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ORIGINAL ARTICLE
Ischemic Heart Disease

Association Between Plasma High-Molecular-Weight Adiponectin and Coronary Plaque Characteristics Assessed by Computed Tomography Angiography in Conditions of Visceral Adipose Accumulation

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Background: Our group has previously reported that visceral adipose tissue (VAT) accumulation was associated with the extent and vulnerable characteristics of coronary plaques using coronary computed tomography angiography (CTA). An investigation of the associations between these coronary lesions with plasma adiponectin and leptin was performed.

Methods and Results: A total of 394 patients (220 men and 174 women) in the study were referred for CTA. Plain abdominal scanning was simultaneously performed to evaluate VAT areas. The median level of plasma high-molecular-weight (HMW) adiponectin in patients with CTA-based obstructive coronary artery disease was significantly lower than that in patients without (men: 1.45 vs. 1.88 μg/ml, P=0.002; women: 2.49 vs. 3.44 μg/ml, P<0.001). Multivariate analyses revealed that a lower HMW adiponectin concentration was significantly associated with the presence (men: P=0.019; women: P=0.018) and involved segment numbers (men: P=0.001; women: P=0.003) of coronary plaques. Furthermore, it was significantly related to coronary plaque with all 3 vulnerable characteristics of positive remodeling, low CT density (≤38 Hounsfield units), and adjacent spotty calcium (men: P=0.019; women: P=0.016). These associations were also observed with VAT areas, but not with plasma leptin concentrations, in both genders.

Conclusions: Lower plasma HMW adiponectin is associated with the presence, extent, and vulnerable characteristics of coronary plaques assessed by CTA in both genders. (*Circ J* 2012; **76:** 1687–1696)

Key Words: Adiponectin; Computed tomography; Plaque

Adipose tissue is not simply an organ of energy storage, but is also a secretory organ that produces a variety of bioactive substances, including adiponectin, leptin, and inflammatory cytokines.[1–3] Adiponectin in particular is abundantly present in the circulation as a low-molecular-weight trimer and medium-molecular-weight hexamer, has a high-molecular-weight (HMW) mass, and has direct anti-inflammatory, insulin-sensitizing, and anti-atherogenic effects.[1–9] Previous studies have shown that plasma adiponectin is decreased in patients with coronary artery disease (CAD),[5,6] especially in those with acute coronary syndrome.[7] Furthermore, HMW adiponectin is considered to have stronger anti-atherogenic effects than other types of adiponectin.[6,8,9]

Coronary computed tomography angiography (CTA) enables the non-invasive visualization of not only lumen narrowing, but also atheromatous changes in the vessel wall.[10–14] We previously reported that CTA allows for reliable analysis of the morphological characteristics of non-calcified coronary plaques (NCP),[11–14] which are frequently observed in coronary lesions in acute coronary syndrome.

We recently reported that visceral adipose tissue (VAT) accumulation is closely associated with the extent and vulnerable characteristics of coronary plaques on CTA.[15,16] However, few data are available concerning the relationships between adipokines such as plasma HMW adiponectin and coronary plaques, especially in terms of their composition and morphol-

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ogy as assessed by CTA. In the present study, we investigated the associations between plasma adiponectin and leptin with the presence, extent, and characteristics of coronary plaques and compared these associations with adiposity measurements and traditional coronary risk factors.

Methods

Study Patients

This study was designed to evaluate the association between CTA-based coronary plaques and adipokines. CTA was performed on patients with suspected CAD. Exclusion criteria were known CAD, previous coronary revascularization, previous pulmonary vein isolation for atrial fibrillation, advanced stage of malignant disease, systemic inflammatory disease, a status of congestive heart failure (New York Heart Association Functional Class ≥II), endocrine disorders, and a history of treatment with thiazolidinediones. We enrolled 432 consecutive patients who underwent CTA between January 2008 and May 2011. A total of 38 patients were excluded from analyses because of poor image quality on CTA caused by motion artifacts (n=25) or inadequate contrast concentration (n=13). Finally, a total of 394 patients (220 men, 174 women) were studied. The individuals were patients with chest pain (n=189), asymptomatic patients with multiple coronary risk factors (n=159), or abnormal electrocardiographic findings (n=46). This study was approved by our hospital's ethical committee, and written informed consent was obtained from all patients.

Risk Factor Assessment and Laboratory Analysis

We recorded traditional coronary risk factors including hypertension (systolic/diastolic blood pressure ≥140/90 mmHg or current use of antihypertensive agents), hypercholesterolemia (low-density lipoprotein cholesterol level ≥140 mg/dl on direct measurement or current use of lipid-lowering drugs), diabetes mellitus (hemoglobin A_{1c} level ≥6.5% and/or current use of hypoglycemic agents), and current smoking as in our previous study.[16] Metabolic syndrome was diagnosed by Japanese criteria[17] and the 10-year coronary heart disease risk was calculated using the Framingham risk score (FRS) algorithm.[18]

Fasting blood samples were obtained from an antecubital vein before CTA, and serum lipid and hemoglobin A_{1c} concentrations were measured in the hospital laboratory. Blood samples were immediately stored at –80°C after centrifugation. Plasma total adiponectin, HMW adiponectin, and leptin concentrations were measured by enzyme-linked immunosorbent assay using commercially available kits (total adiponectin: Otsuka Pharmaceuticals, Tokushima, Japan; HMW adiponectin: Sekisui Medical, Tokyo, Japan; leptin: R&D Systems, Abingdon, UK). Serum high-sensitivity C-reactive protein concentration was measured by nephelometry using a latex particle-enhanced immunoassay (Dade Behring Inc, Tokyo, Japan).

CT Scan Protocol and Image Reconstruction

We used a 64-slice CT scanner (LightSpeed VCT; GE Healthcare, Little Chalfont, Buckinghamshire, UK) for coronary evaluation. Before CTA, a plain scan with prospective electrocardiogram (ECG)-triggering was performed to measure Agatston coronary calcium scores using dedicated software (Smartscore, version 3.5; GE Healthcare).[15,19] The precise scan protocol of the retrospective ECG-gated CTA has been described previously.[13,14] All patients with an initial heart rate of ≥60 beats/min were given an oral β-blocker (40 mg metoprolol). Sublingual nitroglycerin was administered just before scanning. A body-weight-adjusted volume (0.6–0.7 ml/kg) of iodine contrast (Iopamiron 370; Bayer Healthcare, Berlin, Germany) was administered into the antecubital vein over the course of 10 s, followed by 25 ml of saline solution injected at 5.0 ml/s. The CT reconstructed image data were transferred to an offline workstation (Advantage Workstation Ver. 4.2; GE Healthcare) for post-processing and subsequent image analysis.

Evaluation of Coronary CTA Findings

We assessed CTA findings and coronary plaques according to our previous reports.[13,14] Briefly, obstructive CAD was defined as the presence of a >50% stenotic lesion in at least 1 coronary vessel. NCP was defined as either a low-density mass of >1 mm^2, with a CT density of ≤130 Hounsfield units (HU), located within the vessel wall, and containing coronary calcium or as a structure on the vessel wall with a CT density of >130 HU or greater than that of the contrast-enhanced coronary lumen on a plain image. The presence and extent of coronary plaques were determined for each participant and evaluated in accordance with the modified American Heart Association classification with 17 coronary segments.[20]

NCP characteristics on CTA were evaluated by determining the minimum CT density, vascular remodeling index, and adjacent calcium morphology:[13,14,16] a low-density plaque was defined as a lesion with a CT density of ≤38 HU,[13,14,16] vascular positive remodeling (PR) was defined as a remodeling index (proximal reference cross-sectional vessel area/lesion cross-sectional vessel area) of >1.05,[13,14,16,21] and spotty calcium was defined as calcium burden length of <3/2 of vessel diameter and width of <2/3 of vessel diameter.[13,14,16,22]

Measurement of VAT Area

Abdominal scanning was simultaneously performed at the fourth to fifth lumbar levels in the spine position, and 12 single 5-mm slices were obtained during a breath-hold after normal expiration. The VAT and subcutaneous adipose tissue (SAT) areas in each subject were determined from an image at the level of the umbilicus using dedicated software (Virtual Place; AZE Inc, Tokyo, Japan).[15,16]

Statistical Analysis

Categorical variables were presented as number of patients (percentage), and continuous variables were expressed as means ± SD or medians (interquartile range). The Mann-Whitney U-test or the Kruskal-Wallis test was used for group comparisons of continuous variables, and post-hoc testing was performed using the Steel-Dwass method. Spearman correlation analyses were used to describe the bivariate associations. Univariate and multivariate logistic and linear regression analyses were performed to assess the associations between plasma adipokines and obesity-related measurements with the presence, extent, and characteristics of coronary plaques. Multivariate analyses that included plasma adipokines or obesity-related measurements were adjusted for age, hypertension, hypercholesterolemia, diabetes mellitus, and current smoking. The Hosmer-Lemeshow statistic was used to assess model calibration. Receiver-operating characteristic (ROC) curves were constructed from regression models that included HMW adiponectin concentrations and FRS. ROC analyses were used to compare the predictive powers of adiponectin concentrations, leptin concentrations, VAT area, FRS, and the addition of HMW adiponectin concentrations to FRS in prediction of the presence and vulnerable characteristics of NCP. Statistical comparisons of the AUC under ROC curves were performed using a computer program (ROCKIT; Charles E. Metz, Uni-

Table 1. Characteristics of Study Patients and Spearman Correlation Coefficients With Plasma HMW Adiponectin

	Men (n=220)		Women (n=174)	
	Value	r	Value	r
Age (years)	64±10	0.196†	70±8	0.074
BMI (kg/m²)	24.5±2.9	–0.236†	23.8±4.1	–0.281†
WC (cm)	89.8±7.9	–0.271†	85.5±10.7	–0.324†
Hypertension, n (%)	159 (72)	–0.170*	121 (70)	–0.040
Hypercholesterolemia, n (%)	97 (44)	–0.086	102 (59)	–0.146
Diabetes mellitus, n (%)	75 (34)	–0.195†	48 (28)	–0.211†
Current smoking, n (%)	103 (47)	–0.070	15 (9)	–0.129
Triglycerides (mg/dl)	134 (96–194)	–0.284†	111 (83–163)	–0.385†
LDL cholesterol (mg/dl)	119±31	–0.080	115±29	–0.114
HDL cholesterol (mg/dl)	56±16	0.247†	64±16	0.359†
Hemoglobin A_{1c} (%)	6.0±1.1	–0.182†	5.9±0.8	–0.222†
High-sensitivity CRP (mg/L)	0.6 (0.3–1.4)	–0.158*	0.5 (0.3–1.2)	–0.320†
HMW adiponectin (μg/ml)	1.66 (1.04–2.55)		3.11 (2.14–4.29)	
Total adiponectin (μg/ml)	6.59 (4.99–9.05)	0.918†	10.32 (7.58–13.73)	–0.907†
Leptin (ng/ml)	3.50 (2.26–5.27)	–0.372†	7.20 (4.29–11.32)	–0.313†
VAT area (cm²)	122±38	–0.366†	98±45	–0.477†
SAT area (cm²)	122±38	–0.199†	164±73	–0.199†
Metabolic syndrome, n (%)	101 (46)	–0.354†	45 (26)	–0.279†
Framingham risk score (%)	12 (10–20)	–0.163*	8 (3–11)	–0.207†
Medications				
Antihypertensive agents, n (%)	103 (47)	–0.057	103 (59)	–0.139
Lipid-lowering agents, n (%)	52 (24)	–0.069	70 (40)	–0.087
Hypoglycemic agents, n (%)	33 (15)	–0.049	23 (13)	–0.102

All data are presented as number of patients (%), mean±SD, or medians (interquartile range).
BMI, body mass index; WC, waist circumference; LDL, low-density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; HMW, high-molecular-weight; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue.
*P<0.05, †P<0.01.

versity of Chicago). Optimal cut-off values of HMW adiponectin concentrations were determined to provide the highest diagnostic accuracy for prediction of NCP characteristics. Statistical analyses were performed using SPSS 13.0 (SPSS Inc, Chicago, IL, USA). A probability value of P<0.05 was considered significant.

Results

Patient Characteristics and HMW Adiponectin Concentrations

The clinical characteristics of the study patients and Spearman correlation coefficients with plasma HMW adiponectin are shown in Table 1. HMW adiponectin concentrations were inversely correlated with body mass index, waist circumference, VAT and SAT area, frequency of diabetes mellitus and metabolic syndrome, FRS, and concentrations of triglycerides, hemoglobin A_{1c}, and high-sensitivity C-reactive protein in both genders. In contrast, these were positively correlated with high-density lipoprotein cholesterol and total adiponectin concentrations in both genders and with age and frequency of hypertension in men.

HMW Adiponectin Concentrations and Coronary CTA Findings

Coronary CTA findings are shown in Table 2. Of the total 394 patients, 156 (40%, 100 men) had obstructive CAD. Coronary plaques were detected in 303 patients (77%, 185 men), NCP in 271 (69%, 170 men), and calcified plaques in 241 (61%, 144

Table 2. Coronary CTA Findings of Study Patients

Term	Men (n=220)	Women (n=174)
Obstructive CAD, n (%)	100 (45)	56 (32)
Coronary calcium scores	74 (2–354)	34 (0–182)
Presence of coronary plaques, n (%)	185 (84)	118 (68)
Presence of NCP, n (%)	170 (77)	101 (58)
Presence of calcified plaques, n (%)	144 (65)	97 (56)
Extent of coronary plaques (segments)	4 (1–6)	2 (0–4)
Extent of NCP (segments)	2 (1–4)	1 (0–3)
Extent of calcified plaques (segments)	2 (1–3)	1 (0–3)
Positive remodeling, n (%)	122 (55)	65 (37)
Low CT density, n (%)	115 (52)	59 (34)
Spotty calcification, n (%)	99 (45)	54 (31)
All 3 characteristics, n (%)	70 (32)	38 (22)

All data are presented as number of patients (%), mean±SD, or medians (interquartile range).
CTA, computed tomography (CT) angiography; CAD, coronary artery disease; NCP, non-calcified plaque.

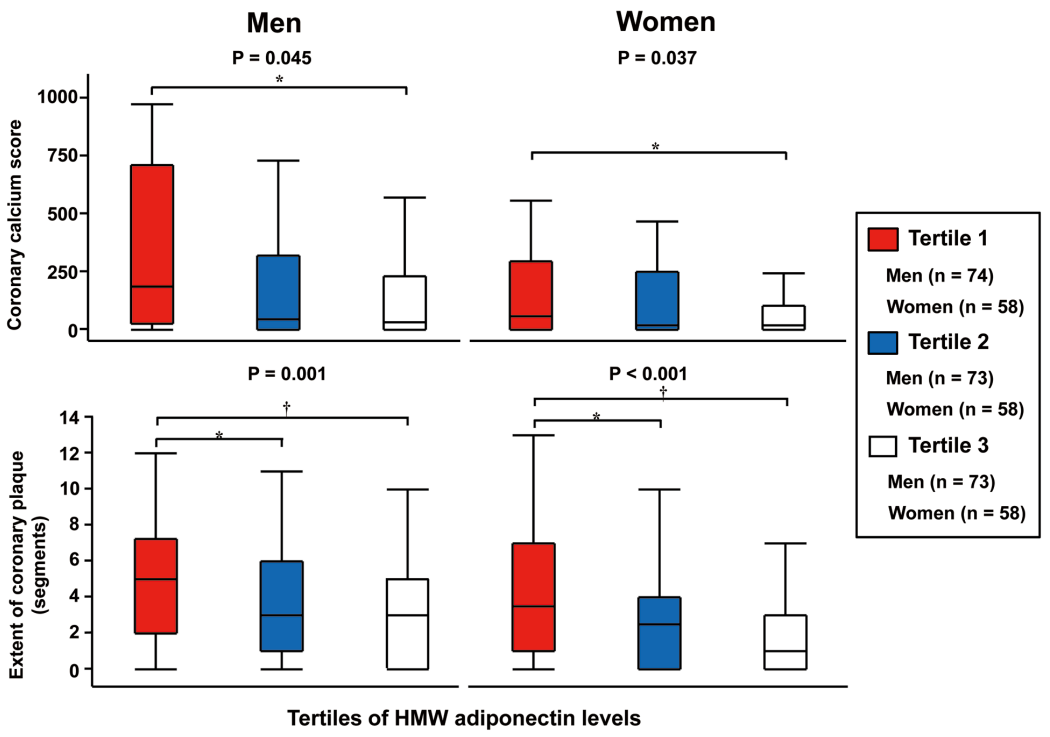

Figure 1. Associations of coronary calcium score and the extent of coronary plaques with high-molecular-weight (HMW) adiponectin concentrations. Patients were divided into tertiles based on HMW adiponectin concentrations (men: <1.32, 1.32–2.17, and >2.17 μg/ml; women: <2.58, 2.58–3.80, and >3.80 μg/ml, respectively). Boxes indicate 25th and 75th percentiles; lines indicate 5th and 95th percentiles for the data. *P<0.05; †P<0.01.

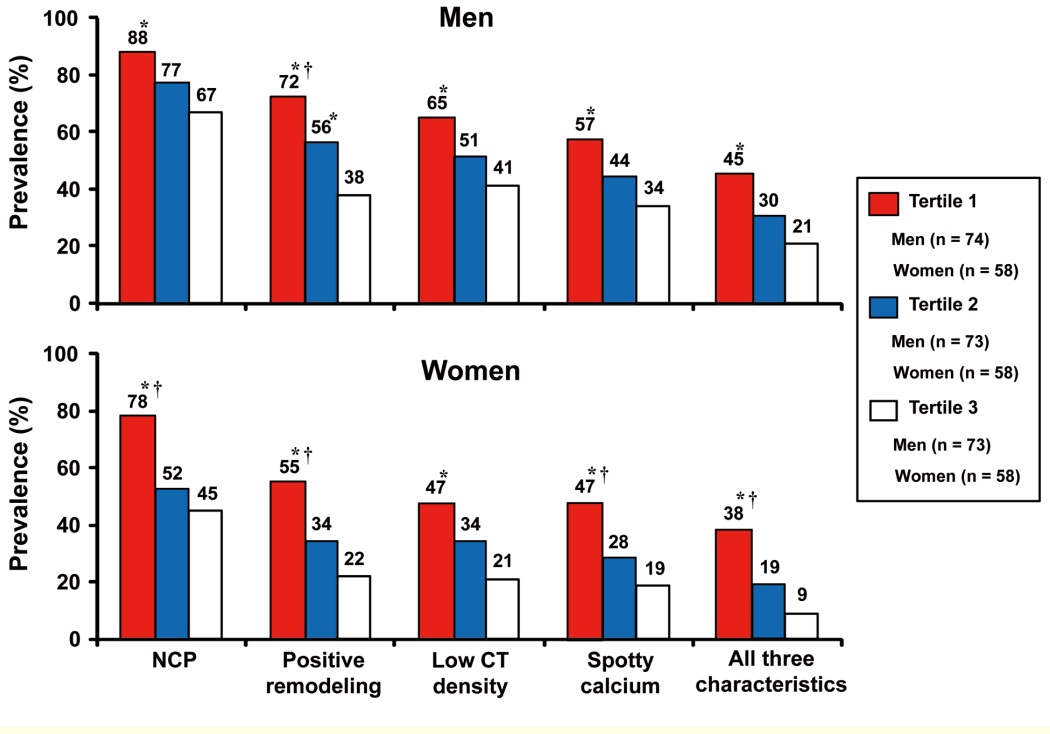

Figure 2. Associations of plasma high-molecular-weight (HMW) adiponectin concentrations and non-calcified coronary plaque (NCP) characteristics. Patients were divided into tertiles based on HMW adiponectin concentrations.

Table 3. Associations of Plasma Adipokines and Obesity-Related Measurements With the Presence and Extent of Coronary Plaques

	Presence					Extent			
	Univariate		Multivariate*			Univariate		Multivariate*	
	OR (95%CI)	P-value	OR (95%CI)	P-value	P-value (HLT)	β-estimate (95%CI)	P-value	β-estimate (95%CI)	P-value
Men									
VAT area (per 10 cm²)	1.32 (1.17–1.52)	<0.001	1.29 (1.12–1.49)	<0.001	0.199	0.51 (0.10–0.92)	<0.001	0.43 (0.08–0.78)	<0.001
SAT area (per 10 cm²)	0.93 (0.86–1.01)	0.100	0.95 (0.87–1.05)	0.311	0.880	0.01 (–0.09–0.11)	0.778	0.03 (–0.06–0.13)	0.521
BMI (5.0 kg/m²)	1.04 (0.57–1.98)	0.912	1.26 (0.61–2.62)	0.530	0.849	0.48 (–0.19–1.15)	0.142	0.34 (–0.34–1.02)	0.328
WC (per 5.0 cm)	1.10 (0.87–1.39)	0.424	1.13 (0.87–1.48)	0.356	0.567	0.25 (–0.01–0.49)	0.055	0.19 (–0.06–0.44)	0.131
HMW adiponectin (per 1.00 μg/ml)	0.71 (0.55–0.91)	0.007	0.74 (0.57–0.95)	0.019	0.553	–0.61 (–0.92 to –0.31)	<0.001	–0.48 (–0.76 to –0.19)	0.001
Total adiponectin (per 1.00 μg/ml)	0.90 (0.82–0.99)	0.038	0.92 (0.83–1.01)	0.087	0.232	–0.15 (–0.27 to –0.03)	0.013	–0.11 (–0.22–0.01)	0.053
Leptin (per 1.00 ng/ml)	1.13 (0.99–1.37)	0.065	1.09 (0.96–1.32)	0.222	0.628	0.09 (–0.01–0.20)	0.069	0.09 (–0.01–0.18)	0.080
Women									
VAT area (per 10 cm²)	1.23 (1.13–1.37)	<0.001	1.19 (1.07–1.33)	0.001	0.581	0.30 (0.20–0.39)	<0.001	0.21 (0.11–0.31)	<0.001
SAT area (per 10 cm²)	1.03 (0.98–1.08)	0.275	1.01 (0.94–1.10)	0.713	0.246	0.04 (–0.03–0.10)	0.265	0.02 (–0.04–0.09)	0.437
BMI (5.0 kg/m²)	1.10 (0.74–1.68)	0.641	1.05 (0.68–1.63)	0.829	0.682	0.33 (–0.21–0.88)	0.232	0.24 (–0.32–0.80)	0.398
WC (per 5.0 cm)	1.16 (0.99–1.37)	0.071	1.14 (0.97–1.35)	0.111	0.312	0.28 (–0.01–0.57)	0.056	0.18 (–0.03–0.40)	0.096
HMW adiponectin (per 1.00 μg/ml)	0.73 (0.60–0.87)	0.003	0.78 (0.64–0.96)	0.018	0.277	–0.52 (–0.76 to –0.30)	<0.001	–0.35 (–0.59 to –0.12)	0.003
Total adiponectin (per 1.00 μg/ml)	0.93 (0.87–0.99)	0.043	0.95 (0.88–1.02)	0.158	0.111	–0.14 (–0.24 to –0.05)	0.003	–0.08 (–0.18–0.01)	0.070
Leptin (per 1.00 ng/ml)	1.06 (0.99–1.13)	0.096	1.05 (0.98–1.12)	0.112	0.271	0.07 (–0.01–0.16)	0.080	0.06 (–0.02–0.14)	0.131

*Adjusted for age, hypertension, hypercholesterolemia, diabetes mellitus, and current smoking.
OR, odds ratio; CI, confidence interval; HLT, Hosmer-Lemeshow test. Other abbreviations as in Table 1.

men). The median segment number of coronary plaque was 4 (1–6) and 2 (0–4) in men and women, respectively, and the median calcium score was 74 (2–354) and 34 (0–182) in men and women, respectively. The numbers of patients with NCP with PR, low CT density, and adjacent spotty calcium were 187 (47%, 122 men), 174 (44%, 115 men), and 153 (39%, 99 men), respectively. A total of 108 patients (27%, 70 men) had NCP with all 3 vulnerable characteristics.

HMW adiponectin concentrations in patients with obstructive CAD were significantly lower than in those without obstructive CAD [men: 1.45 (0.80–2.24) vs. 1.88 (1.36–2.70) μg/ml, P=0.002; women: 2.49 (1.49–3.41) vs. 3.44 (2.57–5.17) μg/ml, P<0.001, respectively]. HMW adiponectin concentrations in men were significantly lower than those in women both with and without obstructive CAD (P<0.001). Coronary calcium scores and involved segment numbers of NCP were inversely correlated with HMW adiponectin concentrations in both genders (**Figure S1**). In addition, coronary calcium scores (men: P=0.045, women: P=0.037) and involved segment numbers of NCP (men: P=0.001, women: P<0.001) gradually decreased across the tertiles of HMW adiponectin concentrations in both genders (**Figure 1**). The frequencies of patients with NCP with PR, low CT density, spotty calcium, and all 3 characteristics also gradually decreased across the tertiles of HMW adiponectin concentrations in both genders (**Figure 2**).

Associations of Plasma Adipokines and Obesity-Related Measurements With the Presence and Extent of Coronary Plaques

In univariate analyses, increased VAT area and lower total and HMW adiponectin concentrations were significantly associated with the presence and extent of coronary plaques in both genders. Furthermore, multivariate analyses revealed that increased VAT area and lower HMW adiponectin concentrations were significantly related to the presence and extent of coronary plaques in both genders. The adjusted odds ratios of HMW adiponectin concentrations (per 1.00 μg/ml) for the presence of coronary plaques were 0.74 (P=0.019) and 0.78 (P=0.018) in men and women, respectively, and those of VAT area (per 10 cm²) were 1.29 (P<0.001) and 1.19 (P=0.001) in men and women, respectively. The adjusted β-estimates of HMW adiponectin concentrations for the extent of coronary plaques were –0.48 (P=0.001) and –0.35 (P=0.003) in men and women, respectively, and those of VAT area were 0.43 (P<0.001) and 0.21 (P<0.001) in men and women, respectively (**Table 3**).

Associations of Plasma Adipokines and Obesity-Related Measurements With NCP Characteristics

In univariate analyses, increased VAT area and lower total and HMW adiponectin levels were significantly associated with the presence of NCP with all 3 characteristics in both genders.

Table 4. Associations of Plasma Adipokines and Obesity-Related Measurements With the Presence and Characteristics of NCP

Term	NCP					All 3 characteristics				
	Univariate		Multivariate*			Univariate		Multivariate*		
	OR (95%CI)	P-value	OR (95%CI)	P-value	P-value (HLT)	OR (95%CI)	P-value	OR (95%CI)	P-value	P-value (HLT)
Men										
VAT area (per 10 cm^2)	1.25 (1.13–1.40)	<0.001	1.20 (1.08–1.35)	0.001	0.111	1.27 (1.17–1.40)	<0.001	1.22 (1.12–1.35)	<0.001	0.529
SAT area (per 10 cm^2)	0.95 (0.88–1.03)	0.192	0.97 (0.89–1.05)	0.381	0.509	1.00 (0.93–1.07)	0.942	1.00 (0.92–1.08)	0.997	0.945
BMI (per 5.0 kg/m^2)	1.08 (0.54–1.62)	0.793	1.07 (0.58–1.95)	0.836	0.100	1.21 (0.74–1.98)	0.446	1.07 (0.64–1.79)	0.805	0.608
WC (per 5.0 cm)	1.04 (0.85–1.28)	0.687	1.02 (0.82–1.27)	0.870	0.397	1.15 (0.94–1.40)	0.098	1.12 (0.92–1.38)	0.225	0.215
HMW adiponectin (per 1.00 μg/ml)	0.73 (0.58–0.91)	0.006	0.76 (0.60–0.96)	0.023	0.486	0.66 (0.49–0.86)	0.001	0.72 (0.54–0.95)	0.019	0.165
Total adiponectin (per 1.00 μg/ml)	0.91 (0.83–0.99)	0.042	0.93 (0.84–1.02)	0.102	0.216	0.89 (0.80–0.98)	0.019	0.92 (0.83–1.01)	0.088	0.264
Leptin (per 1.00 ng/ml)	1.09 (0.98–1.25)	0.118	1.07 (0.95–1.22)	0.233	0.408	1.03 (0.93–1.08)	0.821	1.00 (0.92–1.09)	0.998	0.945
Women										
VAT area (per 10 cm^2)	1.29 (1.18–1.44)	<0.001	1.26 (1.13–1.40)	<0.001	0.304	1.23 (1.13–1.36)	<0.001	1.20 (1.08–1.32)	0.001	0.846
SAT area (per 10 cm^2)	1.03 (0.99–1.08)	0.150	1.04 (0.99–1.09)	0.142	0.241	1.00 (0.95–1.05)	0.900	1.02 (0.96–1.07)	0.571	0.957
BMI (per 5.0 kg/m^2)	1.29 (0.88–1.95)	0.197	1.14 (0.74–1.75)	0.559	0.959	1.37 (0.89–2.13)	0.146	1.29 (0.81–2.06)	0.278	0.906
WC (per 5.0 cm)	1.15 (0.98–1.36)	0.096	1.14 (0.97–1.36)	0.119	0.794	1.16 (0.98–1.38)	0.092	1.13 (0.95–1.37)	0.173	0.963
HMW adiponectin (per 1.00 μg/ml)	0.70 (0.58–0.84)	<0.001	0.75 (0.61–0.92)	0.006	0.571	0.62 (0.47–0.80)	<0.001	0.70 (0.53–0.94)	0.016	0.638
Total adiponectin (per 1.00 µg/ml)	0.92 (0.87–0.99)	0.017	0.94 (0.88–1.01)	0.087	0.419	0.89 (0.81–0.97)	0.011	0.92 (0.84–1.02)	0.096	0.449
Leptin (per 1.00 ng/ml)	1.05 (0.99–1.13)	0.105	1.04 (0.97–1.13)	0.206	0.895	1.03 (0.98–1.09)	0.190	1.02 (0.96–1.08)	0.467	0.551

*Adjusted for age, hypertension, hypercholesterolemia, diabetes mellitus, and current smoking.
Abbreviations as in Tables 1–3.

Multivariate analyses revealed that lower HMW adiponectin concentrations and increased VAT area were significantly related to the presence of NCP with all 3 characteristics in both genders. In contrast, there were no significant associations between NCP characteristics with total adiponectin concentrations, leptin concentrations, body mass index, waist circumference, or SAT area (Table 4).

Comparison of Plasma Adipokines, VAT Area, and FRS for Prediction of the Presence and Vulnerable Characteristics of NCP

All AUC of VAT area and HMW adiponectin levels for prediction of the presence and vulnerable characteristics of NCP were significantly larger than those of total adiponectin concentrations and leptin concentrations in both genders. Moreover, the AUC of VAT areas were significantly larger or tended to be larger than those of HMW adiponectin concentrations (Figure 3). The optimal cut-off values of HMW adiponectin concentrations for the presence of NCP with all 3 characteristics were 0.98 μg/ml and 2.29 μg/ml in men and women, respectively. With these cut-off values, the sensitivities and specificities were 44% and 85% in men and 62% and 68% in women, respectively. Furthermore, the AUC of HMW adiponectin concentrations plus FRS in prediction of the presence of NCP were 0.73 and 0.72 in men and women, respectively, and those in prediction of the presence of NCP with all 3 characteristics were 0.71 and 0.76 in men and women, respectively. These values were significantly larger than those of FRS in both genders, whereas were not significantly different to those of VAT area in both genders (Figure 4).

Discussion

The present study demonstrates that lower plasma HMW adiponectin is significantly associated with the presence and extent of coronary plaques as assessed by CTA in patients with suspected CAD, whereas plasma total adiponectin and leptin concentrations do not have these associations. Furthermore, lower plasma HMW adiponectin is associated with the presence of NCP with vulnerable characteristics.[13,14] These results suggest that, of various adipokines, lower plasma HMW adiponectin could be involved in coronary atherosclerosis and changes in NCP characteristics in conditions of VAT accumulation.

HMW Adiponectin Concentrations and Coronary Atherosclerosis

Our gender-specific study demonstrated that lower plasma HMW adiponectin was closely related to the presence, extent, and vulnerable characteristics of coronary plaques in both genders. Previous studies have documented that men have lower adiponectin concentrations than do women regardless

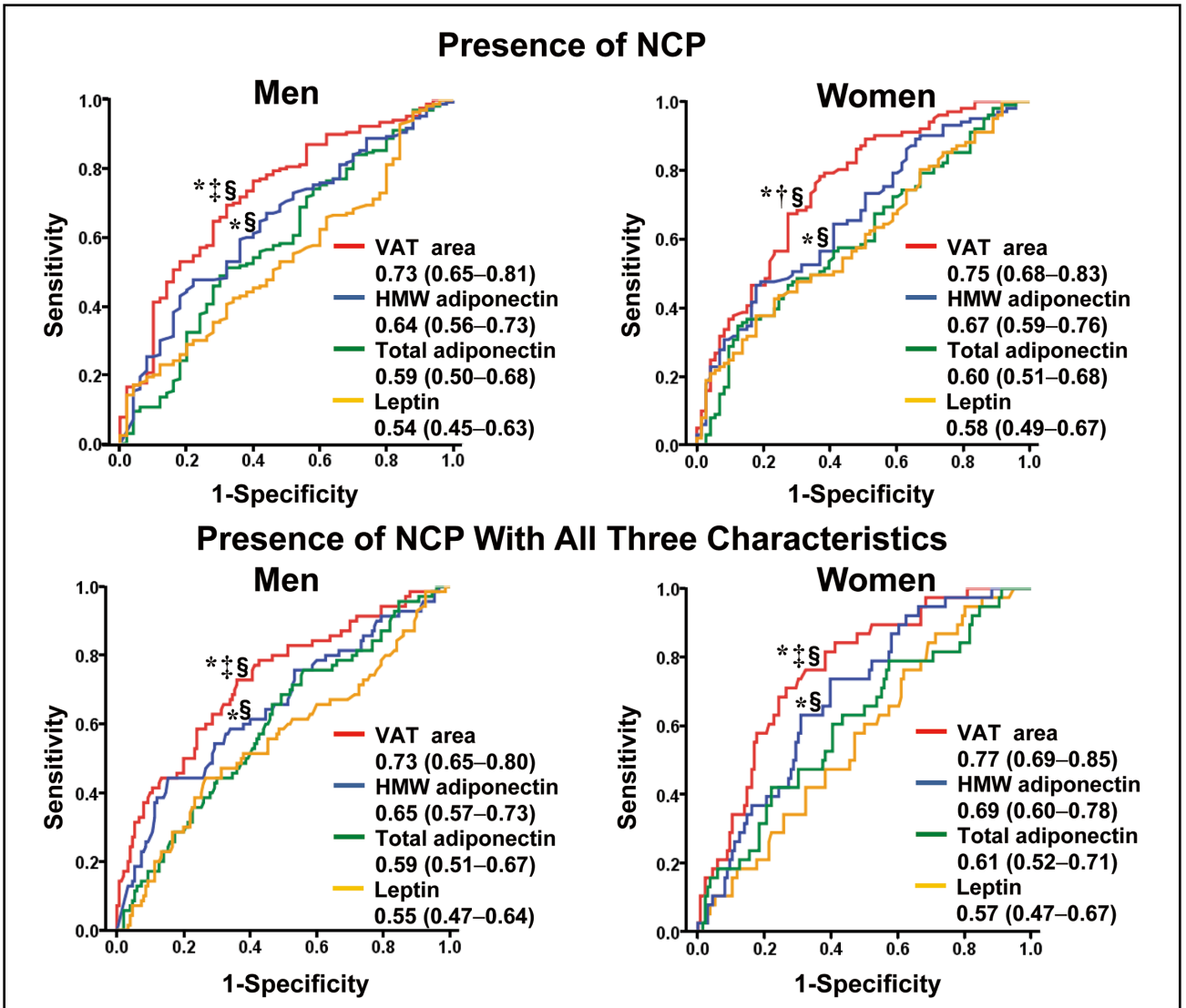

Figure 3. Receiver-operating characteristic curves for prediction of the presence of non-calcified coronary plaque (NCP) and NCP with all 3 vulnerable characteristics.Areas under the curves (AUC) (95% confidence interval) of visceral adipose tissue (VAT) area (red lines), high-molecular-weight (HMW) adiponectin concentrations (blue lines), and leptin concentrations (green lines) were compared in each panel. *P<0.05 vs. AUC of leptin, †P<0.05 and ‡P<0.10 vs. AUC of HMW adiponectin, §P<0.05 vs. AUC of total adiponectin.

of whether they have CAD.[23] We also showed that HMW adiponectin concentrations in men were significantly lower than those in women both with and without CAD.

There are many pathways by which lower plasma adiponectin is causally linked to atherosclerosis. Some possible mechanisms are that plasma adiponectin reduces expression of adhesion molecules in endothelial cells,[24] inhibits macrophage to foam cell transformation, specifically increases tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in macrophages,[25] and suppresses the proliferation and migration of smooth muscle cells.[26] In addition, insulin resistance, which is promoted by lower plasma adiponectin, is thought to accelerate atherogenesis and atherosclerotic plaque instability by inducing proinflammatory activity in vascular and immune cells.[27]

Clinical studies have demonstrated that lower concentrations of plasma adiponectin are related to the extent of angiographic CAD[5,6] and predict progression of coronary artery calcification.[28] We also found a significant association between lower plasma HMW adiponectin and the presence of NCP. Previous CTA studies documented that the presence of NCP, regardless of stenotic severity in lesions, was the strongest predictor of acute cardiac events[29] and that the number of NCP with a calcified component (namely, mixed plaques) was an independent predictor of acute cardiac events.[30]

Broedl et al suggested that serum adiponectin was an independent predictor of NCP as assessed by CTA and might thus contribute to coronary plaque vulnerability.[31] In contrast, we assessed more detailed components of coronary plaques. Interestingly, we clarified that plasma HMW adiponectin was more associated with NCP characteristics than total adiponectin. We have also reported that NCP with these characteristics

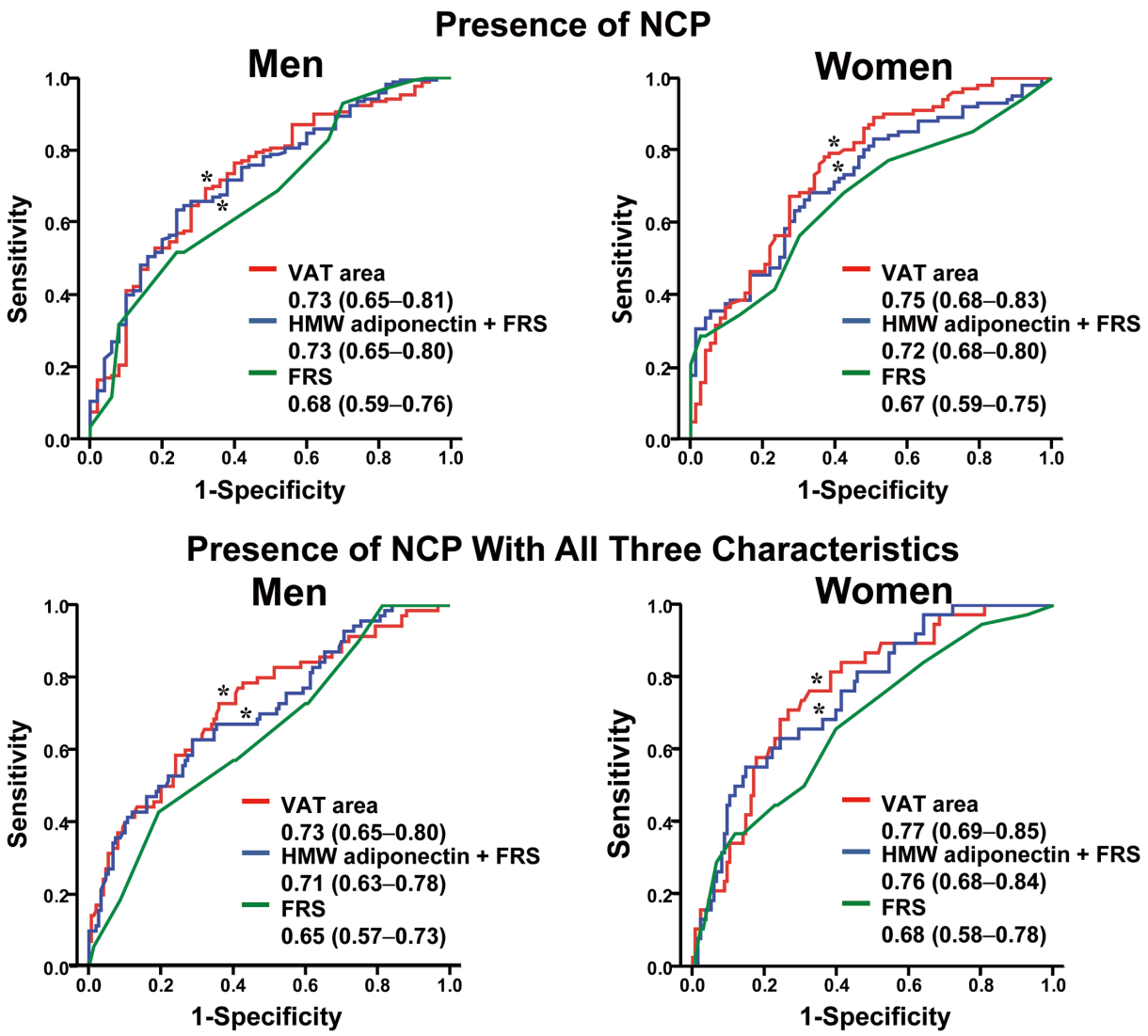

Figure 4. Receiver-operating characteristic curves of visceral adipose tissue (VAT) area, addition of high-molecular-weight (HMW) adiponectin concentrations to Framingham risk score (FRS), and FRS and predictive values for the presence of non-calcified coronary plaque (NCP) and NCP with all 3 characteristics. Areas under the curves (AUC) (95% confidence interval) of VAT area (red lines), addition of HMW adiponectin concentrations to FRS (blue lines), and FRS (green lines) were compared in each panel. *P<0.05 vs. AUC of FRS.

are frequently observed in patients with acute coronary syndrome[14] and in those with VAT accumulation[16] and are inversely related to the effects of lipid-lowering therapy.[32] A recent CTA study has shown that the presence of low-CT-density plaque with PR is highly predictive of acute cardiac events.[33] These results strongly support the notion that lower plasma HMW adiponectin is associated with both vulnerable characteristics and extent of coronary plaques.

Comparison of Plasma Adipokines and VAT Area for Prediction of Coronary Atherosclerosis

We showed that HMW adiponectin concentrations are more useful than total adiponectin and leptin concentrations for predicting the presence and vulnerable characteristics of coronary plaques. Previous studies indicated that HMW adiponectin, rather than total adiponectin, was associated with the extent of CAD[6] and increased arterial stiffness.[9] The current results are consistent with the notion that HMW adiponectin might have higher biologic activity than other types of adiponectin. In addition, plasma adiponectin and leptin have been shown to have inverse relationships to coronary atherosclerosis. Dubey et al reported that higher levels of plasma leptin were related to the complexity of culprit lesions in patients with unstable angina.[34] However, plasma leptin concentrations were not independently associated with coronary atherosclerosis. The differences between the subjects (suspected CAD vs. unstable angina) might explain this discrepancy with previous studies.

Our ROC analyses also demonstrate that the predictive power of VAT area is significantly higher or tends to be higher than that of plasma adiponectin in the prediction of the presence and characteristics of NCP. Our colleagues, Ohashi

et al, previously indicated that the VAT area was a better predictor of arterial stiffness as assessed by cardio-ankle vascular index measurements than were adiponectin levels.[9] However, the measurement of VAT area by CT requires special equipment and radiation exposure. Otherwise, the AUC of HMW adiponectin concentrations in prediction of the presence of NCP (0.64–0.73 and 0.67–0.72 in men and women, respectively) and NCP characteristics (0.65–0.71 and 0.69–0.76 in men and women, respectively) increased after adding FRS. These combined values of HMW adiponectin concentrations and traditional coronary risk assessments of FRS were significantly higher than those of FRS alone, and were similar to those of VAT area in both genders. Thus, in metabolic syndrome caused by VAT accumulation, plasma HMW adiponectin might help to identify patients at high-risk for CAD.

Study Limitations

The potential effects of confounding factors such as impaired glucose tolerance, insulin resistance, and other adipokines on coronary plaque and HMW adiponectin concentrations have not been fully evaluated. This was a cross-sectional study. A longitudinal prospective study is needed to investigate whether plasma adiponectin and leptin concentrations have predictive values to detect patients with coronary atherosclerosis and future coronary events and whether coronary plaque burden and its characteristics are affected by changes in plasma adiponectin or leptin concentrations through reduction of VAT or pharmacologic interventions.

Conclusions

Lower plasma HMW adiponectin is associated with the presence, extent, and vulnerable characteristics of coronary plaques as assessed by coronary CTA in patients with suspected CAD. We suggest that plasma HMW adiponectin might be involved in the atherogenic process in conditions of VAT accumulation. Furthermore, the combined assessments of plasma HMW adiponectin and traditional coronary risk factors, as well as VAT area, can be useful in identifying patients at high-risk for CAD.

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Disclosures

Conflict of interest: None.

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Supplementary Files

Supplementary File 1

Figure S1. Dot-plot graphs of the associations between coronary calcium score and the extent of coronary plaques with high-molecular-weight (HMW) adiponectin concentrations.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circj.CJ-11-1442