JACC: CARDIOVASCULAR IMAGING VOL. 1, NO. 1, 2008

ISSN 1936-878X/08/$34.00
PUBLISHED BY ELSEVIER DOI:10.1016/j.jcmg.2007.09.003

Abnormal Glucose Regulation Is Associated With Lipid-Rich Coronary Plaque

Relationship to Insulin Resistance

Tetsuya Amano, MD, PHD,* Tatsuaki Matsubara, MD, PHD,† Tadayuki Uetani, MD, PHD,* Michio Nanki, MD, PHD,* Nobuyuki Marui, MD, PHD,* Masataka Kato, MD,* Tomohiro Yoshida, MD,* Kosuke Arai, MD,* Kiminobu Yokoi, MD,* Hirohiko Ando, MD,* Soichiro Kumagai, MD,* Hideki Ishii, MD,‡ Hideo Izawa, MD, PHD,‡ Nigishi Hotta, MD, PHD,* Toyoaki Murohara, MD, PHD‡

Nagoya, Japan

OBJECTIVES This study sought to determine lipid and fibrous volume of coronary atherosclerotic plaques in subjects with abnormal glucose regulation (AGR) by integrated backscatter (IB) intravascular ultrasound (IVUS) during percutaneous coronary intervention.

BACKGROUND Abnormal glucose regulation, including impaired glucose regulation (IGR) and diabetes mellitus (DM), has emerged as an important determinant of cardiovascular risk. We hypothesized that AGR would be associated with coronary plaque instability.

METHODS Conventional intravascular ultrasound and IB-IVUS using a 40-MHz (motorized pullback 1 mm/s) intravascular catheter was performed in 172 consecutive patients. The percentage of fibrous area and the percentage of lipid area were automatically calculated by IB-IVUS. Three-dimensional analysis of IB-IVUS images was performed to determine the percentage of lipid volume (%LV) and fibrous volume (%FV). Following the World Health Organization criteria, the subjects were classified into the DM group, the IGR group, and the normal glucose regulation group. The cutoff point for the lipid-rich plaque was defined as %LV $>$44% or %FV $<$52%, which was the 75th percentile of %LV or the 25th percentile of %FV in this study population. Insulin resistance (IR) was defined as the homeostasis model assessment of insulin resistance (HOMA-IR).

RESULTS There were no significant differences in the baseline characteristics except for glucometabolic parameters. The conventional IVUS analysis indicated that the DM group had a significantly increased plaque volume (and percent plaque volume). In the IB-IVUS analysis, as compared with the normal glucose regulation group, the DM and the IGR groups showed a significant increase in %LV (36 $\pm$ 14% and 37 $\pm$ 13% vs. 29 $\pm$ 14%, $p = 0.02$) and a significant decrease in %FV (59 $\pm$ 11% and 58 $\pm$ 11% vs. 64 $\pm$ 11%, $p = 0.03$). The lipid-rich plaque rate was significantly associated with an increasing HOMA-IR in the tertile ($p = 0.008$). On logistic regression analysis after adjusting for confounding and coronary risk factors, the DM group (odds ratio 3.52, 95% confidence interval 1.13 to 11.0, $p = 0.03$) and the IGR group (odds ratio 3.92, 95% confidence interval 1.13 to 13.6, $p = 0.03$) were significantly associated with the lipid-rich plaque.

CONCLUSIONS Coronary lesions in patients with AGR are associated with more lipid-rich plaque content, which may be related to the increased IR in these patients. (J Am Coll Cardiol Img 2008;1: 39–45) © 2008 by the American College of Cardiology Foundation

From the *Department of Cardiology, Chubu-Rosai Hospital, †Department of Internal Medicine, School of Dentistry, Aichi-Gakuin University, and the ‡Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan.

Manuscript received August 30, 2007; revised manuscript received September 20, 2007, accepted September 24, 2007.

JACC: CARDIOVASCULAR IMAGING, VOL. 1, NO. 1, 2008
JANUARY 2008:39–45

Diabetes mellitus (DM) is a well-known risk factor for cardiovascular disease (CVD) (1–3). Recently, special emphasis has been given to impaired glucose regulation (IGR) as a risk factor in patients with as well as without frank DM (4,5). It has been proposed that macrovascular disease starts before the development of DM (6). Ultrasound studies measuring carotid intima-media thickness have shown the relevance of abnormal glucose regulation (AGR) in subclinical atherosclerosis and increased risk of CVD (7–9). Insulin resistance (IR), which mainly accounts for AGR, has also been shown to be related to adverse cardiovascular risk (10–12). We recently reported that the metabolic syndrome, which is predominantly based on IR and the cluster of comorbidities of AGR, is associated with the lipid-rich plaque contributing to the increasing risk of plaque vulnerability (13). Insulin resistance progressively increases when passing from normal glucose regulation (NGR) through IGR to DM. Few studies, however, have assessed the relevant detail of AGR or IR with coronary plaque morphology.

ABBREVIATIONS AND ACRONYMS

%FV = percentage of fibrous volume

%LV = percentage of lipid volume

ACS = acute coronary syndrome

AGR = abnormal glucose regulation

CSA = cross-sectional area

CVD = cardiovascular disease

DM = diabetes mellitus

EEM = external elastic membrane

HOMA-IR = homeostasis model assessment of insulin resistance

IB-IVUS = integrated backscatter intravascular ultrasound

IGR = impaired glucose regulation

IR = insulin resistance

LCSA = lumen cross-sectional area

NGR = normal glucose regulation

OGTT = oral glucose tolerance test

PCI = percutaneous coronary intervention

See page 46

In the present study, we assessed the hypothesis that AGR would be associated with a high content of plaque lipid (portending possible plaque instability) using the integrated backscatter (IB) intravascular ultrasound (IVUS) method to analyze coronary tissue components (13–15).

METHODS

Patients and study design. This study was a prospectively planned observational study for coronary lesions in patients with acute coronary syndrome (ACS) or stable angina pectoris who underwent percutaneous coronary intervention (PCI). Intravascular ultrasound was performed before PCI in 172 consecutive patients between September 2006 and June 2007.

Cardiovascular diagnoses. Acute coronary syndrome included acute myocardial infarction and unstable angina pectoris. The diagnosis of acute myocardial infarction was based on elevation of at least 1 positive biomarker (creatine kinase, creatine kinase-MB, or troponin T), characteristic electrocardiogram changes, and a history of prolonged acute chest pain. Unstable angina pectoris was defined as angina with a progressive crescendo pattern or angina that occurred at rest.

Glucometabolic parameters. Previously known DM was defined as a diagnosis based on the World Health Organization classification (16). The protocol recommended that all patients without previously diagnosed DM should undergo a standard oral glucose tolerance test (OGTT, 75 g). For acutely admitted patients, measurements of fasting blood glucose and insulin were to be taken in stable conditions before hospital discharge. Classification of glucometabolic state in patients without previously diagnosed DM was then made based on OGTT in a stable condition as following:

NGR = OGTT (0 min) <110 mg/dl and OGTT (2 h) <140 mg/dl

Impaired fasting glycemia = OGTT (0 min) ≥110 mmol/l but <126 mg/dl and OGTT (2 h) <140 mg/dl

Impaired glucose tolerance = OGTT (0 min) <126 mg/dl and OGTT (2 h) ≥140 mg/dl but <200 mg/dl

DM = OGTT (0 min) ≥126 mg/dl or OGTT (2 h) ≥200 mg/dl

In the text, IGR refers to both impaired fasting glycemia and impaired glucose tolerance. Abnormal glucose regulation includes IGR and DM. Insulin resistance was defined from the homeostasis model assessment of insulin resistance (HOMA-IR) according to the following formula: HOMA-IR = [fasting insulin concentration (μU/ml) · fasting glucose concentration (mg/dl)/405] (17). Various serum markers, including IR, were measured by commercial radioimmunoassay kits and specific immunoradiometric assay. For this purpose, blood samples were collected from patients before PCI after a 10- to 12-h overnight fast.

Definitions of analysis segments and measurements of IVUS parameters. Quantitative coronary angiography analysis was conducted. Reference diameter and percentage diameter stenosis were measured by a validated automated edge-detection program (CMS-MEDIS Medical Imaging System, Leiden, the Netherlands). Coronary lesions included the proximal and distal sites of the target lesions for PCI. The mean length of the analyzed segment was 37 mm (37 IB-IVUS images) per patient. Severe coronary lesions that could not be crossed by the IVUS catheter were excluded. Conventional 2-dimensional (2D) images were quantified for lumen cross-sectional area (LCSA), external elastic membrane (EEM), cross-sectional area (CSA), and

plaque (P) + media (M) CSA (P + M CSA = EEM CSA − LCSA) using the software of the IVUS system. An eccentricity index of P + M was calculated by the formula of (maximum P + M thickness − minimum P + M thickness)/maximum P + M thickness. A remodeling index was defined as a ratio of EEM CSA at the measured lesion (minimum luminal site) to reference EEM CSA (average of the proximal and distal reference segments). The 2D analysis referred to the segment with minimal luminal area. Three-dimensional (3D) analysis for conventional IVUS images was performed to compute vessel volume, lumen volume, and plaque volume (sum of EEM CSA, LCSA, and P + M CSA at 1-mm axial intervals for the analysis segments). The IB-IVUS analysis was performed as previously reported (13–15). In brief, a personal computer equipped with custom software (IB-IVUS, YD Co., Nara, Japan) was connected to the IVUS imaging system (Clear View, Boston Scientific, Natick, Massachusetts) to obtain radiofrequency signal trigger output. Ultrasound backscattered signals were acquired using a 40-MHz (motorized pullback 1 mm/s) mechanically rotating IVUS catheter, to be digitized and subjected to spectral analysis. Integrated backscatter values for each tissue component were calculated as an average power using a fast Fourier transform, measured in decibels, of the frequency component of backscattered signal from a small volume of tissue (13–15). The percentage of fibrous area (fibrous area/plaque area, %FA) and the percentage of lipid area (lipid area/plaque area, %LA) were automatically calculated by the IB-IVUS system (using commercially available software). The percentage of high signal area (a part of the calcification on the inner surface that could be measured with the formula of IB-IVUS/plaque area) was also calculated. The 3D analysis for IB-IVUS images was performed for fibrous volume, lipid volume, and high signal volume (sum of fibrous, lipid, and high signal area in each CSA at 1-mm axis intervals for the average of 37 IB-IVUS images per patient, respectively). Then the percentage of fibrous volume (fibrous volume/plaque volume, %FV), lipid volume (lipid volume/plaque volume, %LV) and high signal volume were calculated. The quantitative coronary angiography and IVUS measurements were conducted independently by 2 physicians who were blinded to the patient's clinical characteristics. The variability on %LV and %FV determined by 2 physicians was considered from 50 randomly selected records.

Statistical analyses. Statistical analysis was performed using the SAS statistical software package (version 8.02, SAS Institute Inc., Cary, North Carolina). Continuous and categorical variables were expressed as mean ± standard deviation and proportions, respectively. Comparisons of various clinical and IVUS parameters among the 3 groups were evaluated using analysis of variance, and a Bonferroni test was performed for multiple comparisons. We defined the cutoff point for the lipid-rich plaque as %LV >44% or %FV <52%, which was the 75th percentile of %LV or 25th percentile of %FV in the present study population (13,18). Following this definition, multivariate logistic regression analysis was applied to study the predictors of the lipid-rich plaque by adjusting for predefined variables. All variables with a p value

Table 1. Baseline Clinical Characteristics

	NGR (n = 38)	IGR (n = 44)	DM (n = 83)	p Value
Male	24 (63)	33 (77)	56 (68)	0.39
Age, yrs	68 ± 9	69 ± 10	69 ± 9	0.86
Clinical history				
Hypertension	26 (68)	30 (68)	55 (66)	0.96
Current smoker	10 (26)	10 (23)	24 (29)	0.76
Coronary artery disease				
Acute coronary syndrome	10 (26)	13 (30)	19 (23)	0.71
Old myocardial infarction	6 (16)	12 (27)	28 (34)*	0.06
Multiple vessel	19 (50)	23 (52)	52 (63)	0.33
Ejection fraction, %	68 ± 13	65 ± 12	66 ± 12	0.58
Fasting blood sugar, mg/dl	91 ± 11	114 ± 20†	146 ± 51‡	<0.0001
IRI, μU/ml	5 ± 4	12 ± 8†	12 ± 12§	0.002
HOMA-IR	1.1 ± 0.7	3.4 ± 3.0‖	4.2 ± 3.7‡	<0.0001
Blood lipid levels, mg/dl				
Total cholesterol	191 ± 32	190 ± 42	198 ± 35	0.46
Triglycerides	137 ± 63	147 ± 90	154 ± 95	0.61
HDL cholesterol	48 ± 10	46 ± 15	46 ± 12	0.68
LDL cholesterol	116 ± 28	119 ± 33	121 ± 29	0.71
C-reactive protein, mg/l	2.7 ± 4.3	4.3 ± 8.5	3.7 ± 7.0	0.61
Medication				
Aspirin	34 (90)	42 (96)	78 (94)	0.53
Ticlopidine	23 (61)	31 (71)	53 (64)	0.63
Statins	21 (55)	21 (48)	35 (42)	0.41
ACE-I/ARB	18 (47)	21 (48)	39 (47)	>0.99
Nitrates	33 (87)	43 (98)	76 (92)	0.29
Calcium-channel blockers	18 (47)	13 (30)	33 (40)	0.25
Beta-blockers	21 (55)	24 (55)	34 (41)	0.20
Insulin	0 (0)	0 (0)	14 (17)§	0.0004

p = analysis of variance; p values for fasting blood sugar, IRI, HOMA-IR, and insulin were Bonferroni adjusted. Values are mean ± standard deviation or number of patients (percentage). *p < 0.05 (vs. NGR); †p < 0.01 (vs. NGR); ‡p < 0.0001 (vs. NGR and IGR); §p < 0.001 (vs. NGR); ‖p < 0.005 (vs. NGR).

ACE-I = angiotensin-converting enzyme inhibitor; ARB = angiotensin II type 1 receptor antagonist; DM = diabetes mellitus; HDL = high-density lipoprotein; HOMA-IR = homeostasis model assessment of insulin resistance; IGR= impaired glucose regulation; IRI = immunoreactive insulin; LDL = low-density lipoprotein; NGR = normal glucose regulation.

<0.2 at univariate analysis and other confounding variables were considered in the model. A p value <0.05 was considered statistically significant.

RESULTS

Study populations and baseline characteristics. An IVUS was performed on 172 consecutive patients during the study period. Seven patients (3 patients with DM, 2 patients with IGR, and 2 patients with NGR) were excluded because the IVUS catheter would not cross or IB-IVUS data were not available. Finally, conventional and IB-IVUS analyses were completed on 165 patients: 83 in the DM group, 44 in the IGR group, and 38 in the NGR group. There were no significant clinical differences among the 3 groups except for glucometabolic parameters (Table 1).

Quantitative parameters of conventional and IB-IVUS. Table 2 shows the conventional IVUS findings. In the 2D analysis, there were no significant differences in various parameters among the 3 groups. The 3D analysis indicated that plaque volume per lesion length (p = 0.02) and percentage of plaque volume (p = 0.002) were significantly increased in the DM group compared with the other 2 groups. In the IB-IVUS analysis, as compared with the NGT group, the DM group and the IGR group showed a significant increase in %LV (36 ± 14% and 37 ± 13% vs. 29 ± 14%, p = 0.02) (Fig. 1A) and a significant decrease in %FV (59 ± 11% and 58 ± 11% vs. 64 ± 11%, p = 0.03) (Fig. 1B). There were no significant differences in high signal volume among the 3 groups (Fig. 1C). On logistic regression analysis after adjusting for confounding (age, gender, and body mass index) and coronary (incidence of ACS, prevalence of

Table 2. Data for Conventional Intravascular Ultrasound

	NGR (n = 38)	IGR (n = 44)	DM (n = 83)	p Value
Vessel area, mm^2	10.8 ± 4.1	11.3 ± 3.8	11.6 ± 3.9	0.36
Lumen area, mm^2	3.6 ± 2.1	3.8 ± 2.6	3.4 ± 1.9	0.61
Plaque area, mm^2	7.2 ± 3.7	7.5 ± 3.0	8.2 ± 3.6	0.15
Plaque burden, %	65 ± 15	66 ± 16	69 ± 15	0.10
Eccentricity index	0.58 ± 0.07	0.58 ± 0.08	0.60 ± 0.08	0.20
Remodeling index	0.96 ± 0.20	1.00 ± 0.17	0.97 ± 0.20	0.52
Vessel volume, mm^3/mm	11.9 ± 4.5	11.8 ± 3.9	12.2 ± 4.4	0.69
Lumen volume, mm^3/mm	5.6 ± 2.5	5.6 ± 2.6	5.2 ± 2.4	0.39
Plaque volume, mm^3/mm	6.1 ± 2.9	6.1 ± 2.3	6.9 ± 2.9*	0.02
Percent plaque volume, %	51 ± 12	53 ± 12	57 ± 17†,‡	0.002

p = analysis of variance; p values for plaque volume and percent plaque volume were Bonferroni adjusted. Values are mean ± standard deviation. *p < 0.05 (vs. NGR and IGR); †p < 0.01 (vs. IGR); ‡p < 0.005 (vs. NGR).
Abbreviations as in Table 1.

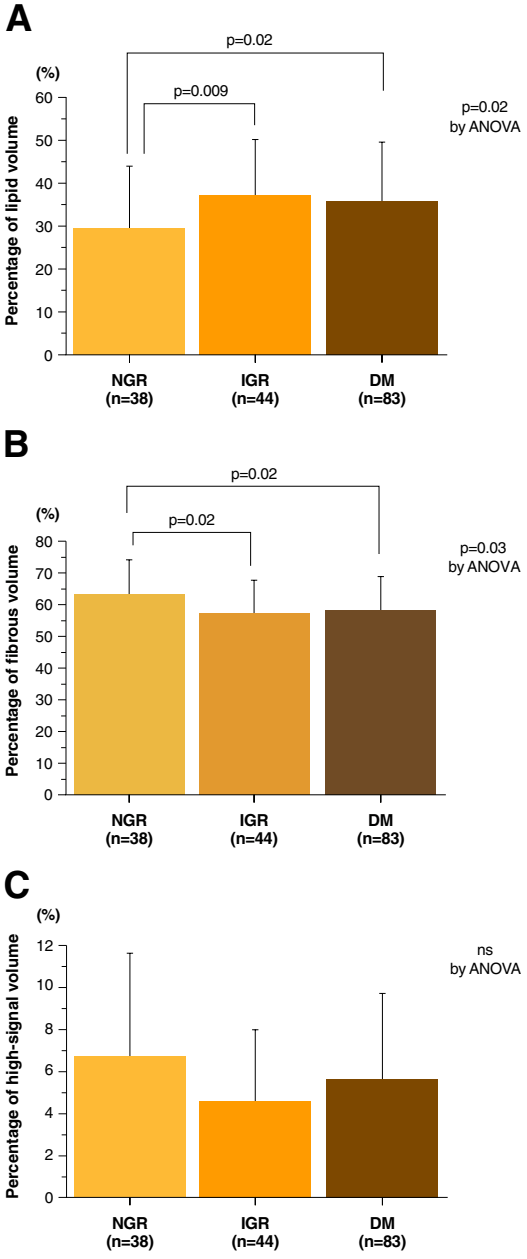

Figure 1. Comparisons of IB-IVUS Parameters Among the 3 Groups

(A) Percentage of lipid volume (%LV). **(B)** Percentage of fibrous volume (%FV). **(C)** Percentage of high signal volume. Coronary arteries in patients with impaired glucose resistance (IGR) and diabetes mellitus (DM) significantly increased in %LV (37 ± 13% and 36 ± 14% vs. 29 ± 14%, p = 0.02) and significantly decreased in %FV (58 ± 11% and 59 ± 11% vs. 64 ± 11%, p = 0.03) compared with those with normal glucose regulation (NGR). ANOVA = analysis of variance; IB-IVUS = integrated backscatter intravascular ultrasound.

hypertension, smoking status, elevated C-reactive protein, and use of statin and insulin) risk factors, the DM group (odds ratio 3.52, 95% confidence interval 1.13 to 11.0, p = 0.03) and the IGR group (odds ratio 3.92, 95% confidence interval 1.13 to 13.6, p = 0.03) were significantly associated with the lipid-rich plaque (Table 3). The lipid-rich plaque rate was significantly associated with an increasing HOMA-IR in the tertile (p = 0.008) (Fig. 2). Figure 3 shows the representative images of conventional and 2D IB-IVUS color-coded maps of coronary lesions with the lowest (Fig. 3A) or the highest (Fig. 3B) tertile of HOMA-IR. The %LA and %FA were 30% and 68% in Figure 3A and 46% and 49% in Figure 3B, respectively. The correlation of %LV and %FV measured by 2 physicians who conducted IVUS measurement independently was r = 0.91 (p < 0.01) and r = 0.92 (p < 0.01), respectively.

Table 3. Logistic Regression Model for Prediction of Lipid-Rich Plaque

Variable	Odds Ratio	95% Confidence Interval	p Value
Abnormal glucose regulation	3.65	1.25–10.7	0.02
Diabetes mellitus	3.52	1.13–11.0	0.03
Impaired glucose regulation	3.92	1.13–13.6	0.03
Acute coronary syndrome	2.35	1.02–5.39	0.04
Hypertension	2.09	0.86–5.09	0.10
C-reactive protein (>3 mg/l)	1.33	0.59–2.98	0.50
Smoking	1.13	0.48–2.65	0.79

Adjusted for confounding factors (age, gender, and body mass index) and use of insulin and statin. Each listed variable was adjusted for all other variables.

DISCUSSION

The main finding of this study is that IGR as well as DM is significantly associated with an increase in %LV and a decrease in %FV and that the prevalence of IGR and DM are independent predictors for lipid-rich plaque. Furthermore, the highest tertile of HOMA-IR (>3.4) had significantly increased lipid-rich plaque rates.

Although DM is well known to be a major CVD risk factor (19), the increased risk for CVD is apparent already at a pre-diabetic state (4,20), and ACS significantly affects mortality, morbidity, and quality of life in these patients. It has been reported that disruption or erosion of vulnerable plaques and subsequent thrombus are the most frequent causes of ACS (21,22) and that coronary plaque instability is mainly relevant to the lipid-rich plaque (13–15). In the present study, lipid-rich plaque defined as an increase in %LV and a decrease in %FV was significantly associated with the prevalence of ACS, consistent with previous reports showing the relationship between ACS and lipid-rich plaque (13–15). Furthermore, even after adjusting for the confounding and pre-defined variables, DM and IGR were independently associated with lipid-rich plaque. These results suggest that patients with AGR might have lipid-rich plaque, resulting in the development of adverse cardiac events.

Insulin resistance progressively increases when passing from NGR through IGR to DM (23). Impaired glucose regulation will develop only when insulin secretion fails to compensate fully for IR (24), resulting in postprandial hyperglycemia. Such a mechanism could be sufficient to contribute to progression of atherosclerosis even in the IGR phase (25). In the present study, IR defined as HOMA-IR was significantly increased in patients with IGR and DM compared with those with NGR. Furthermore, the lipid-rich plaque rates were significantly associated with an increasing tertile of HOMA-IR. Metabolic syndrome is chiefly based on IR and the cluster of comorbidities of AGR. In light of the present results, IR might be a primary contributor to our previous findings showing the association between metabolic syndrome and lipid-rich plaque (13).

The lipid-rich plaque defined in the present study might not be considered a predominant

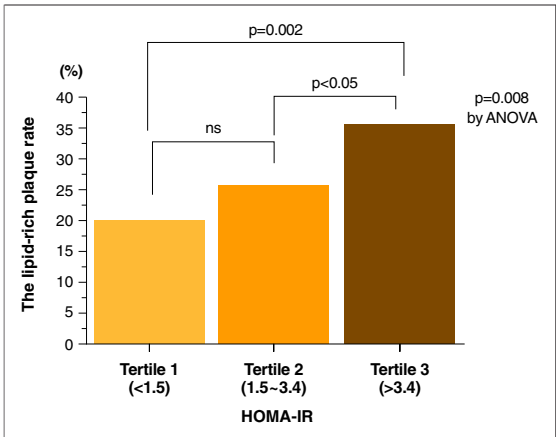

Figure 2. The Lipid-Rich Plaque Rate According to the Tertile of HOMA-IR

Insulin resistance (IR) was defined from the homeostasis model assessment of insulin resistance (HOMA-IR). The cutoff point for the lipid-rich plaque was defined as percentage of lipid volume (%LV) >44% or percentage of fibrous volume (%FV) <52%, which was the 75th percentile of %LV or the 25th percentile of %FV in this study population. The lipid-rich plaque rate was significantly associated with an increasing tertile of HOMA-IR (p = 0.008 by analysis of variance [ANOVA]). These results suggest the relationship between IR and greater lipid-rich plaque content.

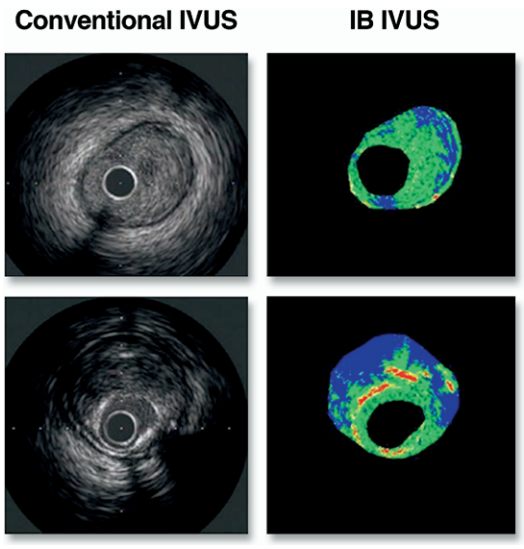

Figure 3. Representative Images of Conventional and 2D IB-IVUS Color-Coded Maps of Coronary Artery Plaques

The percentage of lipid area (%LA) and the percentage of fibrous area (%FA) were automatically calculated by IB-IVUS. The %LA and %FA were **(top panels)** 30% and 68% in patients with the lowest tertile of the HOMA-IR, and **(bottom panels)** 46% and 49% in patients with the highest tertile of HOMA-IR. **Blue** = lipid pool; **green/yellow** = fibrous lesion; **red** = high signal lesion. 2D = 2-dimensional; other abbreviations as in Figures 1 and 2.

marker of plaque instability. With a slightly different methodology (virtual histology and IVUS radiofrequency analysis), another Japanese group (26) recently showed that the amount of lipid content was not higher and the amount of fibrotic tissue was not lower in patients with ACS compared with stable patients. Although this report provides important insight into ruptured plaques, it focused on plaques after the occurrence of rupture measured at the minimal luminal site. There are scant IVUS data defining plaque instability before the occurrence of rupture. Sano et al. (15) have shown the morphology of plaque instability before the occurrence of ACS. In that study of plaques before ACS using IB-IVUS, the %LA was greater in the vulnerable plaque than in the stable plaque. However, a higher lipid content did not necessarily translate into mote vulnerable plaques. Cap thickness (beyond the resolution of IB-IVUS) is another major player in the field. True plaque instability means an active change from 1 point in time to another, resulting in plaque rupture. Therefore, a longitudinal and prospective study is needed to assess the precise prognostic value of the lipid-rich plaque in the development of future coronary events.

Study limitations. In the present study, although it is hypothesized that lipid-rich plaques are those contributing to plaque instability, these data were not examined. Taken together with other results, larger studies should confirm present findings before any preventive or therapeutic implication could be suggested.

CONCLUSIONS

In conclusion, coronary lesions in patients with AGR are associated with lipid-rich plaque, which may be related to the increased IR in these patients. Further study is needed to provide therapeutic information on the need for any intervention to reduce IR even in the IGR state.

Reprint requests and correspondence: Dr. Tetsuya Amano, Department of Cardiology, Chubu-Rosai Hospital, Kohmei 1-10-6, Minato-ku, Nagoya, 455-8530, Japan. *E-mail: amanot@med.nagoya-u.ac.jp.*

REFERENCES

1. Buse JB, Ginsberg HN, Bakris GL, et al. Primary prevention of cardiovascular diseases in people with diabetes mellitus: a scientific statement from the American Heart Association and the American Diabetes Association. Circulation 2007;115:114–26.
2. Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993;16:434–44.
3. Manson JE, Colditz GA, Stampfer MJ, et al. A prospective study of maturity-onset diabetes mellitus and risk of coronary heart disease and stroke in women. Arch Intern Med 1991;151:1141–7.
4. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events: a meta regression analysis of published data from 20 studies of 95783 individuals followed for 12.4 years. Diabetes Care 1999;22:233–40.
5. DECODE Study Group, the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161:397–405.
6. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals. JAMA 1990;263:2893–998.
7. Bonora E, Kiechl S, Oberhollenzer F, et al. Impaired glucose tolerance, type II diabetes mellitus, and carotid atherosclerosis: prospective results from the Bruneck Study. Diabetologia 2000;43:156–64.
8. O'Leary DH, Polak JF, Kronmal RA, et al. Distribution and correlates of sonographically detected carotid artery disease in the Cardiovascular Health Study: the CHS Collaborative Research Group. Stroke 1992;23:1752–60.

9. Hanefeld M, Koehler C, Schaper F, et al. Postprandial plasma glucose is an independent risk factor for increased carotid intima-media thickness in non-diabetic individuals. Atherosclerosis 1999;144:229–35.
10. Tenerz Å, Norhammar A, Silveria A, et al. Diabetes, insulin resistance and the metabolic syndrome in patients with acute myocardial infarction without previously known diabetes. Diabetes Care 2003;26:2770–6.
11. Ruige JB, Assendelft WJJ, Dekker JM, et al. Insulin and risk of cardiovascular disease: a meta-analysis. Circulation 1998;97:996–1001.
12. Fujiwara T, Saitoh S, Takagi S, et al. Development and progression of atherosclerotic disease in relation to insulin resistance and hyperinsulinemia. Hypertens Res 2005;28:665–70.
13. Amano T, Matsubara T, Uetani T, et al. Impact of metabolic syndrome on tissue characteristics of angiographically mild to moderate coronary lesions: integrated backscatter intravascular ultrasound study. J Am Coll Cardiol 2007,49:1149–56.
14. Kawasaki M, Takatsu H, Noda T, et al. In vivo quantitative tissue characterization of human coronary artery plaques by use of integrated backscatter intravascular ultrasound and comparison with angioscopic findings. Circulation 2002;105:2487–92.
15. Sano K, Kawasaki M, Ishihara Y, et al. Assessment of vulnerable plaques causing acute coronary syndrome using integrated backscatter intravascular ultrasound. J Am Coll Cardiol 2006;47:734–41.
16. Report of the WHO Consultation, Definition, Diagnosis and Classification of Diabetes Mellitus and Its Complications. Part 1: Diagnosis and Classification of Diabetes Mellitus. Geneva: World Health Organization, Department of Non-communicable Disease Surveillance, 1999.
17. Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985;28:412–9.
18. Honda O, Sugiyama S, Kugiyama K, et al. Echolucent carotid plaques predict future coronary events in patients with coronary artery disease. J Am Coll Cardiol 2004;43:1177–84.
19. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in non diabetic subjects with and without prior myocardial infarction. N Engl J Med 1998;339:229–34.
20. The DECODE Study Group on behalf of the European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and non-cardiovascular disease? Dia betes Care 2003;26:688–96.
21. Little WC, Constantinescu M, Applegate RJ, et al. Can coronary angiography predict site of a subsequent myocardial infarction in patients with mild-to-moderate coronary artery disease? Circulation 1988;78:1157–66.
22. Ambrose JA, Tannenbaum MA, Alexopoulos D, et al. Angiographic progression of coronary artery disease and the development of myocardial infarction. J Am Coll Cardiol 1988; 12:56–62.
23. Tripathy D, Carlsson M, Almgren P, et al. Insulin secretion and insulin sensitivity in relation to glucose tolerance: lessons from the Botnia study. Diabetes 2000;49:975–80.
24. Beck-Nielsen H, Groop LC. Metabolic and genetic characterization of prediabetic states: sequence of events leading to non-insulin-dependent diabetes mellitus. J Clin Invest 1994;94: 1714–21.
25. Rossetti L, Giaccari A, DeFronzo RA. Glucose toxicity. Diabetes Care 1990;13:610–30.
26. Surmely JF, Nasu K, Fujita H, et al. Coronary plaque composition of culprit/target lesions according to the clinical presentation: a virtual histology intravascular ultrasound analysis. Eur Heart J 2006;27:2939–44.