Hypoadiponectinemia is Associated With Impaired Glucose Tolerance and Coronary Artery Disease in Non-Diabetic Men

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Background Impaired glucose tolerance (IGT) is a significant risk factor for cardiovascular disease, but is not always recognized in the clinical setting. An anti-atherogenic adipocytokine, adiponectin, is decreased in type 2 diabetes mellitus, but its role in non-diabetic subjects has not been clarified. The hypothesis investigated in the present study was that plasma adiponectin levels correlate with IGT and coronary artery disease (CAD) in non-diabetic men.

Methods and Results Glucose intolerance was evaluated by an oral glucose tolerance test and plasma adiponectin levels were measured in 232 non-diabetic men who underwent coronary angiography. Patients with IGT (n=102) had significantly lower adiponectin levels than those with normal glucose tolerance (n=130) (4.47 [3.23–6.39] vs 5.85 [3.99–8.65] $\mu\text{g/ml}$, $p=0.003$). Plasma adiponectin levels were associated with IGT in multiple logistic regression analysis (odds ratio (OR) 0.623, 95% confidence interval (CI) 0.397–0.980; $p=0.041$). Non-diabetic patients with CAD (n=122) had lower adiponectin levels than those without CAD (n=110) (4.60 [3.32–6.38] vs 6.08 [4.10–9.88] $\mu\text{g/ml}$, $p<0.001$). Multiple logistic regression analysis demonstrated adiponectin independently correlated with the presence of CAD (OR 0.432, 95% CI 0.256–0.728; $p=0.002$).

Conclusions Hypoadiponectinemia is associated with IGT and CAD in non-diabetic men, suggesting that the adiponectin level can provide valuable information regarding the risk of CAD even in non-diabetic subjects. (Circ J 2007; 71: 1703–1709)

Key Words: Adiponectin; Coronary artery disease; Impaired glucose tolerance; Non-diabetic patients

Type 2 diabetes mellitus (T2DM) is an established risk factor for cardiovascular disease, and is associated with a significantly worse prognosis in patients with coronary artery disease (CAD).¹ However, even in non-diabetic subjects, those with postprandial hyperglycemia are known to have an increased risk of cardiovascular events.² Postprandial hyperglycemia in non-diabetic subjects is defined as impaired glucose tolerance (IGT) following an oral glucose tolerance test (OGTT), and IGT is considered a pre-stage of the onset of T2DM. Studies have revealed that IGT, but not impaired fasting glucose, is strongly associated with cardiovascular disease risk,^{2,3} but IGT is not always recognized in the clinical setting because these patients often have normal fasting blood glucose levels and need an OGTT to be detected.

Adiponectin, an adipocyte-derived plasma protein, has antidiabetic properties and plays an important role in the development of T2DM. Plasma levels of adiponectin are

significantly decreased in patients with T2DM⁴ and conversely, high levels of adiponectin are independently associated with a reduced risk of the future onset of T2DM in apparently healthy subjects.⁵ In addition, there is increasing evidence that adiponectin has anti-atherogenic properties,⁶ and we recently reported a significant inverse association between plasma adiponectin levels and atherosclerotic burden.⁷ Low levels of adiponectin are known to be associated with CAD⁸ and increased risk of future myocardial infarction.⁹ Thus, hypoadiponectinemia is thought to be involved in the development of T2DM and atherosclerotic disease. However, the importance of adiponectin in non-diabetic subjects remains to be elucidated.

The hypothesis tested in the present study was that plasma levels of adiponectin are already decreased in patients with IGT and adiponectin levels can predict CAD in non-diabetic subjects. To investigate this, we evaluated glucose intolerance by an OGTT and measured plasma levels of adiponectin in non-diabetic men with or without CAD.

Methods

Study Population

The study subjects were non-diabetic men who underwent coronary angiography at Kumamoto University Hospital from January 2000 through June 2005 because of an abnormality on ECG or angina-like symptoms. All patients underwent a 75-g OGTT. Selective coronary angiography

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Table 1 Baseline Clinical Characteristics of 232 Non-Diabetic Men

	NGT (n=130)	IGT (n=102)	p value
Age (years)	66.3±9.4	64.3±9.8	0.115
BMI (kg/m ²)	23.0±2.9	24.4±2.9	<0.001
Current smoking	37 (28)	24 (24)	0.454
Hypertension	67 (52)	73 (72)	0.003
Systolic BP (mmHg)	128.3±18.6	133.5±19.5	0.039
Diastolic BP (mmHg)	75.2±10.0	78.9±12.4	0.013
Total cholesterol (mg/dl)	185.3±37.3	188.9±33.3	0.448
HDL-cholesterol (mg/dl)	51.9±16.0	47.5±12.8	0.023
LDL-cholesterol (mg/dl)	117.6±31.0	122.9±30.9	0.196
Triglycerides (mg/dl)	99.0 (70.0–131.5)	123.0 (88.0–160.0)	0.003
Hypercholesterolemia	55 (43)	49 (48)	0.492
Fasting glucose (mg/dl)	88.1±7.9	91.2±8.7	0.005
Fasting insulin (μU/ml)	6.2±3.5	7.8±4.8	0.002
2-h glucose (mg/dl)	104.9±23.0	165.4±19.3	<0.001
2-h insulin (μU/ml)	48.0±40.2	110.2±90.4	<0.001
Hemoglobin A _{1c} (%)	5.27±0.40	5.43±0.44	0.005
HOMA-IR	1.35±0.81	1.77±1.11	<0.001
HOMA-I (%)	97.3±67.4	108.5±75.6	0.234
Adiponectin (μg/ml)	5.83 (4.10–8.41)	4.42 (3.26–5.98)	<0.001
Creatinine (mg/dl)	0.94±0.22	0.93±0.21	0.656
hs-CRP (mg/L)	0.70 (0.40–1.50)	0.80 (0.50–2.10)	0.115
Family history of MI	34 (26)	24 (24)	0.760
History of OMI	16 (12)	20 (20)	0.146
LVEF (%)	64.0±14.9	66.2±12.5	0.253
CAD	59 (45)	63 (62)	0.019
Medications			
-blockers	25 (19)	13 (13)	0.252
Calcium antagonists	62 (48)	65 (64)	0.021
ACE inhibitors	31 (24)	27 (26)	0.760
ARB	17 (13)	17 (17)	0.562
Nitrates	29 (22)	31 (30)	0.213
Aspirin	59 (45)	57 (56)	0.146
HMG-CoA reductase inhibitors	27 (21)	28 (27)	0.302

Values are mean±SD or median value (25th to 75th percentile range) or n (%).

NGT, normal glucose tolerance; IGT, impaired glucose tolerance; BMI, body mass index; BP, blood pressure; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-I, homeostasis model assessment of pancreatic β -cell function; hs-CRP, high-sensitivity C-reactive protein; MI, myocardial infarction; OMI, old MI; LVEF, left ventricular ejection fraction; CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARBs, angiotensin II receptor blockers.

Fig 1. (a) Box-and-whisker plot showing plasma levels of adiponectin in men with normal glucose tolerance (NGT) and impaired glucose tolerance (IGT). (b) Box-and-whisker plot showing plasma levels of adiponectin in non-diabetic men with (n=122) and without (n=110) coronary artery disease (CAD). (c) Box-and-whisker plot showing plasma levels of adiponectin in men with NGT and IGT, with and without CAD. In these plots, lines within boxes represent median values; the upper and lower borders of the boxes represent the 75th and 25th percentiles, respectively; and the upper and lower bars outside the boxes represent the 90th and 10th percentiles, respectively.

Table 2 Logistic Regression Analysis for IGT in Non-Diabetic Men

Factor	Simple regression		Multiple regression	
	OR (95%CI)	p value	OR (95%CI)	p value
Age (per year)	0.978 (0.952–1.005)	0.115	0.989 (0.958–1.020)	0.485
BMI (per kg/m ²)	1.187 (1.078–1.306)	0.001	1.092 (0.978–1.220)	0.116
Current smoking (yes)	0.773 (0.426–1.403)	0.398		
Hypertension (yes)	2.367 (1.364–4.106)	0.002	2.183 (1.204–3.957)	0.010
Total cholesterol (per mg/dl)	1.003 (0.996–1.010)	0.446		
HDL-cholesterol (per mg/dl)	0.978 (0.959–0.997)	0.026	0.993 (0.972–1.015)	0.521
LDL-cholesterol (per mg/dl)	1.006 (0.997–1.014)	0.196		
Triglycerides (per doubling)	1.760 (1.165–2.660)	0.007	1.275 (0.649–2.503)	0.481
Fasting glucose (per mg/dl)	1.047 (1.014–1.082)	0.005	1.034 (0.998–1.071)	0.066
Adiponectin (per doubling)	0.464 (0.315–0.684)	<0.001	0.623 (0.397–0.980)	0.041
hs-CRP (per doubling)	1.125 (0.954–1.327)	0.160		

OR, odds ratio; CI, confidence interval. Other abbreviations as in Table 1.

was performed using the Judkins technique, and CAD was defined as an organic stenosis $\geq 75\%$ in at least 1 of the major coronary arteries. Patients with acute coronary syndromes were excluded from the study, as were patients with malignant disease, infectious disease, chronic inflammatory disease, autoimmune disease, and advanced renal disease (serum creatinine level >2.5 mg/dl). Among 269 men fulfilling the criteria, 37 were excluded because they were diagnosed as having DM following an OGTT. Accordingly, this study enrolled 232 consecutive non-diabetic men. Written informed consent was given by each patient before participation in the study. The study was performed in accordance with the ethics principles in the Declaration of Helsinki and the study protocol was approved by the ethics committee of our institution.

OGTT

A 75-g OGTT was performed after an overnight fast in order to identify patients with IGT or normal glucose tolerance (NGT) as defined by the criteria of the World Health Organization (IGT: fasting glucose level <126 mg/dl, 140 mg/dl $\leq$ 2-h post-load glucose level <200 mg/dl; NGT: fasting glucose level <110 mg/dl, 2-h post-load glucose level <140 mg/dl).¹⁰ The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as: $\text{HOMA-IR} = (\mu\text{U/ml} \times \text{mg/dl}) / (405)$.¹¹ The homeostasis model assessment of pancreatic β -cell function (HOMA-I) was calculated as: $\text{HOMA-I} = [\mu\text{U/ml}/(\text{mg/dl})] = (\text{fasting insulin} \times 360) / (\text{fasting glucose} - 63)$.¹¹

Blood Sampling and Measurement of Plasma Adiponectin

Venous blood samples were obtained in the early morning from all subjects after a 12-h fast. Plasma samples were immediately stored at -80°C for subsequent assay of adiponectin levels by enzyme-linked immunosorbent assay (adiponectin ELISA kit, Otsuka Pharmaceutical, Tokyo, Japan) as described previously.^{7,12}

Statistical Analysis

Results for normally distributed continuous variables are expressed as the mean value $\pm$ SD, and those for continuous variables with skewed distributions are expressed as the median value (interquartile range). Comparisons of continuous variables were analyzed with the unpaired t-test and the Mann-Whitney U-test, as appropriate. Categorical variables are presented by frequency counts, and intergroup comparisons were analyzed by a χ^2 test. Associations between the

presence of IGT and CAD risk factors including high-sensitivity C-reactive protein (hs-CRP), and those between the presence of CAD and all other parameters were first analyzed by simple logistic regression analysis and then by multivariate analysis, in which age and significant factors in the univariate analysis were entered. The base-2 logarithms ($\log_2$) of the plasma levels of adiponectin, triglycerides, and hs-CRP were used in all the logistic regression analyses to account for a skewed distribution of these parameters.¹³ Thus, odds ratios (ORs) for these variables reflect the change in odds for an increase of 1 $\log_2$ (the equivalent of a doubling of the value) in the measured value. Comparisons of plasma levels of adiponectin in patients with NGT or IGT, with or without CAD, were assessed by the Kruskal-Wallis and the Mann-Whitney U-tests. Incremental effects on the prevalence of CAD of the combination of hypercholesterolemia and lower levels of adiponectin (or IGT) were also evaluated by a χ^2 test. Hypercholesterolemia was defined as low-density lipoprotein-cholesterol levels >140 mg/dl or use of HMG-CoA reductase inhibitors, and lower levels of adiponectin were arbitrarily defined as <5.00 $\mu\text{g/ml}$, the 50th percentile of the distribution of adiponectin levels in the study patients. Statistical significance was defined as $p < 0.05$. All analyses were performed using Stat View-5.0 software (SAS Institute Inc, Cary, NC, USA).

Results

Adiponectin and IGT

The baseline clinical characteristics of the 232 non-diabetic men are summarized in Table 1. Patients with IGT ($n=102$) had a significantly higher body mass index (BMI), incidence of hypertension, triglycerides, fasting glucose, fasting insulin, hemoglobin A_{1c} (HbA_{1c}), HOMA-IR, and prevalence of CAD, and a significantly lower high-density lipoprotein (HDL)-cholesterol level than patients with NGT (Table 1). Plasma levels of adiponectin in patients with IGT were significantly lower than those in patients with NGT (4.42 [3.26–5.98] vs 5.83 [4.10–8.41] $\mu\text{g/ml}$, $p < 0.001$) (Table 1; Fig 1a). In simple logistic regression analysis, BMI, hypertension, HDL-cholesterol, triglycerides, fasting glucose, and plasma adiponectin levels were significantly associated with IGT (Table 2). Multiple logistic regression analysis demonstrated that the plasma level of adiponectin was a significant independent determinant of IGT (OR 0.623, 95% confidence interval (CI) 0.397–0.980; $p=0.041$) (Table 2). In addition to the fasting glucose level, other glucose tolerance-related variables such as fasting insulin

Table 3 Logistic Regression Analysis for CAD in Non-Diabetic Men

Factor	Simple regression		Multiple regression	
	OR (95%CI)	p value	OR (95%CI)	p value
Age (per year)	1.047 (1.018–1.077)	0.001	1.091 (1.050–1.131)	<0.001
BMI (per kg/m ²)	1.077 (0.986–1.177)	0.098		
Current smoking (yes)	0.760 (0.423–1.365)	0.359		
Hypertension (yes)	2.477 (1.444–4.249)	0.001	2.066 (1.043–4.090)	0.037
Total cholesterol (per mg/dl)	1.001 (0.994–1.008)	0.835		
HDL-cholesterol (per mg/dl)	0.963 (0.942–0.983)	<0.001	0.973 (0.949–0.998)	0.033
LDL-cholesterol (per mg/dl)	1.004 (0.996–1.013)	0.319		
Triglycerides (per doubling)	1.757 (1.161–2.660)	0.008	1.496 (0.869–2.576)	0.146
Hypercholesterolemia (yes)	3.749 (2.159–6.507)	<0.001	3.202 (1.657–6.187)	<0.001
Fasting glucose (per mg/dl)	1.015 (0.984–1.047)	0.344		
Fasting insulin (per μ U/ml)	1.043 (0.978–1.112)	0.202		
2-h glucose (per mg/dl)	1.009 (1.001–1.016)	0.020	1.001 (0.991–1.011)	0.805
2-h insulin (per μ U/ml)	1.004 (1.000–1.007)	0.073		
Hemoglobin A _{1c} (per %)	1.166 (0.624–2.179)	0.631		
HOMA-IR (per count)	1.231 (0.929–1.632)	0.147		
HOMA-I (per %)	0.999 (0.996–1.003)	0.755		
Adiponectin (per doubling)	0.366 (0.244–0.550)	<0.001	0.432 (0.256–0.728)	0.002
hs-CRP (per doubling)	1.189 (1.005–1.406)	0.043	1.145 (0.927–1.414)	0.208
Family history of MI (yes)	1.714 (0.932–3.152)	0.083		

Abbreviations as in Tables 1,2.

Fig 2. (a) Bar graph showing incremental effect on the prevalence of coronary artery disease (CAD) of the combination of hypercholesterolemia (low-density lipoprotein-cholesterol levels >140 mg/dl or use of HMG-CoA reductase inhibitors) and impaired glucose tolerance (IGT). (b) Bar graph showing incremental effect on the prevalence of CAD of the combination of hypercholesterolemia and lower levels of adiponectin (<5.00 μ g/ml; arbitrarily defined as the 50th percentile of the distribution of adiponectin levels in the study patients). NGT, normal glucose tolerance; Hyper-Chol, hypercholesterolemia; Normo-Chol, normocholesterolemia; Low Adipo, low levels of adiponectin; High Adipo, high levels of adiponectin.

(OR 1.110, 95% CI 1.034–1.191; $p=0.004$), and HbA_{1c} (OR 2.550, 95% CI 1.315–4.944; $p=0.006$) were also significantly associated with IGT in simple logistic regression analysis. Multivariate analysis including these variables and the adiponectin levels revealed that HbA_{1c} (OR 2.258, 95% CI 1.088–4.688; $p=0.029$) and adiponectin (OR 0.532, 95% CI 0.352–0.805; $p=0.003$) were significantly and independently associated with IGT.

Adiponectin and CAD in Non-Diabetic Men

Non-diabetic patients with CAD ($n=122$) had significantly lower adiponectin levels than those without CAD ($n=110$) (4.45 [3.17–5.81] vs 6.32 [4.17–8.79] μ g/ml, $p<0.001$) (Fig 1b). Simple logistic regression analysis showed that age, hypertension, HDL-cholesterol, triglycerides, hypercholesterolemia, 2-h glucose, hs-CRP, and plasma adiponectin level were associated with CAD in non-diabetic men (Table 3). Multiple logistic regression analysis revealed that age (OR 1.091, 95% CI 1.050–1.131; $p<0.001$), hypertension (OR 2.066, 95% CI 1.043–4.090; $p=0.037$), HDL-cholesterol (OR 0.973, 95% CI 0.949–0.998; $p=0.033$), hypercholesterolemia (OR 3.202, 95% CI 1.657–6.187; $p<0.001$), and plasma adiponectin levels (OR 0.432, 95% CI 0.256–0.728; $p=0.002$) significantly and independently correlated with the presence of CAD in non-diabetic men (Table 3).

Adiponectin and CAD in Men With NGT or IGT

Among 130 men with NGT, those with CAD ($n=59$) had significantly lower plasma levels of adiponectin than those without CAD ($n=71$) (4.91 [3.40–7.24] vs 6.42 [4.55–9.35] μ g/ml, $p<0.001$) (Fig 1c). Moreover, among 102 men with IGT, plasma levels of adiponectin in the men with CAD ($n=63$) were also significantly lower than in the men without CAD ($n=39$) (3.97 [3.02–5.28] vs 4.91 [4.00–8.14] μ g/ml, $p=0.005$) (Fig 1c). Adiponectin levels in NGT patients with CAD were comparable to those in IGT patients without CAD.

Simple logistic regression analysis among the patients with NGT and those with IGT showed that plasma adiponectin levels were significantly associated with CAD (NGT:

crude OR 0.413, 95% CI 0.245–0.695, $p=0.001$; IGT: crude OR 0.349, 95% CI 0.175–0.694, $p=0.003$). After adjustment for age, BMI, smoking status, hypertension, HDL-cholesterol, triglyceride levels, and hypercholesterolemia, plasma levels of adiponectin remained a significant determinant of the presence of CAD in both groups of patients (NGT: adjusted OR 0.477, 95% CI 0.248–0.916, $p=0.026$; IGT: adjusted OR 0.237, 95% CI 0.090–0.621, $p=0.003$).

IGT, Lower Adiponectin, and CAD

Among 232 non-diabetic men, IGT was significantly associated with CAD in simple logistic regression analysis (OR 1.944, 95% CI 1.147–3.296; $p=0.014$). After adjustment for hypercholesterolemia, IGT remained a significant determinant of the presence of CAD in non-diabetic men (OR 1.929, 95% CI 1.106–3.364; $p=0.021$). In addition, IGT in combination with hypercholesterolemia showed a significant incremental effect on the risk of CAD in non-diabetic men ($p<0.001$) (Fig 2a).

When the cut-off value of adiponectin levels was defined as 5.00 $\mu\text{g/ml}$ (the 50th percentile of the distribution in the study patients), lower levels of adiponectin were significantly associated with CAD in simple logistic regression analysis (OR 2.160, 95% CI 1.278–3.652; $p=0.004$). Moreover, lower levels of adiponectin in combination with hypercholesterolemia demonstrated a significant incremental effect on the risk of CAD ($p<0.001$) (Fig 2b).

Discussion

In the present study, we demonstrated that men with IGT had significantly lower plasma adiponectin levels than those with NGT, and that non-diabetic men with CAD had significantly lower plasma adiponectin levels than those without CAD. Moreover, the plasma level of adiponectin was an independent determinant of IGT and CAD in non-diabetic men. These results suggest that plasma levels of adiponectin are already decreased in patients with IGT before the onset of overt diabetes, and that adiponectin levels may be a useful marker for identifying patients at high risk for CAD even in non-diabetic subjects.

It is well established that T2DM is a significant risk factor for cardiovascular disease; however, non-diabetic subjects with postprandial hyperglycemia (which is defined as IGT) are also at higher risk of cardiovascular disease.^{2,3} Previous studies demonstrated that adiponectin levels are decreased in patients with T2DM⁴ and CAD, including vasospastic angina.^{8,14,15} Individuals with high concentrations of adiponectin are less likely to develop T2DM,⁵ and lower adiponectin levels are significantly associated with the future development of myocardial infarction.⁹ Although these observations indicate that low levels of adiponectin may contribute to the development of T2DM and atherosclerotic disease, the importance of adiponectin in non-diabetic subjects has not been elucidated. In Pima Indians, it has been shown that adiponectin levels in subjects with IGT and early diabetes (≤ 10 years duration) were lower than in subjects with NGT.¹⁶ A recent study in Japanese Americans showed lower levels of adiponectin in IGT subjects than in NGT subjects, although the difference was not statistically significant.¹⁷ However, those studies included both men and women, and there is a significant gender difference in adiponectin levels.¹² Furthermore, precise evaluation including the presence or absence of CAD in non-diabetic subjects has not been performed.

In this study, we showed that men with IGT had significantly lower levels of adiponectin than those with NGT. Previous studies demonstrated a significant association between insulin resistance and IGT,¹⁸ however, the precise pathophysiology of IGT has not been well clarified. It is well known that plasma levels of adiponectin decrease with the accumulation of visceral adipose tissue,⁶ and in rhesus monkeys, adiponectin is reduced in parallel with progression of insulin resistance.¹⁹ In addition, increased serum concentrations of adiponectin have been shown to be associated with increased insulin sensitivity and glucose tolerance in humans.²⁰ Thus, decreased levels of adiponectin concomitant with visceral fat accumulation may lead to insulin resistance and the development of IGT, which is considered a pre-stage of T2DM.

We also demonstrated that non-diabetic men with CAD had significantly lower levels of adiponectin than those without CAD, and that the adiponectin level was an independent determinant of CAD, even in non-diabetic men. Although the precise mechanism of decreased adiponectin levels in patients with CAD has not been elucidated, it is conceivable that reduced levels of this anti-atherogenic molecule may lead to the development of atherosclerosis. Adiponectin could reduce atherosclerosis by inhibiting endothelial expression of adhesion molecules,²¹ macrophage-to-foam cell transformation²² and vascular smooth muscle cell proliferation.²³ In addition, we have reported a reduction of plasma adiponectin in the early phase of acute myocardial infarction,²⁴ and accumulation of adiponectin has been demonstrated in the walls of injured vessels but not in intact vessels.²² Therefore, increased consumption of circulating adiponectin in active atheroma might also bring about the reduction of adiponectin levels in patients with CAD.

Several lines of evidence demonstrate that IGT itself is a significant risk factor for cardiovascular disease. However, IGT is often not diagnosed in the clinical setting because of nearly normal fasting glucose levels and not performing an OGTT. In 2001, the National Cholesterol Education Program Adult Treatment Panel III introduced clinical criteria for defining the metabolic syndrome²⁵ in which fasting glucose levels were used to identify patients with glucose intolerance, because an OGTT is not routinely performed in the clinical setting. However, it has been shown that impaired fasting glucose is not significantly associated with cardiovascular events.^{2,3} Indeed, in the present study, which focused on non-diabetic subjects, the fasting blood glucose level was not a significant determinant of CAD in logistic regression analysis, whereas IGT was significantly associated with CAD. In identifying patients at high risk for CAD among non-diabetic subjects, it is important to detect IGT in addition to hypercholesterolemia, an established risk factor for CAD. In this study, we demonstrated a significant incremental effect on the prevalence of CAD of the combination of hypercholesterolemia and IGT, and similarly, hypercholesterolemia and hypo-adiponectinemia. From the viewpoint of CAD risk stratification in non-diabetic subjects, the significant association between adiponectin and IGT demonstrated in this study suggests that the measurement of adiponectin levels is a practical screening tool for IGT in the clinical setting, and can provide valuable information regarding the risk of CAD in non-diabetic subjects.

It has been reported that previously undiagnosed DM and IGT are frequently observed in patients with acute myo-

cardiac infarction at hospital admission²⁶ and such newly detected abnormal glucose tolerance is a strong predictor for future cardiovascular events.²⁷ Importantly, the treatment of IGT may prevent the development of overt diabetes²⁸ and IGT may be a modifiable risk factor for cardiovascular disease. A recent clinical study in Hispanic women with prior gestational diabetes demonstrated that treatment with thiazolidinedione, a peroxisome proliferator-activated receptor- α agonist, preserved pancreatic β -cell function and reduced the risk of the development of T2DM.²⁹ Our results suggest that there might be therapeutic potential of thiazolidinedione, which is known to increase adiponectin,³⁰ in patients with IGT and hypoadiponectinemia. Increasing adiponectin levels by thiazolidinedione may be a potentially useful therapeutic strategy to improve glucose tolerance and reduce the risk of cardiovascular events, even in non-diabetic subjects with hypoadiponectinemia. However, further prospective clinical studies are required to clarify these issues because we did not evaluate the effect of such agents in the present study.

The major limitations of this study are the relatively small sample size, as well as the specific study subjects who underwent coronary angiography. The present study population might not represent ordinal non-diabetic subjects, and thus further studies in a large number of general subjects are required to confirm our results. The definition of CAD in this study was an angiographic documented organic stenosis of $\geq 75\%$; however, it is currently recognized that evaluation of coronary plaque instability in addition to the degree of luminal stenosis, is important in assessing the risk of acute cardiovascular complications in patients with CAD. Thus, it is unclear whether the measurement of plasma adiponectin levels can be useful in predicting acute vascular complications in non-diabetic subjects. Moreover, we could not gather all the data regarding waist and hip circumferences, which reflect visceral and subcutaneous adiposity. Visceral fat accumulation is thought to cause insulin resistance, and whether lower levels of adiponectin correlate with IGT, independent of waist circumference, needs to be further evaluated.

In conclusion, men with IGT had significantly lower plasma adiponectin levels than those with NGT, and the adiponectin level was an independent determinant of CAD in non-diabetic men. Hypoadiponectinemia is significantly associated with IGT and CAD in non-diabetic men, and our results suggest that the measurement of adiponectin levels would be useful for the evaluation of IGT and provide valuable information regarding the risk of CAD even in non-diabetic subjects.

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