operator with high-resolution B-mode ultrasonography on a single machine (Toshiba SSA-270A, Tokyo, Japan) with a 7.5 MHz linear array transducer. All recordings were obtained with the patient resting in a supine position, with the head turned slightly to the contralateral side. Intima-media thickness was the distance between the lumen intima interface and media adventitia interface. Measurements of carotid IMT were conducted at three differential plaque free sites: the greatest thickness and two other points, 1 cm upstream and 1 cm downstream from the site of the greatest thickness. The mean of the three determinations of right and left IMT was defined as mean IMT.

Statistical analysis

Descriptive statistics are presented as mean values ± SD. To approximate a normal distribution, log transformed data on leptin and CRP were used in the analysis. Spearman correlation coefficients were used to estimate the correlations between serum CRP concentration, physical measurements, clinical characteristics, and insulin resistance. Stepwise multiple linear regression analysis was performed to investigate the relationship between CRP concentration as a dependent variable and BMI, fat mass, TAT, SAT and VAT as independent variables, after adjustment for age, gender. Statistical analyses were conducted using SPSS for Windows, version 11.0 (SPSS Inc., Chicago, IL, USA), and $P < 0.05$ was considered to be statistically significant.

Results

Clinical characteristics of subjects

The baseline characteristics of 150 patients with type 2 diabetes mellitus are shown in Table 1. Compared with women, men had higher WC, TAT, VAT, fasting glucose and HOMA-IR, TG, mean IMT, smoking rate. In addition, CRP and leptin levels were significantly higher in women compared with men (CRP 2.34 ± 1.65 mg/L vs. 1.72 ± 2.01 mg/L, $P < 0.01$; leptin 9.82 ± 6.78 µg/L vs. 4.76 ± 2.44 µg/L, $P < 0.01$) (Table 1).

Correlations between serum CRP and anthropometric measurements and metabolic variables

The correlations between the serum CRP concentration and the other factors examined in this study are illustrated in Table 2. After adjustment for age and gender, CRP values were positively correlated BMI, WC, fat percent, TAT, VAT, insulin, HOMA-IR, PAI-1, mean IMT and leptin (Table 2, Fig. 1). The associations with CRP were stronger for parameters of visceral obesity (WC and VAT) than for the other obesity parameters such as BMI, fat percent and TAT.

Multiple regression analysis for the relationship between anthropometric measurements and metabolic variables

The stepwise multiple regression was done with CRP as a dependent variable and candidate risk factors (anthropometric variables, insulin, PAI-1, leptin) as independent variables. As a result, serum CRP was significantly associated with leptin ($\beta = 0.326$, $P = 0.01$) and visceral adipose tissue ($\beta = 0.265$, $P = 0.035$) in diabetic patients (Table 3).

Table 1 Characteristics of the study subjects

	Male ($n = 82$)	Female ($n = 68$)
Age (years)	51.9 ± 9.9	52.8 ± 11.1
BMI (kg/m^2)	24.2 ± 2.7	23.9 ± 4.2
WC (cm)	88.4 ± 9.0	81.7 ± 11.7*
Fat (%)	33.1 ± 7.2	31.7 ± 5.5
TAT (cm^2)	281.4 ± 91.9	248.2 ± 117.9*
SAT (cm^2)	126.7 ± 49.3	138.9 ± 84.7
VAT (cm^2)	154.7 ± 60.2	109.3 ± 59.1*
Systolic BP (mmHg)	129.9 ± 10.7	126.9 ± 9.1
Diastolic BP (mmHg)	80.2 ± 9.2	79.1 ± 8.4
Fasting glucose (mmol/L)	8.28 ± 2.76	6.98 ± 2.39†
Fastin insulin (µIU/mL)	8.80 ± 4.98	7.77 ± 7.04
HbA$_{1C}$ (%)	8.01 ± 1.88	7.48 ± 2.31
HOMA-IR	3.24 ± 2.16	2.41 ± 2.46*
TC (mmol/L)	4.96 ± 0.91	4.60 ± 2.16
TG (mmol/L)	2.04 ± 1.64	1.44 ± 0.72†
HDL-C (mmol/L)	1.19 ± 0.29	1.33 ± 0.38
LDL-C (mmol/L)	2.85 ± 1.01	2.65 ± 0.89
CRP (mg/L)	1.72 ± 2.01	2.34 ± 1.65*
PAI-1 (ng/mL)	33.50 ± 20.36	32.91 ± 24.92
Leptin (µg/L)	4.76 ± 2.44	9.82 ± 6.78†
Smoker (%)	14.6	2.9†
Mean IMT (mm)	0.89 ± 0.20	0.78 ± 0.17*

Values are mean ± SD

BMI body mass index, *WC* waist circumference, *TAT* total adipose tissue, *SAT* subcutaneous adipose tissue, *VAT* visceral adipose tissue, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostasis model assessment of insulin resistance, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *CRP* C reactive protein, *PAI-1* plasminogen activator inhibitor-1, *IMT* intima media thickness

* $P < 0.05$, † $P < 0.01$

Discussion

This study has demonstrated the independent association between VAT and CRP as well as the relationship between leptin and CRP in type 2 diabetic patients.

It has been reported that the CRP level is associated with central obesity [15–18]. Several prior studies have shown a correlation between CRP and VAT measured directly with CT in nondiabetic populations [18, 27]. But there are few reports on the association between serum CRP concentration and VAT in type 2 diabetic patients. In this study, the CRP level showed significant positive correlations with parameters of obesity, and the correlations were stronger with parameters of visceral obesity (WC and VAT) than other obesity parameters such as BMI, fat percent, and TAT. Iwasaki et al. [28] have recently demonstrated that serum CRP is significantly associated with the VAT in Japanese type 2 diabetic patients. The reason for the link

Table 2 Correlation of logCRP to measures of variables in diabetic patients (adjusted for age, gender)

	γ	P
BMI	0.257	<0.01
Waist circumference	0.293	<0.01
Fat percent	0.213	<0.01
TAT	0.263	<0.01
SAT	0.167	0.083
VAT	0.296	<0.01
Systolic BP	0.013	0.90
Diastolic BP	0.207	0.07
Fasting glucose	0.017	0.94
Fastin insulin	0.189	0.047
HbA$_{1C}$	0.010	0.92
HOMA-IR	0.172	0.045
TC	0.140	0.14
TG	0.070	0.46
HDL-C	−0.135	0.16
LDL-C	0.049	0.61
PAI-1	0.206	<0.01
Log (Leptin)	0.322	<0.01
Mean IMT	0.132	0.042

BMI body mass index, *WC* waist circumference, *TAT* total adipose tissue, *SAT* subcutaneous adipose tissue, *VAT* visceral adipose tissue, *HbA1c* hemoglobin A1c, *HOMA-IR* homeostasis model assessment of insulin resistance, *TC* total cholesterol, *TG* triglyceride, *HDL-C* high-density lipoprotein cholesterol, *LDL-C* low-density lipoprotein cholesterol, *CRP* C reactive protein, *PAI-1* plasminogen activator inhibitor-1, *IMT* intima media thickness

Table 3 Stepwise multiple regression analyses with log CRP as a dependent variable (adjusted for age, gender)

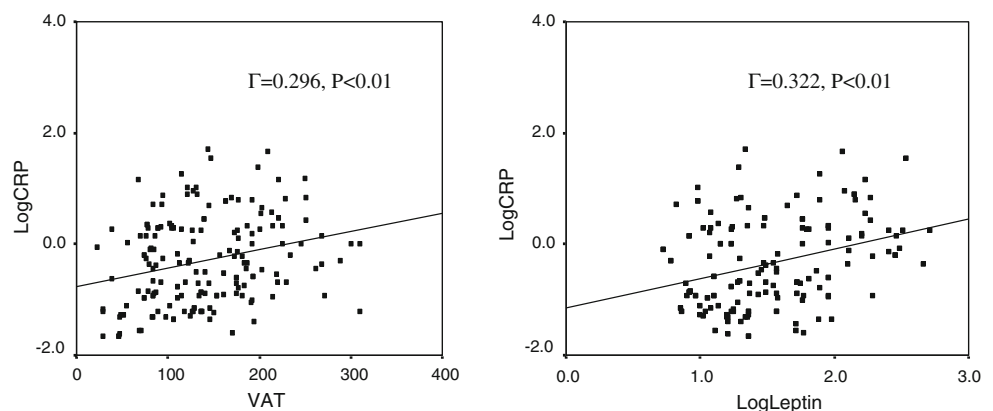|	Standardized coefficient (β)	P value
Log (leptin)	0.326	0.010
VAT	0.265	0.035

$R^2 = 22.8\%$

cytokine synthesis [29]. Although we have showed here that visceral adiposity was significantly correlated with serum CRP in type 2 diabetic patients, but we could not determine whether visceral adiposity directly elevates IL-6 and TNF-α.

In agreement with previous trials, our results showed higher levels of CRP and leptin in women compared with men. In a study by Lear et al. on Chinese subjects, gender was an independent predictor of CRP level after adjusting for WHR, age, smoking status, and alcohol, indicating that at a given WHR, women have higher CRP levels than men [30], and the MESA data [31] and additional evidence from Khera et al. support the present findings in MESA that CRP concentrations differ by gender [32].

Several studies have reported higher leptin level in women compared to men, and according to Saad et al. [33], women had 40% higher leptin level than men with similar fat mass, and Abdulah et al. [34] have attributed this gender difference to a difference in adipocyte function between men and women. So far, gender differences in CRP and leptin seem to be interrelated, but its mechanism is not known yet.

In this study, we examined how CRP is related with other coronary risk factors, and as a result, CRP values were positively correlated insulin, HOMA-IR, PAI-1 and carotid IMT after adjustment for age and gender. In agreement of previous studies [28], we found strong relationships between CRP and the factors associated with insulin resistance and atherosclerosis.

Leptin is a peptide hormone secreted by adipocyte which controls body weight by regulating appetite and energy metabolism [35]. Previous studies on the

between serum CRP concentrations and obesity is not fully understood, and a possible mechanism that has been proposed deals with IL-6 and TNF-α, which are secreted from adipose tissue as proinflammatory cytokines. The high circulating concentrations of IL-6 and TNF-α stimulate the production of CRP by liver [27]. In particular, the reason for visceral adiposity being more related to CRP can be explained by the fact that visceral adipose tissue is more active than subcutaneous adipose tissue with regard to

Fig. 1 Linear regression analysis looking at the relation between leptin and CRP on a log scale

relationship between serum CRP and leptin were mostly conducted on healthy normal subjects and obese subjects [21–23], and there is only one study done on diabetes patients by Yanagawa et al. [36]. We found a significant correlation between leptin and CRP (β coefficient = 0.326, $P = 0.01$) on a log scale. Serum leptin is an important independent factor associated with CRP in Korean type 2 diabetic patients, and this is in agreement with results by Yanagawa et al. No mechanism has been proven to explain the relationship between CRP and leptin. Some have proposed that IL-6 and TNF-α secreted from adipose tissue not only stimulate the CRP production from liver but also the leptin secretion [37, 38], and others have demonstrated that leptin secreted from adipose tissue induces the production of IL-6, which then increases the production of CRP [39]. Another possibility is that leptin directly acts on liver to increase the production of CRP, and it was proven by an in vitro experiment, in which leptin has induced the CRP production in isolated human liver cells [23, 40, 41].

In summary, it can be concluded that serum CRP level is significantly associated with obesity, especially the visceral adipose tissue, and serum leptin is another important independent factor associated with CRP in Korean type 2 diabetic patients.

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