

Inflammation, Insulin Resistance, and Glucose Intolerance in Acute Myocardial Infarction Patients without a Previous Diagnosis of Diabetes Mellitus

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We examined the prevalence of impaired glucose metabolism and its association with inflammation and insulin resistance (IR) in acute myocardial infarction (AMI) patients without a previous diagnosis of diabetes. This prospective study enrolled 52 AMI patients, and 75-g oral glucose tolerance testing was performed on 30 patients at discharge and again 3 months later. We also measured serum adiponectin, high sensitive C-reactive protein, and IL-6 on both occasions. Data were compared with those of 30 type 2 diabetic patients without a history of AMI. Forty percent and 36.7% of AMI patients had impaired glucose tolerance (IGT) at discharge and at 3 months, respectively. The corresponding proportions for

newly diagnosed diabetes are 33.0% and 30.0%. At discharge, AMI patients with IGT or diabetes showed higher high sensitive C-reactive protein and IL-6 levels compared with AMI patients with normal glucose tolerance or control type 2 diabetic patients. Furthermore, AMI patients with IGT or diabetes exhibited higher IR and lower serum adiponectin levels than AMI patients with normal glucose tolerance at 3 months after discharge. Previously undiagnosed diabetes and IGT are common in Korean patients with AMI. These glycometabolic abnormalities are associated with inflammation, IR, and serum adiponectin levels. (*J Clin Endocrinol Metab* 90: 175–180, 2005)

THE GLYCOMETABOLIC STATE of patients at hospital admission for acute myocardial infarction (AMI) and the long-term mortality of patients with (1) and without (2) diagnosed diabetes are related. A recent study reported that previously undiagnosed diabetes and impaired glucose tolerance (IGT) are common in Caucasian patients with AMI, and that these abnormalities can be detected by oral glucose tolerance test early in the postinfarction period (3). Moreover, insulin infusion in patients with AMI has been shown to reduce long-term mortality by 30–50% in diabetic and nondiabetic patients (4, 5). In addition, insulin has been recently shown to exert antiinflammatory effects in humans *in vitro* and *in vivo* (6, 7). In an epidemiological study, C-reactive protein (CRP), a marker of systemic inflammation, was found to be a stronger predictor of future cardiovascular events than low density lipoprotein cholesterol (8). The major stimulant of CRP secretion, IL-6, was found to predict future cardiovascular events in prospective studies (9). Moreover, recent studies have showed that the CRP level might be a powerful predictor of mortality in AMI patients (10, 11).

Insulin resistance (IR) is being increasingly recognized as a chronic, low level, inflammatory state. Atherosclerosis,

which is generally accepted to be an inflammatory disease (12), and IR share similar pathophysiological mechanisms, mainly due to the action of the two proinflammatory cytokines, TNF- α and IL-6 (13). Ariza *et al.* (14) demonstrated that IR is associated with a significant predictive risk of myocardial infarction even in the absence of any of the other traditional cardiac risk factors. Moreover, the recently discovered adipocytokine, adiponectin, is reduced in IR, type 2 diabetes, and coronary artery disease (15–17). Nakamura *et al.* (18) reported that low adiponectin concentrations correlate independently with the development of acute coronary syndrome.

In this study we explored the prevalence of the glucose intolerance state in Korean AMI patients without a previous diagnosis of diabetes. We also investigated whether elevated acute phase reactants (CRP) and their major cytokine mediator (IL-6) are associated with glucose intolerance. Furthermore, differences in IR and adiponectin concentrations according to glucose tolerance were examined.

Subjects and Methods

Study subjects

We enrolled 52 consecutive patients admitted to the coronary care units of Korea University Guro Hospitals for AMI between October 1, 2001, and June 15, 2002. We excluded patients with known diabetes mellitus or random serum glucose concentrations over 11.1 mmol/liter on two occasions. Subjects with active infection were also excluded. Patient data were compared with those of 30 age-, sex-, and body mass index-matched type 2 diabetic patients without a history of AMI. These type 2 diabetes patients were composed of 11 patients treated with only sulfonylurea and 19 patients treated with diet and exercise therapy. The mean duration of their diabetes was 2.4 ± 1.8 yr, and their mean hemoglobin A_{1c} (HbA_{1c}) level was 6.6 ± 0.6 . Informed consent was ob-

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Abbreviations: AMI, Acute myocardial infarction; CK-MB, creatine kinase MB isoenzyme; CRP, C-reactive protein; CV, coefficient of variation; CVD, cardiovascular disease; HbA_{1c}, hemoglobin A_{1c}; HOMA, homeostasis model assessment; hsCRP, high sensitive C-reactive protein; IGT, impaired glucose tolerance; IR, insulin resistance; NGT, normal glucose tolerance.

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tained from all subjects before they participated in the study, which was approved by the ethical committee at our institution.

Study design and methods

We measured random blood glucose concentrations at admission to the coronary care units, and the concentrations of overnight fasting blood glucose and HbA_{1c}. The concentrations of capillary fasting blood glucose were measured daily until hospital discharge. After a 12-h overnight fast, a standardized 75-g oral glucose tolerance test was performed before discharge (d 3 or 4). Blood chemistry was analyzed at the Korea University Guro Hospital laboratory (Seoul, Korea). Fasting serum total cholesterol, triglycerides, and high density lipoprotein cholesterol levels were determined enzymatically using a chemical analyzer (Hitachi 747, Tokyo, Japan). LDL cholesterol was calculated using the formula of Friedewald *et al.* (19). A glucose oxidase method was employed to measure plasma glucose, and a human insulin-specific RIA kit (Linco Research, Inc., St. Charles, MO) was used to measure insulin level. The kit used had a reactivity of less than 0.2% with human proinsulin. IR was calculated by homeostasis model assessment (HOMA) (20). HbA_{1c} was analyzed by HPLC using a Variant II analyzer (Bio-Rad Laboratories, Hercules, CA). Capillary blood was measured using an ACCU-CHEK Active System (Roche, Mannheim, Germany). High sensitive CRP (hsCRP) levels were measured using a CRP ELISA kit (Immunodiagno, Bensheim, Germany), and its intra- and interassay coefficients of variation (CVs) were 6.5% and 10.4%, respectively. The IL-6 level was determined using a Quantikine HS IL-6 kit (R&D Systems, Inc., Minneapolis, MN), and their intra- and interassay CVs were 6.8% and 8.6%, respectively. Serum adiponectin levels were measured using a human adiponectin RIA kit (Linco Research, Inc.), and their intra- and interassay CVs were 3.2% and 6.5%, respectively. Three months after discharge, we repeated the 75-g oral glucose tolerance test in AMI patients after a 12-h overnight fast and repeated all biochemical tests.

We defined diabetes mellitus and IGT according to the World Health Organization (WHO) 1998 criteria (21) and the fasting blood glucose criteria adopted by the American Diabetes Association (22). Myocardial infarction was defined using the criteria jointly recommended by the European Society of Cardiology and the American College of Cardiology (23, 24). Thus, patients were diagnosed as having an AMI if they had two values of serum troponin T greater than 0.05 g/liter or a creatine kinase MB isoenzyme (CK-MB) level greater than 10 μg/liter together with either typical symptoms (chest pain for >15 min, pulmonary edema in the absence of valvular heart disease, cardiogenic shock, or arrhythmia such as ventricular fibrillation or ventricular tachycardia), new Q-waves in at least two of the 12 standard electrocardiographic leads,

or electrocardiogram changes indicating acute ischemia (ST elevation, ST depression, or T wave inversion).

Statistical analysis

The data from the study participants are presented as the mean ± SD or as the median and first and third quartiles for data not normally distributed. Data not normally distributed were subjected to natural log transformations. We tested the significance of the differences among the three groups [AMI patients with normal glucose tolerance (NGT), AMI patients with IGT or diabetes, and control type 2 diabetes without AMI] using ANOVA with Tukey's multiple comparison. Changes in IR and inflammation between discharge and 3 months after discharge were analyzed using the paired *t* test. Relationships among hsCRP, IL-6, HOMA of IR, and serum adiponectin were examined using Pearson's correlation coefficient. Data were analyzed using SPSS for Windows (version 10.0, SPSS, Inc., Chicago, IL), and *P* < 0.05 (two-tailed) was accepted as significant.

Results

We enrolled 52 consecutive patients admitted to the coronary care unit of Korea University and performed 75-g oral glucose tolerance testing on 30 of these patients before discharge and again 3 months later. The reasons for not testing were overt diabetes (*n* = 12), death (*n* = 3), concomitant disease (*n* = 2), and unwillingness (*n* = 5). Table 1 shows the baseline characteristics of patients at the time of admission according to the glucose tolerance state 3 months after discharge and the corresponding characteristics of the control type 2 diabetic patients without a history of AMI. The mean age of AMI patients was 60.1 ± 9.1 yr, and their mean fasting blood glucose level was 6.0 ± 0.7 mmol/liter at discharge and 6.2 ± 0.7 mmol/liter 3 months later. The mean 2-h postload blood glucose concentration of AMI patients was 9.8 ± 3.2 mmol/liter at discharge and 8.7 ± 2.8 mmol/liter 3 months later. Table 2 shows the lipid profiles and blood glucose levels of AMI patients at the time of admission and 3 months later *vs.* glucose tolerance levels; no significant difference in lipid profiles was observed with respect to glucose tolerance over a 3-month period.

TABLE 1. Baseline characteristics of patients with AMI according to glucose tolerance after 3 months of follow-up and those of control patients with diabetes

	Diabetes without AMI (<i>n</i> = 30)	AMI with NGT (<i>n</i> = 10)	AMI with IGT or diabetes (<i>n</i> = 20)
Age (yr)	58.4 ± 6.0	60.9 ± 9.6	59.7 ± 9.0
Male sex (%)	73.3	70.0	75.0
Body mass index (kg/m ²)	25.0 ± 2.2	25.1 ± 1.2	25.0 ± 1.5
Systolic blood pressure (mm Hg)	131.4 ± 14.8	133.9 ± 10.5	131.6 ± 10.4
Diastolic blood pressure (mm Hg)	80.4 ± 10.1	83.8 ± 4.8	82.2 ± 3.9
Family history of diabetes (%)	0	0	0
Previous disorder (%)			
Myocardial infarction	0	10.0	10.0
Angina pectoris	0	10.0	15.0
Heart failure	0	10.0	0
Hypertension	0	30.0	35.0
Current smoker (%)	40.0	70.0	45.0
Hyperlipidemia (treated, %)	0	0	5.0
Treatment during hospital (%)			
Thrombolysis	0	0	0
Primary PTCA	0	80.0	90.0
Aspirin	0	100	100
ACE inhibitors	0	90.0	95.0
Lipid-lowering agents	0	80.0	90.0

ACE, Angiotensin-converting enzyme; NGT, normal glucose tolerance; IGT, impaired glucose tolerance; PTCA, percutaneous transluminal coronary angioplasty.

TABLE 2. Biochemical characteristics of patients with AMI according to glucose tolerance after 3 months of follow-up and those of control patients with diabetes

	Diabetes without AMI	AMI with NGT	AMI with IGT or diabetes
Total cholesterol (mmol/liter)			
At discharge	4.9 ± 1.0	4.2 ± 0.6	4.4 ± 0.9
3 months after discharge		3.7 ± 0.7	4.0 ± 1.1
HDL cholesterol (mmol/liter)			
At discharge	1.2 ± 0.4	1.0 ± 0.2	1.0 ± 0.2
3 months after discharge		1.2 ± 0.2	1.0 ± 0.2
LDL cholesterol (mmol/liter)			
At discharge	3.0 ± 1.0	2.6 ± 0.6	2.8 ± 0.8
3 months after discharge		1.9 ± 0.6	2.4 ± 1.0
Triglycerides (mmol/liter) ^a			
At discharge	1.5 (0.9–1.9)	1.1 (0.9–1.4)	1.1 (0.9–1.5)
3 months after discharge		1.1 (0.8–1.6)	1.2 (0.9–1.7)
Fasting glucose (mmol/liter)			
At discharge	6.8 ± 1.3 ^a	5.4 ± 0.4	6.3 ± 0.6 ^a
3 months after discharge		5.7 ± 0.4	6.4 ± 0.7 ^a
Postload 2-h glucose (mmol/liter)			
At discharge		7.0 ± 1.0	11.2 ± 2.9 ^a
3 months after discharge		6.2 ± 1.0	10.0 ± 2.5 ^a
HbA _{1c} (%)			
At discharge	6.6 ± 0.6 ^a	5.5 ± 0.3	5.8 ± 0.6 ^a
3 months after discharge		5.6 ± 0.3	6.1 ± 0.5 ^a

HDL, High-density lipoprotein; LDL, low-density lipoprotein.

^a *P* < 0.05 vs. AMI with NGT.

Figure 1 shows the prevalence of glucose abnormalities at discharge and 3 months after discharge in AMI patients. Forty percent and 36.7% of AMI patients had IGT at discharge and at 3 months, respectively. The corresponding proportions for newly diagnosed diabetes patients were 33.0% and 30.0% according to the WHO criteria (21). If a diagnosis had been made using fasting blood glucose only, diabetes would have been diagnosed in 10.0% and 20.0% of AMI patients, respectively. At the 3-month test, seven of eight AMI patients with NGT at discharge remained in NGT. The remaining patient developed diabetes. Eight AMI patients among 12 AMI patients with IGT at discharge remained in IGT 3 months later. One of them developed diabetes, and three of them returned to NGT after 3 months. Seven AMI patients among 10 AMI patients with diabetes at

discharge remained diabetic 3 months later. The remaining three patients showed IGT 3 months after AMI.

Figure 2 shows differences in inflammatory markers between AMI patients with NGT, AMI patients with IGT or diabetes, and control type 2 diabetic patients. At discharge, serum hsCRP and IL-6 levels were significantly higher in AMI patients with IGT or diabetes than in AMI patients with NGT or in control type 2 diabetic patients. However, these differences were not significant 3 months after discharge. Furthermore, AMI patients with IGT or diabetes exhibited higher IR and lower serum adiponectin levels than AMI patients with NGT 3 months after discharge.

In AMI patients, serum hsCRP levels were related to serum IL-6 level at discharge ($r = 0.51$; $P = 0.004$), and serum adiponectin concentrations showed a negative correlation with IR at 3 months after discharge ($r = -0.46$; $P = 0.019$). Peak CK-MB levels were significantly correlated with serum hsCRP levels ($r = 0.52$; $P = 0.007$). However, peak CK-MB levels were not associated with IL-6, adiponectin, insulin levels or the IR index. During the 3-month period, serum hsCRP and IL-6 concentrations decreased significantly ($P < 0.001$, respectively); however, IR and serum adiponectin levels did not change significantly.

Discussion

In this study we confirmed a high prevalence of abnormal glucose metabolism in Korean patients with AMI, which concurs with the results of a study in Caucasian patients (3). The high prevalence of this glycometabolic abnormality was obvious despite the exclusion of patients with previously diagnosed diabetes or with blood glucose concentrations more than 11.1 mmol/liter at hospital admission. The proportion of abnormal glucose tolerance in AMI patients was similar at 3 months after discharge, when the effects of acute stress and inflammation should have subsided. The preva-

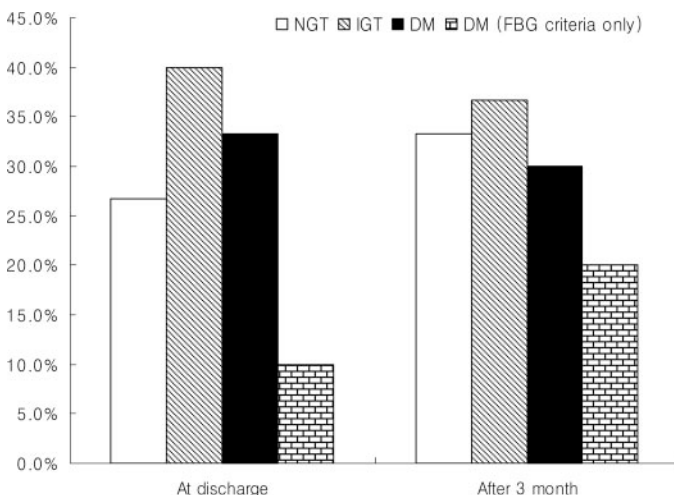


FIG. 1. Prevalence of glucose abnormalities at discharge and 3 months after discharge in patients with myocardial infarction. DM, Diabetes mellitus; FBG, fasting blood glucose.

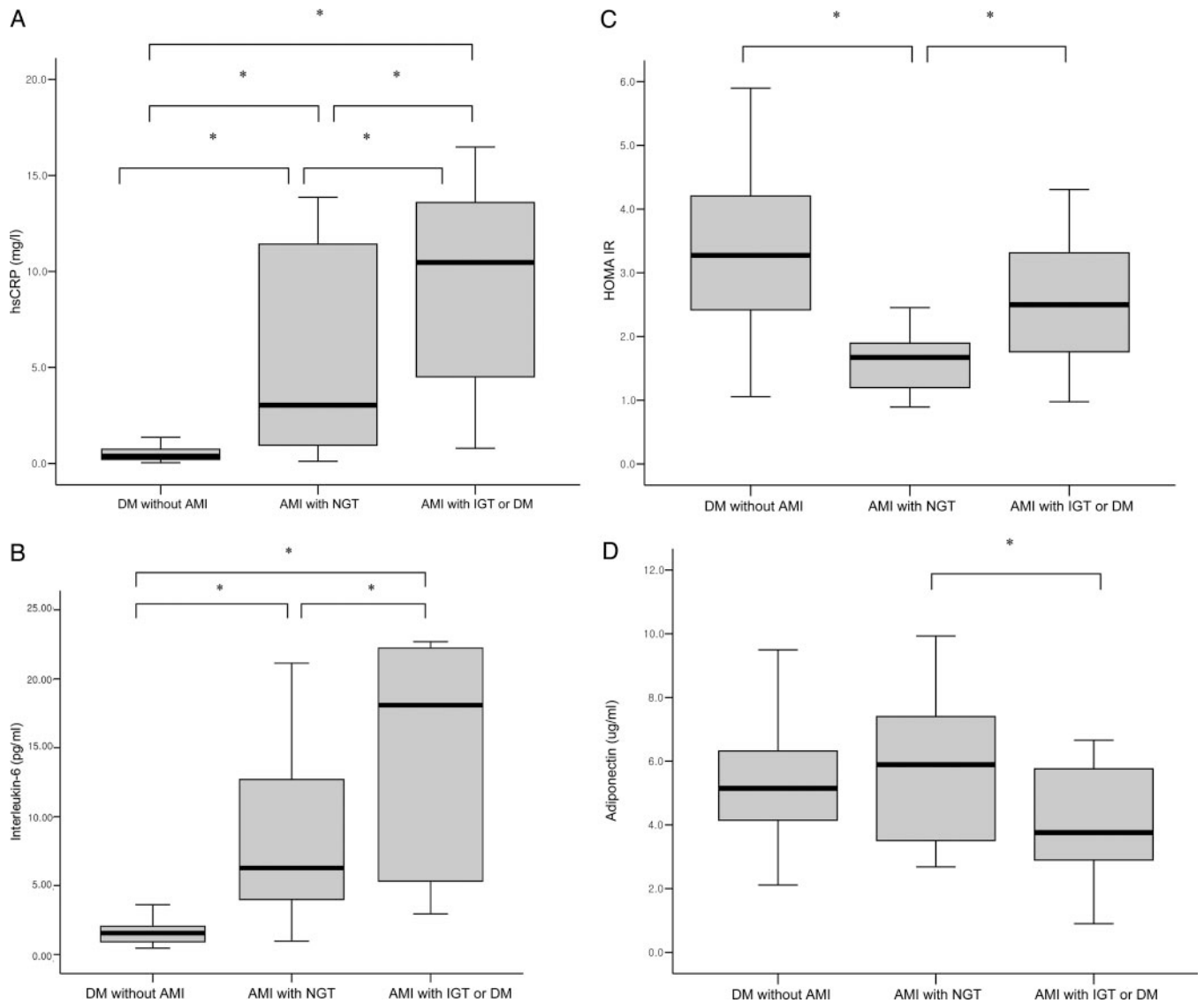


FIG. 2. Differences in hsCRP (A) and IL-6 (B) serum levels among type 2 diabetic patients without AMI, AMI patients with NGT, and AMI patients with IGT or diabetes at discharge were determined. Differences in IR (C) and adiponectin (D) among type 2 diabetic patients without AMI, AMI patients with NGT, and AMI patients with IGT or diabetes at 3 months after discharge were also determined. DM, Diabetes mellitus. The box plot displays the 25th percentile, median, and 75th percentile and the minimum and maximum levels as horizontal lines outside the box. *, $P < 0.05$.

lence of IGT and diabetes in this study were much higher than that found in our previous study, which was performed in same region. In our previous study the prevalence rates of unknown diabetes according to the WHO criteria and American Diabetes Association criteria (fasting blood glucose criteria only) were 8.9% and 3.4% in nondiabetic subjects over the age of 60 yr (25).

It has been established that overt diabetes is associated with a markedly increased risk of cardiovascular disease (CVD). Recently published evidence indicates that postload hyperglycemia could be of greater importance than fasting blood glucose. In the Funagata diabetes study, researchers concluded that IGT, but not impaired fasting glucose, was a risk factor for CVD (26). Analyses of the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) study also showed that abnormalities in 2-h

glucose were better predictors of mortality from all-cause mortality and from CVD than fasting glucose alone (27). In our study, using fasting blood glucose criteria only, diabetes was diagnosed in only 10% of AMI patients at discharge compared with 33.0% according to WHO criteria (21). This suggests that oral glucose tolerance testing may be needed for AMI patients even without fasting hyperglycemia.

The presence of diabetes increases short- and long-term mortality rates after AMI (28). A recent study reported that hyperglycemia at admission to the hospital is a predictor of long-term prognosis even in nondiabetic patients, and that insulin-glucose infusion improves outcome, at least in patients with overt diabetes (29, 30). Therefore, early detection of fasting and postchallenge hyperglycemia in patients with AMI may be important in terms of identifying high risk individuals.

IR is a significant risk factor for CVD. Adiponectin, one of the adipocytokines, is a mediator of insulin sensitivity. Adiponectin increases insulin sensitivity, in part by inhibiting hepatic glucose output (31) and by increasing the insulin action of peripheral tissue (*i.e.* skeletal muscle) (32). Hotta *et al.* (15) reported reduced adiponectin levels in patients with diabetes and in those with coronary artery disease. A recent study showed that low adiponectin concentrations correlate independently to the development of acute coronary syndrome (18). In this study we found that IR and adiponectin levels are associated with glucose tolerance in AMI patients without a previous diagnosis of diabetes.

IR is increasingly being recognized as a chronic, low grade inflammatory state. This relationship is bidirectional and may create a vicious cycle, *i.e.* any process linked to chronic inflammation will reduce insulin action, and IR will lead to a worsening of inflammation (13). Central obesity plays an important role in IR and associated CVD. Visceral fat cells show increased production of IL-6 and TNF- α production, and elevated production of these cytokines is associated with increased plasma free fatty acid, elevated CRP, and glucose intolerance (33, 34). Indeed, elevated IL-6 and CRP are predictors of the development of CVD (34). Moreover, atherosclerosis itself is currently considered an inflammatory disease (12). Glucose induces proinflammatory changes, including activator protein-1, matrix metalloproteinase, and tissue factor, which regulate processes that are potentially relevant to atherosclerotic plaque rupture and thrombosis (35). Mohanty *et al.* (36) reported that glucose challenge stimulates reactive oxygen species generation. Increased free fatty acid also induces oxidative stress and has a proinflammatory effect (37). Recently, insulin has been shown to have an antiinflammatory effect in patients with AMI, and these effects may contribute to the clinical benefits of insulin in patients with AMI (38). In this study we found that acute phase reactants (CRP) and their major cytokine mediator (IL-6) were associated with glucose tolerance in AMI patients at discharge.

A limitation of this study is the use of medication that may have affected inflammation. Specific treatment regimens, such as statins and antiplatelet agents, are known to alter inflammation (39). This may have affected our inflammatory marker results 3 months after discharge. However, the discontinuance of these medications was not possible, and patients grouped according to glucose tolerance showed similar patterns of statin and antiplatelet therapy.

Our results show that previously undiagnosed diabetes and IGT are common in Korean AMI patients, and these glycometabolic abnormalities are associated with IR and inflammation. Our results suggest that risk identification by oral glucose tolerance testing may be helpful in AMI patients without a previous diagnosis of diabetes.

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