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Hyperleptinemia as a Robust Risk Factor of Coronary Artery Disease and Metabolic Syndrome in Type 2 Diabetic Patients

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Abstract. Leptin has been linked to adiposity, insulin resistance, and coronary artery disease (CAD). We examined whether the leptin concentrations are associated with the risk of CAD and metabolic syndrome (MS). The plasma leptin concentrations were measured in 556 diabetic patients (341 men and 215 women). The odds ratio (OR) of CAD and MS were increased on moving from the lowest quartile (Q1) of leptin concentration to the highest quartile (Q4) and remained significant after adjusting for age, sex, BMI, concentrations of total cholesterol, triglyceride, or high-sensitivity C-reactive protein (hsCRP), and treatment modalities for hyperglycemia. The frequency of CAD was highest in the insulin resistant group (Q4 of homeostasis model assessment-insulin resistance index [HOMA-IR]) at Q4 of leptin concentration (34.5%), compared with that of Q4 of leptin (26.4%) or HOMA-IR (21.9%). In multivariate analysis, plasma leptin concentration was identified as the most significantly independent predictor for CAD (OR 10.24, 95% CI 3.01 to 45.05). Other variables with associated with CAD were age, sex, hypertension, low-HDL cholesterolemia, and hsCRP. In conclusion, hyperleptinemia might be an independent risk factor for CAD and MS in diabetic subjects. And the simultaneous measurement of insulin resistance and leptin concentration might be helpful for screening subjects with a high-risk of CAD.

Key words: Coronary artery disease, Hyperleptinemia, Insulin resistance, Metabolic syndrome
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OBESITY has induced many public health problems related to metabolic syndrome (MS), including glucose intolerance, hypertension, hyperinsulinemia, and dyslipidemia. These complexes are known to increase the risk of cardiovascular disease [1]. However, the precise mechanisms by which obesity leads to insulin resistance and eventually cardiovascular disease remain to be a puzzle.

Leptin, the soluble 16-kDa protein product of the adipose-specific obese (*Ob*) gene in adipocyte [2], has been suggested to be an important regulator of body weight by the brain. The leptin concentrations correlate closely with the body fat stores [3]. A recent report showed a strong association between the fasting insulin level and the leptin concentration, which was independent of BMI and waist-hip ratio [4]. Leptin also appears to be related to the other markers of cardiovascular disease and MS, including plasma triglyceride, apolipoprotein B [5], or C-reactive protein concentrations [6], and has effects on the vascular function and thrombosis [7, 8]. Therefore, an increased plasma leptin has been recognized as a linker between obesity and MS or cardiovascular disease [9, 10].

In light of these observations, we hypothesized that hyperleptinemia might constitute an additional component of MS and signal a high risk of coronary artery

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disease (CAD) in diabetic patients, and determined whether hyperleptinemia could be an alternative index for estimating the risk of CAD and MS. This study also determined the cutoff value of leptin to define CAD and MS based on the Adult Treatment Panel III criteria [11].

Patients and methods

Five hundred fifty-six patients (341 men and 215 women) with type 2 diabetes mellitus who visited an outpatient clinic for glycemic control, were enrolled in this study. All patients showed a stable HbA1c level and were taking a stable dose of hypoglycemic agents for at least 6 months prior to the study. The exclusion criteria included insulin treatment, pregnancy, endocrinopathies except diabetes, a history of treatment with anti-obesity drugs, thiazolidinediones, or corticosteroid, an abnormal renal function as determined from the age-adjusted creatinine-clearance values, symptoms indicative of CAD within 6 months (unexplained dyspnea and chest or epigastric discomfort) and abnormal ECG findings (ST-segment depression, T-wave change, intraventricular conduction defects, or atrial abnormalities) without a confirmation by angiography, as well as weight loss of more than 3 kg during the past 6 months.

All the participants underwent standard examination/testing, which included: the fasting glucose, total cholesterol, high-density lipoprotein (HDL)-cholesterol, triglyceride, high-sensitivity C-reactive protein (hsCRP), insulin, and leptin concentrations; measurements of blood pressure, height, weight, and waist circumference, a resting ECG; and a questionnaire concerning cardiovascular and other diseases. As an indicator of insulin resistance, this study used the index for a homeostasis model assessment (HOMA-IR), which was calculated as follows: HOMA-IR = [fasting plasma glucose (mmol/L) × fasting serum insulin (μU/mL)]/22.5. If the subjects had questionable symptoms (15 patients), abnormal resting ECG (12 patients), and in whom there were doubts about the state of the coronary artery such as carotid or peripheral atherosclerosis (8 patients), they were consulted to a cardiologist for coronary angiography. The subjects were regarded having CAD if they had a history of a previous myocardial infarction (30 patients), percutaneous coronary intervention (25 patients), or coronary artery bypass graft surgery (11 patients), and newly proven obstructive CAD on angiography (27 patients). The study was approved by the Ethics Committee of Yonsei University College of Medicine, and informed consent was obtained from each subject.

As detailed in the Adult Treatment Panel III report [11], MS was defined when two or more of the following criteria were present: hypertriglyceridemia, low HDL-cholesterolemia, hypertension, and/or abdominal obesity. Dyslipidemia was defined as a hypertriglyceridemia (≥1.7 mmol/L [≥150 mg/dL]), low HDL-cholesterolemia (<1.0 mmol/L [<40 mg/dL] in men and <1.3 mmol/L [<50 mg/dL] in women), or in patients using hypolipidemic agents. Hypertension was defined as a systolic pressure of at least 130 mmHg, and a diastolic blood pressure of at least 85 mmHg. Patients using antihypertensive agents were also considered as having hypertension. In this study, abdominal obesity was defined as waist circumference of ≥90 cm in men and ≥80 cm in women, according to the Asia-Pacific criteria [12].

The serum glucose concentrations were determined using the glucose oxidase method. The plasma insulin and leptin concentrations were measured by a radioimmunoassay using a double-antibody method and a commercially available radioimmunoassay kit (Linco Research, Inc., St. Charles, MO). The coefficients of variation of intra- and inter-assays in leptin measurement were 3.7~7.5% and 3.2~8.9%, respectively. The serum cholesterol and triglyceride concentrations were measured enzymatically. The hsCRP concentration was quantified using a nephelometer II (Dade Behring Diagnostics, Marburg, Germany).

Statistical analyses were performed by using the SPSS 11.0 software package (SPSS Inc, Chicago). The groups were determined in men and women separately, according to quartiles of the distribution of the leptin concentration. The intergroup comparisons were performed by using a one-way ANOVA test followed by a Scheffe's post hoc test. The associations between the leptin and other continuous variables were determined using the Pearson correlation coefficients, after the logarithmic transformations of some variables (such as leptin or hsCRP concentrations) to correct their skewed distribution. The prevalence and risk relation of CAD or MS among the groups were compared using a χ^2-test. Logistic regression, which was adjusted for age, sex, BMI, total cholesterol or triglyceride concentrations, hsCRP, and treatment modalities

for hyperglycemia, was used to analyze the associations between the quartiles of the leptin concentration and the presence of either CAD or MS. The lowest quartile of the leptin concentration was used as the reference category (odds ratio [OR], 1.00). Also, OR of various cardiovascular risk factors for CAD were calculated using univariate and multivariate logistic regression analysis. Receiver operating characteristic (ROC) curve analyses were performed to determine the sensitivity and specificity using the leptin concentration as a forecaster of CAD and MS. A $P<0.05$ was considered significant.

Results

The subjects were classified according to the quartile (Q) based on their leptin concentrations after separating the men and women; the mean values are 1.87 ng/mL (95% confidence interval [CI]: 1.78 to 1.96 ng/mL) and 3.78 ng/mL (3.50 to 4.06 ng/mL) for Q1, 2.97 ng/mL (2.90 to 3.03 ng/mL) and 6.16 ng/mL (6.00 to 6.31 ng/mL) for Q2, 4.17 ng/mL (4.06 to 4.30 ng/mL) and 9.21 ng/mL (8.90 to 9.51 ng/mL) for Q3, and 7.73 ng/mL (7.15 to 8.30 ng/mL) and 18.97 ng/mL (16.77 to 21.20 ng/mL) for the Q4, in the men and women, respectively. The clinical characteristics according to the quartiles of the leptin concentration are shown in Table 1. No differences in terms of age, duration of diabetes, blood pressure, fasting glucose or HbA1c, and HDL-cholesterol were observed among groups (Table 1). On moving form Q1 to Q4, the BMI, waist circumference, and the frequency using metformin for treatment of hyperglycemia increased, while the frequency using sulphonylurea or combination therapy of sulphonylurea and metformin decreased. The concentrations of total cholesterol, triglyceride, hsCRP, or insulin, HOMA-IR, and the prevalence of CAD and MS increased as the leptin concentration were higher. A positively strong association with CAD was also observed according to the quartiles of HOMA-IR (data not shown), although lesser significant than those of leptin concentration. While the frequency of CAD in the highest quartile of the leptin concentration and HOMA-IR was 26.4% (37/140) and 25.2% (34/135), respectively, the frequency of CAD in the group simultaneously belonging to both the highest quartiles of HOMA-IR and leptin was 34.5% (19/55) (Fig. 1).

The log (leptin) closely related with BMI (r = 0.42,

Table 1. Clinical characteristics of the subjects by the quartile of the leptin concentration

	Q1	Q2	Q3	Q4	P
Sex (M/F)	85/53	85/54	85/54	86/54	
Age (year)	53.5 ± 9.2	52.5 ± 10.6	53.2 ± 11.5	50.5 ± 11.5	NS
Duration of diabetes (year)	6.2 ± 5.6	6.3 ± 5.8	5.9 ± 5.1	5.8 ± 5.5	NS
Current smoker (%)	12.3	12.9	11.5	11.4	NS
BMI (kg/m^2)	23.5 ± 2.5	24.9 ± 2.4	25.8 ± 2.7	27.7 ± 3.7	<0.001
Waist circumference (cm)	82.5 ± 6.7	86.6 ± 6.5	88.9 ± 6.9	92.8 ± 8.8	<0.001
Systolic blood pressure (mmHg)	133 ± 17	131 ± 20	134 ± 18	131 ± 17	NS
Diastolic blood pressure (mmHg)	83 ± 10	81 ± 10	83 ± 11	82 ± 10	NS
Treatment of diabetes (%)					0.03
Sulphonylurea (SU)	28.6	18.2	19.5	15.5	
Metformin (MET)	37.1	38.5	43.5	56.3	
SU+MET	34.3	43.3	37.0	28.2	
Glucose (mmol/L)	8.7 ± 2.8	8.3 ± 2.6	8.7 ± 2.6	8.1 ± 2.4	NS
HbA1c (%)	8.0 ± 1.9	7.9 ± 1.8	7.9 ± 1.6	7.8 ± 1.5	NS
Total cholesterol (mmol/L)	4.68 ± 0.88	4.73 ± 1.01	4.97 ± 0.93	5.02 ± 1.11	0.008
HDL-cholesterol (mmol/L)	1.22 ± 0.28	1.14 ± 0.26	1.11 ± 0.26	1.09 ± 0.26	NS
Triglyceride (mmol/L)	1.72 ± 1.20	2.03 ± 1.28	2.27 ± 1.65	2.46 ± 1.85	0.003
hsCRP (mg/L)	1.51 ± 2.22	1.97 ± 4.02	2.36 ± 4.45	2.75 ± 4.32	0.010
Insulin (pmol/L)	44.1 ± 30.1	59.9 ± 37.5	68.2 ± 34.4	89.6 ± 38.0	<0.001
HOMR-IR	2.33 ± 2.21	2.92 ± 2.12	3.75 ± 2.75	4.50 ± 2.89	<0.001
Coronary artery disease (%)	4.3	16.5	19.4	26.4	<0.001
Metabolic syndrome (%)	52.2	66.9	82.0	85.7	<0.001

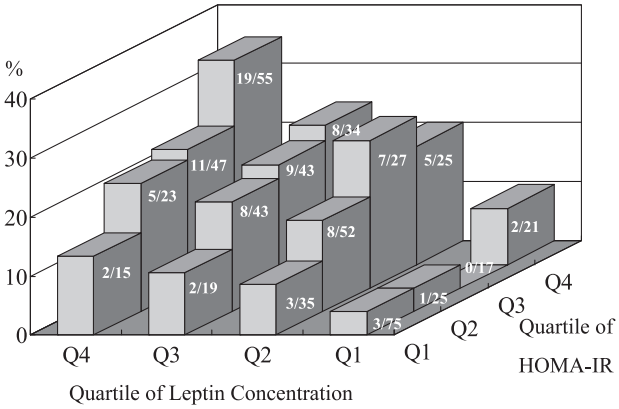

Fig. 1. Frequency of coronary artery disease by the quartiles of the leptin concentration at different insulin resistance (HOMA-IR) quartiles.

Table 2. Odd ratios and 95% CIs of coronary artery disease and the metabolic syndrome by quartile (Q) of the leptin concentration

	Unadjusted	Adjusted*
Coronary artery disease		
Q1 (138)	1.00	1.00
Q2 (139)	3.73 (1.43–9.76)	3.66 (1.27–10.53)
Q3 (139)	3.67 (1.41–9.49)	3.74 (1.30–10.75)
Q4 (140)	5.01 (1.93–12.56)	3.76 (1.21–11.69)
P for trend	<0.001	0.008
Metabolic syndrome		
Q1 (138)	1.00	1.00
Q2 (139)	1.86 (1.14–3.01)	1.38 (0.81–2.33)
Q3 (139)	4.07 (2.42–7.22)	2.28 (1.18–4.42)
Q4 (140)	5.41 (3.08–9.82)	3.62 (1.96–6.66)
P for trend	<0.001	<0.001

* Adjusted for age, sex, BMI, the concentrations of total cholesterol, triglyceride, or high-sensitivity C-reactive protein, and treatment modalities for hyperglycemia.

P<0.001) and waist circumference (r = 0.30, P<0.001). The log (leptin) correlated with the total cholesterol, HDL-cholesterol, and log (hsCRP) (r = 0.24, r = –0.26, and r = 0.29, respectively, P<0.01), and remained significant after adjusting for age, sex, and BMI. In addition, the log (leptin) correlated strongly with the log (insulin) (r = 0.51, P<0.001) and log (HOMA-IR) (r = 0.39, P<0.001) after adjustment.

The logistic regression results showing the ORs for the CAD and MS according to the quartiles for the leptin concentrations are listed in Table 2. There was a significant trend in the increasing risk for CAD and MS (P for trend <0.001, respectively) across the quartiles of leptin concentration. The subjects in the highest quartile (Q4) of the leptin concentration experienced a more than five-fold increased risk having CAD and MS compared to those in the lowest quartile (Q1) (OR 5.01, 95% CI 1.93 to 12.56 and OR 5.41, 95% CI 3.08 to 9.82, respectively). The trends remained statistically significant, even though the magnitude of these associations were reduced slightly after adjusting for age, sex, BMI, the concentrations of total cholesterol, triglyceride, or hsCRP, and the type of oral hypoglycemic agents used.

Table 3. Univariate odd ratios for the coronary artery disease

	Odd ratio	95% CI	P value
Age	1.09	1.06–1.15	<0.001
Sex (women)	0.72	0.42–1.23	0.020
BMI	1.09	1.05–1.26	0.048
Waist circumference	1.04	1.01–1.07	0.038
Current smoker	1.14	1.05–1.30	0.025
Hypertension	4.17	2.16–8.05	<0.001
Hypertriglyceridemia	2.24	1.27–3.92	0.005
Low-HDL cholesterolemia	3.02	1.69–5.39	<0.001
Log (HOMA-IR)	2.71	1.11–6.65	0.010
Log (hsCRP)	2.37	1.31–4.30	0.005
Log (leptin)	2.80	1.21–6.15	0.010

Table 4. Multivariate odd ratios for the coronary artery disease

	Odd ratio	95% CI	P value
Age	1.08	1.04–1.14	<0.001
Sex (women)	0.67	0.37–0.91	0.020
BMI	1.13	0.92–1.40	NS
Waist circumference	1.02	0.86–1.56	NS
Current smoker	1.12	0.94–2.01	NS
Hypertension	2.35	1.04–5.31	0.041
Hypertriglyceridemia	1.43	0.89–2.52	NS
Low-HDL cholesterolemia	4.76	2.04–11.12	<0.001
Log (HOMA-IR)	1.40	0.44–4.75	NS
Log (hsCRP)	2.04	1.10–4.31	0.045
Log (leptin)	10.24	3.01–45.05	<0.001

In the logistic regression analysis, age, sex, BMI, waist circumference, current smoker, hypertension, hypertriglyceridemia, low-HDL cholesterolemia, HOMA-IR, hsCRP, and leptin were found to be a univariate predictor of CAD (Table 3). The most powerful variable associated with CAD in multivariate analysis was the leptin concentration (OR 10.24, 95% CI 3.01 to 45.05) (Table 4). Other variables associated with CAD were age, sex, hypertension, low-HDL cholesterolemia, and hsCRP.

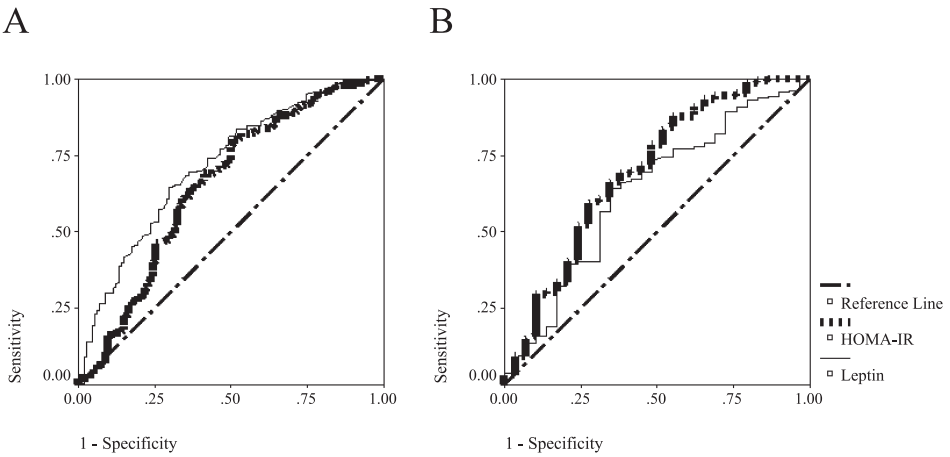

Fig. 2. Receiver operating characteristic (ROC) analyses for the leptin concentration and HOMA-IR as a predictor of the presence or absence of the metabolic syndrome in men (A) and women (B). The leptin concentration of 3.10 and 5.76 ng/mL in men and women, respectively, were chosen as a discriminator value to predict the presence of the metabolic syndrome (specificity of 74% and 70% and sensitivity of 71% and 54% in the men and the women, respectively), and the area under the ROC curve (AUC) was 0.76 in men and 0.66 in women.

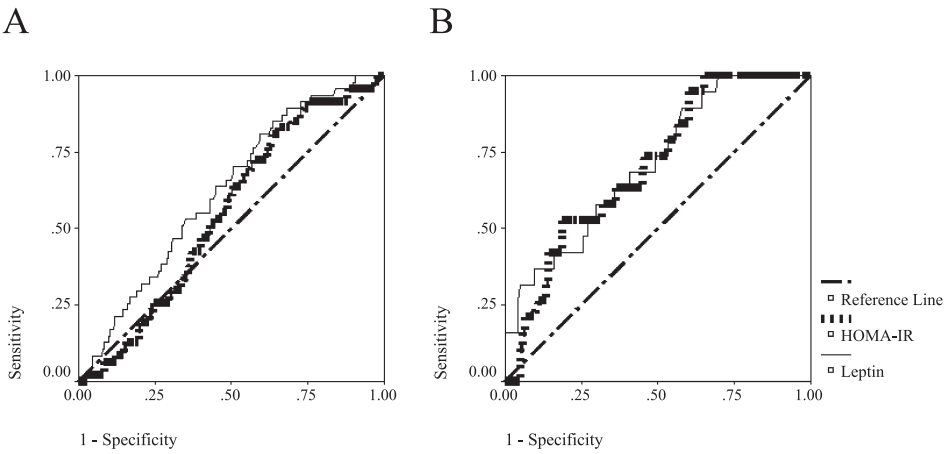

Fig. 3. Receiver operating characteristic (ROC) analyses for the leptin concentration and HOMA-IR as a predictor of the presence or absence of the coronary artery disease in men (A) and women (B). The area under the ROC curve (AUC) of leptin and HOMR-IR were 0.62 (95% CI 0.54–0.70) and 0.55 (95% CI 0.47–0.63) in men and 0.71 (95% CI 0.60–0.83) and 0.70 (95% CI 0.59–0.81) in women, respectively.

The abilities of leptin and HOMA-IR to differentiate patients with or without MS were assessed using ROC curve analyses (Fig. 2). In men, the leptin concentration had a higher area under the ROC curve (AUC) (0.76, 95% CI 0.70 to 0.83) than the HOMA-IR (0.68, 95% CI 0.58 to 0.78). In the cases of women, AUCs of leptin and HOMA-IR were similar (0.66 and 0.68, respectively). Leptin concentrations of 3.10 (specificity of 74% and sensitivity of 70%) and 5.76 ng/mL (specificity of 71% and sensitivity of 54%) in men and women, respectively, were found to be the discriminating cutoff for MS. In contrast, HOMA-IR of 2.22 and 2.30 in men and women, respectively, were found to be the cut-off value for discriminating the presence of MS. Also, the ROC curve analyses to differentiate patients with or without CAD showed that the AUCs of leptin and HOMA-IR were 0.62 (95% CI 0.54 to 0.70) and 0.55 (95% CI 0.47 to 0.63) in men and 0.71 (95% CI 0.60 to 0.83) and 0.70 (95% CI 0.59 to 0.81) in women (Fig. 3). The cut-off values of leptin for discriminating the presence of CAD was 3.62 (specificity of 62% and sensitivity of 55%) and 8.75 ng/mL (specificity of 69% and sensitivity of 60%) in men and women, respectively.

Discussion

Previous studies have reported that leptin might be a risk factor of cardiovascular disease in the general population. This study showed that the leptin concentration was independently related with the greater prevalence of CAD and MS in diabetic patients, and had the ability to discriminate subjects not only with or without MS, but also with or without CAD. These results strongly suggested that leptin, a solely adipocyte-derived hormone, might be one mechanism by which body fatness is linked to the cardiovascular disease and that the leptin concentration might provide additional information than other risk factors, such as inflammation, insulin resistance, hypertension, dyslipidemia, or anthropometric indices, for evaluating the risk of CAD and MS.

Long-term longitudinal studies indicate that obesity is not only related to, but also independently predicts cardiovascular disease [1, 13]. Nevertheless, no clear culprits to link any risk factor to induce cardiovascular disease under obesity have been identified. Recently, hyperleptinemia has been recognized as a mediator between obesity and cardiovascular disease [9, 10]. Leptin itself is a potent inhibitor of food intake and increases energy expenditure [14]. Paradoxically, the leptin concentrations increase with obesity and correlate strongly with the body fat stores in both sexes [3], and, hyperphagia and hyperleptinemia are common features of obesity. This means that high leptin concentrations in obese individuals might reflect resistance to the effects of this hormone in peripheral organs [15, 16]. Because obesity induces insulin-resistance, it is plausible that the coexistence of hyperleptinemia and hyperinsulinemia may be explained by leptin resistance.

As demonstrated by other studies, we also observed the close correlation between leptin and insulin or HOMA-IR, which was independent of BMI. And the risk having CAD and MS in the highest quartile of the leptin concentration were significantly higher compared to that in the lowest quartile, even after adjustment for age, BMI or other cardiovascular risk factors. These results concur with recent studies, which reported that hyperleptinemia was an independent risk factor for CAD and closely associated with features of metabolic syndrome [9, 10, 17, 18]. However, it should be noted that in few of these studies were data from the diabetic population provided. In addition, this study suggested the cutoff values of leptin concentration for predicting the presence of MS or CAD. Leptin concentration had a better power for determining the presence of MS or CAD than HOMA-IR, at least in men, and was the strongest independent risk predictor of CAD in multivariate analysis.

Nevertheless, the HOMA-IR still could not be considered to be less predictive than the leptin concentration. HOMA-IR was known to be an independent predictor of both prevalent and incident cardiovascular disease [19]. However, considering the highest frequency of CAD in the group that had the highest quartile of HOMA-IR and simultaneously had the highest quartile of the leptin concentration, the leptin concentration also might be a good marker of CAD to keep up with the HOMR-IR. Therefore, both measurements of HOMA-IR and leptin concentration could be more useful for screening those subjects with a high risk of CAD, compared with measuring only the insulin resistance.

The direct impact of leptin on cardiovascular disease may be largely obscured. However, there are emerging evidences to suggest that leptin may mediate the adverse effects on the cardiovascular system. Higher leptin concentrations are associated with an impaired arterial distensibility [20], and patients with a restenosis after coronary stenting had higher leptin levels than those without a restenosis [21]. Furthermore, the direct influence of leptin on the vascular biology is supported by the *ob/ob* mice, which lacks leptin and consequently becomes hyperphagia and obesity but is nevertheless resistant to atherosclerosis [22]. However, the administration of leptin removes this protective effect against atherosclerosis. The atherosclerosis risk in heterozygotes is intermediate between the *ob/ob* homozygote and the control mouse, which suggest a dose-response relation between the leptin levels and the atherosclerotic process [23]. These adverse effects of leptin on cardiovascular system are likely due to several various factors such as increased sympathetic activity, enhanced platelet aggregation, increased oxidative stress, and cardiac hypertrophy [8, 24–27].

Adiponectin also is an important adipocytokine exclusively expressed in adipose tissue. Unlike letpin to over-secrete in obesity, the adiponectin concentrations are decreased with obesity [28], insulin resistance and diabetes [29], or dyslipidemia [30], and hypoadiponectinemia or low high molecular weight to total adiponectin ratio is considered as a marker of CAD

[31–33]. However, Qasim *et al*. showed that only leptin had strong association with coronary atherosclerosis, although both leptin and adiponectin were associated with metabolic and inflammatory markers [34]. We also measured the adiponectin concentrations in 156 patients. While leptin was strongly associated with MS or CAD even after controlling adiponectin, adiponectin per se showed no association with MS and CAD (data not shown). The interrelationship between these adipocytokines and CAD still remains to be clarified.

This study had several limitations. Because this study was performed only in a Korean population, our findings may not be generalized to other racial and ethnic groups. Moreover, some traditional risk factors for CAD, such as BMI, smoking, or hypertriglyceridemia, were underestimated in this study. We supposed that it was because most of patients with a history of previous CAD already changed their lifestyle (strict diet control or abstinence of smoking), before enrollment in this study. Also, the number of participants in this study was too low to confirm the above results, and this study was cross-sectional. Finally, we did not measure both the leptin and adiponectin in all subjects. Therefore, this study could not entirely examine the association of leptin and adiponectin with CAD or MS.

In conclusion, we found that the leptin concentration was an independent risk factor associated with CAD and MS after controlling for traditional cardiovascular risk factors and that the leptin concentration may be a predictor for future coronary events in diabetic population. The simultaneous measurement of insulin resistance and leptin concentration might be helpful for screening the subjects with high-risk of CAD. Furthermore, identifying the mechanism of leptin on cardiovascular system suggests that the intervention reducing leptin concentration may be an important modality to prevent CAD.

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