Type 2 diabetes mellitus (DM) is a well-recognized risk factor for morbidity and mortality of coronary heart disease (CHD), and the presence of diabetes markedly worsens the prognosis of patients with acute coronary syndrome (ACS).1–4 Macrovascular disease such as CHD is now believed to precede the development of diabetes,5–7 however, and impaired glucose tolerance (IGT), a prediabetic state, is already established as an important risk factor for CHD.8–10 Some 30% of hospitalized patients with acute myocardial infarction (AMI) are reported to suffer from diabetes,4 and several recent studies suggest that the prevalence of diabetes in CHD patients is as high as 40–50%, when the patients undergo an oral glucose tolerance test (OGTT).11–13

An elevated serum level of low-density lipoprotein (LDL)-cholesterol is well established as a major risk factor for CHD in both diabetic and nondiabetic patients. However, qualitative features of LDL particles are also suspected to play an important role in the development of CHD, particularly in view of the predominance of small dense LDL (sd-LDL) particles.14–16 LDL particles are heterogeneous in size, density, and lipid composition, and have been divided into 2 distinct phenotypes: pattern A with a higher proportion of large, buoyant LDL particles, and pattern B with a predominance of sd-LDL particles.16 It has been suggested that sd-LDL are highly atherogenic because of their higher penetration into the arterial wall, a higher binding affinity for arterial wall proteoglycan, a lower binding affinity for the LDL receptor, a prolonged plasma half-life, and a lower resistance to oxidative stress compared with the large buoyant LDL.14,15 In studies consistent with reports from the West,17,18 our group identified the sd-LDL phenotype as an independent risk factor for CHD in Japanese (both males and females), an ethnic group with lower serum cholesterol levels and less massive obesity than Caucasians.19–21 Although these sd-LDL particles are typical in diabetic dyslipidemia,4 a high prevalence of the sd-LDL phenotype has also been noted even in CHD patients without diabetes.17–22 We hypothesized that the high prevalence of sd-LDL in ACS patients without diabetes is related to a prediabetic state and the goal of this study was to clarify this issue by comparing LDL particle diameter and abnormal glucose regulation in patients with ACS.

Methods

Subjects

We retrospectively analyzed data on 465 consecutive patients admitted to the coronary care unit of Showa University Hospital with a diagnosis ACS (291 males, 91 females with AMI; 35 males, 12 females with unstable angina pectoris) between January 1, 2002 and December 31, 2004. Twenty-eight male and 8 female patients were excluded because they died in hospital. The diagnoses were based on

Background

Although small dense low-density lipoprotein (sd-LDL) has an established association with diabetic dyslipidemia, previous studies have failed to show an association between sd-LDL and diabetes among coronary heart disease patients. This study investigated the prevalence of sd-LDL and abnormal glucose regulation in acute coronary syndrome (ACS).

Methods and Results

LDL size at the onset of ACS was measured by nondenatured gradient gel electrophoresis in 314 of 429 consecutive patients. Sd-LDL was prevalent in 54% of the patients, irrespective of the presence of previously known diabetes (50% vs 60% in nondiabetes and diabetes, respectively). Diabetes was present in 122 (28%) of the patients, and 110 patients without diabetes underwent an oral glucose tolerance test. Impaired glucose tolerance (IGT) and newly detected diabetes were found in as many as 44% and 22% of the patients tested, even though their hemoglobin A1c levels were in the normal range (5.3±0.5%). The prevalence of sd-LDL was significantly higher in patients with glucose intolerance than in those with normal glucose tolerance (61% vs 42%).

Conclusion

IGT and diabetes were far more common than normal glucose regulation in ACS patients, and the abnormal glycometabolism was closely associated with highly atherogenic sd-LDL. (Circ J 2006; 70: 393–401)
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DM was defined as fasting blood glucose ≥ 126 mg/dl or the use of antihypertensive medications. A systolic or diastolic blood pressure >140 or >90 mmHg, respectively, or the use of antihypertensive medications. Hypertension was defined as pressures were measured at least twice on admission and the averaged values were used. Hypertension was defined as systolic or diastolic blood pressure > 140 or > 90 mmHg, respectively, or the use of antihypertensive medications. 

Previous CHD, %
Myocardial infarction
Angina pectoris
Hypertension, %
Treatment, %
Current smoker, %
Family history of CHD, %
Previous CHD, %
Smoking
ACE-I
ARB
Calcium antagonist
β-blockers
Lipid-lowering agents
Hypertension, %
Angina pectoris
Myocardial infarction
Previous CHD, %
Current smoker, %
Family history of CHD, %

Data are mean±SD. *p<0.05 vs corresponding Non-DM group, †p<0.05 vs corresponding measured group.
LDL, low-density lipoprotein; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NA, not available; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance.
Waist, glucose, insulin, apo A1, and apoB were measured in the indicated number of patients (n) in each group.

Table 1 Clinical and Biochemical Characteristics of Patients in Whom LDL Size was Measured and Those in Whom it was Not

<table>
<thead>
<tr>
<th>Overall</th>
<th>Measured group</th>
<th>Unmeasured group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-DM</td>
<td>DM</td>
<td>Non-DM</td>
</tr>
<tr>
<td>n (males)</td>
<td>429 (326)</td>
<td>219 (183)</td>
</tr>
<tr>
<td>Age, years</td>
<td>66.6±12</td>
<td>65.4±12</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>23.3±4.1</td>
<td>23.6±3.9</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>87.3±10</td>
<td>86.1±9.9</td>
</tr>
<tr>
<td>(n=126)</td>
<td>(n=78)</td>
<td>(n=27)</td>
</tr>
<tr>
<td>Obesity, %</td>
<td>28</td>
<td>31</td>
</tr>
<tr>
<td>SBP, mmHg</td>
<td>128.3±25</td>
<td>126.1±23</td>
</tr>
<tr>
<td>DBP, mmHg</td>
<td>70.0±15</td>
<td>69.9±14</td>
</tr>
<tr>
<td>Family history of CHD, %</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>36</td>
<td>39</td>
</tr>
<tr>
<td>Previous CHD, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment, %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>97</td>
<td>98</td>
</tr>
<tr>
<td>ACE-I</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>ARB</td>
<td>55</td>
<td>54</td>
</tr>
<tr>
<td>Calcium antagonist</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>β-blockers</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>Lipid-lowering agents</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>Fasting glucose, mg/dl</td>
<td>126.1±55</td>
<td>99±12</td>
</tr>
<tr>
<td>2-h glucose, mg/dl</td>
<td>170.5±61</td>
<td>170.8±61</td>
</tr>
<tr>
<td>(n=90)</td>
<td>(n=65)</td>
<td></td>
</tr>
<tr>
<td>Fasting insulin, μU/ml</td>
<td>8.3±7.4</td>
<td>8.4±8.5</td>
</tr>
<tr>
<td>2-h insulin, μU/ml</td>
<td>87.8±65</td>
<td>88.9±64</td>
</tr>
<tr>
<td>(n=90)</td>
<td>(n=65)</td>
<td></td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>2.6±3.0</td>
<td>2.1±2.3</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>116.6±66</td>
<td>120.3±66</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dl</td>
<td>43.7±12</td>
<td>43.4±13</td>
</tr>
<tr>
<td>Low HDL cholesterol, %</td>
<td>41</td>
<td>46</td>
</tr>
<tr>
<td>LDL cholesterol, mg/dl</td>
<td>121.6±36</td>
<td>121.1±33</td>
</tr>
<tr>
<td>High LDL cholesterol, %</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>Apo A1, mg/dl</td>
<td>111±21</td>
<td>112±22</td>
</tr>
<tr>
<td>Apo B, mg/dl</td>
<td>94.3±24</td>
<td>94.8±23</td>
</tr>
<tr>
<td>LDL particle size, Å</td>
<td>235.5±5.4</td>
<td>235.3±5.4</td>
</tr>
</tbody>
</table>

Data are mean±SD. *p<0.05 vs corresponding Non-DM group, †p<0.05 vs corresponding measured group.
LDL, low-density lipoprotein; DM, diabetes mellitus; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; CHD, coronary heart disease; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; NA, not available; HOMA-IR, Homeostasis Model Assessment-Insulin Resistance.

Waist, glucose, insulin, apo A1, and apoB were measured in the indicated number of patients (n) in each group.

clinical symptoms, electrocardiographic changes, blood examinations, and coronary arteriography. Patients reporting smoking ≥1 cigarette per day on admission were classified as current smokers. Resting systolic and diastolic blood pressures were measured at least twice on admission and the averaged values were used. Hypertension was defined as a systolic or diastolic blood pressure >140 or >90 mmHg, respectively, or the use of antihypertensive medications. DM was defined as fasting blood glucose ≥126 mg/dl or the use of hypoglycemic medications. Obesity was defined as a body mass index (BMI) >25 kg/m², based on the criterion of the Japan Society for the Study of Obesity. Patients using lipid-lowering medications or meeting the criteria of the Japan Atherosclerosis Society for hyper-LDL-cholesterolemia (>3.62 mmol/L or >140 mg/dl) and hypo-high-density lipoprotein (HDL)-cholesterolemia (<1.03 mmol/L or <40 mg/dl) were defined as hyperlipidemic.

OGTT, Lipoprotein and Metabolic Parameter Analysis
Blood samples for lipid analysis and hemoglobin (Hb) A1c were obtained on admission. Serum was stored at 4°C and used for the assay within 3 days after sampling. Total cholesterol, triglyceride, HDL-cholesterol, HbA1c, glucose, creatinine, and lipoprotein(a) were measured by standard laboratory procedures. Serum apolipoproteins (apo) were determined by an immunoturbidimetric assay (Daiichi Chemicals Co, Tokyo, Japan). LDL-cholesterol was measured by direct homogeneous assay of the serum using detergents without using the Friedewald formula. Peak LDL particle diameter was determined by 2–16% nondenatured polyacrylamide gel electrophoresis according to the method of Nichols et al. Pattern A was defined as a diameter of more than 255 Å and pattern B was defined as a diameter equal to or less than 255 Å.

Patients without a previous history of diabetes underwent a standard OGTT (75 g glucose dissolved in 225 ml water) after a 12-h overnight fast at the hospital discharge.
or the first visit to the clinic after discharge (9.4±0.9 days), unless the physician and/or patient did not agree to perform the test. We defined DM and IGT according to the criteria of Japanese Diabetic Association (1998): normal glucose tolerance (NGT) = fasting glucose (0 min) <110 mg/dl and 2-h glucose (120 min) <140 mg/dl; DM = fasting glucose (0 min) ≥ 126 mg/dl or 2-h glucose (120 min) ≥ 200 mg/dl; IGT = neither NGT nor DM. Patients with a previous diagnosis of diabetes or with a fasting plasma glucose ≥ 126 mg/dl and HbA1c ≥ 6.5% were defined as overt DM. Patients newly diagnosed with DM by OGTT were defined as preclinical DM. Immunoreactive insulin (IRI) was measured by radioimmunoassay. In the other patients who did not undergo OGTT, fasting glucose and IRI were measured during hospitalization. Insulin resistance was estimated based on Homeostasis Model Assessment-Insulin Resistance (HOMA-IR) levels calculated by fasting glucose level×fasting insulin level/405. The insulinogenic index is equal to the increase in insulin secretion (IRI at 30 min–IRI at pre-OGTT) divided by that of plasma glucose (glucose at 30 min–glucose at pre-OGTT).

Statistical Analysis

Statistical analyses were completed using Statview 5.0 software (SAS Institute, Cary, NC, USA). Comparisons of metabolic parameters between 2 groups were done with the unpaired-t-test. Comparisons of metabolic parameters among different glucose-regulation groups were done by one way analysis of variance (ANOVA). The Bonferroni/Dunn post hoc test was used when a significant group effect was observed. Changes in the plasma concentrations of glucose and insulin during an OGTT were analyzed with repeated measures of ANOVA. The total area under the curve (AUC) was calculated to estimate the overall response of plasma glucose and insulin concentrations at 4 time points (pre, 30 min, 1 h and 2 h) during an OGTT (expressed in units of mg·h^-1·dl^-1 for glucose and μU·h^-1·ml^-1 for insulin). The correlation coefficients between 2 variable parameters were determined by Pearson’s simple linear regression analysis. The difference in frequency data was determined by the chi-square test. Statistical significance was accepted at p<0.05.

Results

LDL size was measured in 314 unselected patients on admission. We did not have data for individuals admitted during weekends, after hours, and/or holiday seasons. Table 1 shows the clinical and metabolic characteristics of the overall study population and of the patients divided into 4 groups based on the measurement of LDL particle size and presence of DM (diagnosed in 122 patients). Among the non-DM patients, those in whom LDL size was not measured were significantly older and had a significantly lower BMI, lower incidence of taking lipid-lowering agents and of high LDL-cholesterol than those in whom it was measured. Other parameters, including clinical background, fasting glucose, HbA1c, and serum lipid levels,
were similar between the measured and unmeasured groups in both the non-DM and DM populations. The LDL size was similar between non-DM and DM patients.

Table 2 shows the clinical characteristics of patients divided into 2 groups based on the presence or absence of previously diagnosed overt DM. All the clinical and metabolic parameters, except for fasting glucose and HbA1c, were similar between the 2 groups.

Of 307 non-DM patients 110 underwent an OGTT and Table 3 shows the differences in clinical characteristics and metabolic parameters between patients who participated and those who did not. Although the patients who did not participate were older and had a lower BMI than those who did, no notable differences were observed between the groups with regard to glucose, HbA1c, IRI, lipids, LDL particle diameter, and apo A1 and apo B levels. Thirty-seven patients (34%) had NGT, and 44% and 22% had IGT and newly detected preclinical DM, respectively. Fasting glucose exceeded 126 mg/dl (129 mg/dl) with HbA1c =5.5% in only 1 of the 25 preclinical DM patients, whereas the 2-h glucose level equaled or exceeded 200 mg/dl in the other 24. A HbA1c level of 6.5% and a fasting glucose of
118 mg/dl were measured in only 1 of 48 IGT patients, and the HbA1c level was less than 6.5% in the other 47.

Table 4 shows the clinical and metabolic parameters among the 4 groups (NGT, IGT, preclinical DM, and overt DM). The fasting glucose and HbA1c levels in the NGT, IGT, and preclinical DM groups were significantly lower than those in the overt DM group but more or less similar to each other. The changes of both glucose and IRI differed significantly among the patients divided into 3 groups (NGT, IGT, and newly detected preclinical DM) (Fig 1). The 2-h glucose and 2-h IRI levels were significantly higher in the IGT group than in the NGT group, whereas the 2-h IRI levels were slightly higher in the IGT group than in the preclinical DM group. Fig 2 presents the comparison of the insulinogenic index, early-phase insulin secretion, and the AUC of IRI in these 3 groups. The insulinogenic index significantly decreased in the IGT and preclinical DM groups compared with the NGT, and decreased more in the preclinical DM than in the IGT group. The AUC of insulin was comparable among the 3 groups, and 3 patients with NGT and 2 patients with IGT had the highest AUC of insulin (>290 μU·h⁻¹·ml⁻¹, 95 percentile). Triglyceride, HDL-cholesterol, LDL-cholesterol and the apo A1, and apo B levels were similar among all 4 groups. The LDL particle diameter gradually decreased across categories of increasing glucose intolerance, but these differences were not statistically different.

Fig 3 shows the prevalence of the sd-LDL phenotype (pattern B) in the presence or absence of overt DM and in the presence or absence of abnormal glucose regulation detected by OGTT. Although the prevalence of pattern B was similar irrespective of the presence of overt DM, it was slightly higher in patients with IGT and preclinical DM than in patients with NGT. The prevalence of sd-LDL was significantly higher in patients with glucose intolerance than in those with NGT.
In correlation coefficients between LDL particle size and various parameters, the LDL size was weakly but significantly related to triglyceride ($r=–0.164, p=0.0040$), HDL-cholesterol ($r=0.255, p=0.0001$), apo B ($r=–0.290, p<0.0001$), age ($r=0.175, p=0.0019$), BMI ($r=–0.124, p=0.0282$), HbA1c ($r=–0.149, p=0.0085$) and fasting glucose ($r=–0.136, p=0.0159$) in the overall study population. Among the patients who underwent OGTT, the LDL size weakly correlated with the 1-h glucose ($r=–0.189, p=0.0729$), the 2-h glucose ($r=–0.180, p=0.0851$), and the AUC of the glucose ($r=–0.191, p=0.0699$), but not with fasting glucose and HbA1c.

Discussion

The present study demonstrates the clinical importance of glucose metabolism and sd-LDL in Japanese patients with ACS. Sd-LDL particles are established as closely associated with DM, although the findings from the present study and our previous reports have shown that overt DM has little influence on the predominance of sd-LDL among CHD patients. Glucose metabolism abnormalities gradually develop over a prolonged period in the prediabetic state, and recent evidence suggests that CHD develops as early as the prediabetic state, as well as overt DM. Approximately 30% of the ACS patients in the present study had overt diabetes, which was similar to that reported in studies of Caucasians although the findings from the present study and our previous reports have shown that overt DM has little influence on the predominance of sd-LDL among CHD patients. Glucose metabolism abnormalities gradually develop over a prolonged period in the prediabetic state, and recent evidence suggests that CHD develops as early as the prediabetic state, as well as overt DM. At the same time, however, as many as 66% of the ACS patients without previously known DM were newly diagnosed with diabetes and IGT (evaluated by OGTT), even though their HbA1c levels were in the normal range (5.3±0.5%). Consequently, more than 75% of the present ACS patients seemed to have abnormal glycometabolism, which could not be fully detected by fasting blood examination or HbA1c levels. Similar findings using OGTT have been reported in other recent studies. According to a Swedish study, 67% of 164 AMI patients without previously diagnosed DM showed newly detected disease and IGT at hospital discharge. The Euro Heart Survey showed that 58% of 923 ACS patients had DM and IGT. A small study (n=30) of Korean AMI patients also revealed newly detected DM and IGT at hospital discharge in 66% of patients without previously known disease. Hashimoto et al have very recently shown the similar results. In their study, 47% of the non-DM ACS patients with fasting glucose less than 126 mg/dl and an HbA1c less than 6.0% had glucose intolerance evaluated by OGTT performed at least 2 weeks after onset of ACS. Though the high prevalence of glucose intolerance in the ACS patients might have been a stress hormonal response induced by ACS, the Swedish study confirmed reproducible results of OGTT at 4 or 5 days and at 3 months after AMI. Although insulin secretion under stressful events such as ACS may differ between Japanese and Caucasians, the high prevalence of glucose intolerance seems to imply not only metabolic states caused by ACS but metabolic states that lead to ACS. To the best of our knowledge, however, the present study is the first to demonstrate a close association of sd-LDL measured at the onset of ACS and a remarkably high prevalence of IGT and preclinical DM as well as overt DM. Thus, patients with preclinical DM and IGT might have been hidden within the populations of non-DM CHD patients in previous studies.

Most studies from Western countries have shown that sd-LDL is an integral feature of insulin resistance, which coexists with hyperinsulinemia, obesity (especially visceral obesity), hypertension, hypertriglyceridemia, and low HDL-cholesterol. A very recent paper from the Insulin Resistance Atherosclerosis Study has reported that the LDL size gradually and significantly decreased across categories of increasing glucose intolerance (NGT, IGT and DM) among African Americans, Hispanics, and non-Hispanic whites. Approximately half of the overall popu-
lation from that study were obese (BMI = 30), and BMI, triglyceride and HDL-cholesterol levels also differed significantly among the subjects manifesting different patterns of glucose intolerance. Tenerz et al reported gradual elevations in serum triglyceride levels across subgroups of glucose intolerance (NGT, IGT and diabetes), as well as a significant association between metabolic syndrome and IGT, among AMI patients. In the present study, the BMI, fasting insulin, HOMA-IR, triglyceride, HDL-cholesterol, and apo B levels were similar among the 3 patterns of glucose tolerance. The LDL size decreased slightly and gradually as the glucose intolerance increased, but both decreases failed to reach statistical significance. This may be related to the similar metabolic characteristics related to insulin resistance syndrome among the 3 groups and the small size of the study population, a population with a relatively high incidence of pattern B compared with the population of healthy subjects without CHD. In addition, the LDL size was not evaluated when the OGTT was performed. In the determinations of the LDL particle sizes at both admission and hospital discharge (15.2 ± 9.9 days) in the 162 consecutive ACS patients investigated in our preliminary study, the LDL sizes were similar at admission and at discharge (256.0 ± 6.2 vs 256.2 ± 5.3 Å, no statistical difference by paired t-test), and 69% of the patients showed the same LDL phenotype at the 2 measurement points (unpublished data). However, the LDL phenotype changed in 28 of 78 patients with pattern B and in 22 of 84 patients with pattern A. On the basis of these findings, we speculate that in some of the patients the LDL particle size differed when the OGTTs were performed.

The diagnosis of insulin resistance is complex and cannot be easily performed in clinical practice. In the Helsinki Policemen Study, not the fasting insulin levels but the higher quintiles of the AUC of insulin during OGTT were significant risk for CHD during the 22-year study compared with the lowest quintile of AUC of insulin. On the other hand, the Quebec Cardiovascular Study demonstrated that fasting hyperinsulinemia was an independent predictor of CHD in French Canadian men. Yanase et al have recently shown that high HOMA-IR and fasting hyperinsulinemia are risk factors for coronary events among CHD patients with NGT. The fasting insulin and the HOMA-IR levels of CHD patients with coronary events in their study (9.1 ± 8.1 μU/ml and 2.1 ± 1.96, respectively) are similar to those in the present non-DM ACS patients. In the present study, the AUC of the IRI did not differ between the NGT and IGT groups, and 4 patients with NGT and 7 patients with IGT had a high AUC of insulin (>229.6 μU·h⁻¹·ml⁻¹, 90 percentile). These findings suggest that insulin resistance might be present in some NGT patients as well as IGT patients. On the other hand, the LDL particle size did not correlate with the fasting IRI, 2-h IRI, AUC of IRI or HOMA-IR levels, and approximately 80% of patients without overt DM showed HOMA-IR less than 2.5 in the present study. These findings suggest that insulin resistance was not evident in the majority of the present ACS patients. In addition, an impaired prompt secretion of insulin was found in the IGT patients, and was further exacerbated in the preclinical DM patients. Glucose intolerance can thus be concluded to be predominantly attributed to impaired initial insulin secretion rather than insulin resistance, as previously found in the recent reports of Japanese patients with type 2 diabetes and with CHD. Though the high prevalence of sd-LDL could not be conclusively associated with insulin resistance, it was certainly more strongly associated with impaired postprandial glucose regulation rather than with fasting glucose levels in the non-DM ACS patients.

The LDL size is strongly affected by serum triglyceride and HDL-cholesterol levels. Our group has recently shown that LDL particle size significantly correlates with triglyceride levels in the fasting state and at all time points after oral fat ingestion. We also have found that the prevalence of sd-LDL might increase in the postprandial state in response to postprandial hypertriglyceridemia, irrespective of the presence of DM. Even the non-fasting patients in our study had somewhat low serum triglyceride levels compared with patients investigated in other studies, including our own, and more than 70% of patients were normotriglyceridemic even in the non-fasting state. These results may relate to intravenous heparin injections in the emergency room. Even so, more than half of the patients showed the sd-LDL phenotype, and the LDL particle diameter was weakly but significantly correlated with triglyceride concentrations and positively correlated with HDL-cholesterol levels. The sd-LDL in patients with IGT and/or preclinical DM might be associated with not only postprandial hyperglycemia but postprandial hyperlipidemia as well.

**Study Limitations**

First, this was a retrospective study, and many of the patients did not undergo the OGTT or measurement of LDL particle size on admission. The BMI of the patients who participated was higher than those of the patients who did not. The tested and non-tested patients exhibited similar clinical characteristics and metabolic parameters, however, and more than 70% of them had a BMI of less than 25. Thus, although the present results might overestimate the prevalence of sd-LDL and/or glucose intolerance, they are likely to be applicable to all ACS patients. All cardiologists and patients need to know the clinical significance of glucose tolerance in ACS without previously known DM. Second, the time point of blood sampling may affect the LDL-cholesterol, HDL-cholesterol, and triglyceride values. Noting that lipids and lipoproteins may decrease within the first month after the onset of ACS, and further, that few previous studies have evaluated the LDL size at the onset of ACS, we decided to draw the serum samples for the measurement of lipids and lipoproteins on admission. Third, the serum lipid levels were not measured when the OGTTs were performed. As a result, associations between triglyceride levels and different patterns of glucose intolerance may not have been revealed. Future studies are needed to evaluate the association of sd-LDL with postprandial glucose and triglyceride metabolisms, and to prospectively examine how the amelioration of insulin resistance and improvement of glucose regulation by pharmacological and/or lifestyle interventions influences changes in the LDL particle size and serum lipid levels. Fourth, the present study lacks a control group against which the ACS patients can be compared. Based on the Diabetes Epidemiology: Collaborative Analysis of Diagnostic criteria in Asia study, the prevalence of IGT and preclinical DM was 15.3% and 3.4%, respectively, which are 25% of the values observed in our ACS patients. In addition, recent several studies support our results.
Conclusion

The present study results suggest that a high prevalence of s-d LDL, a highly atherogenic lipoprotein, is closely associated with abnormal glucose tolerance, a condition far more common than normal glucose metabolism in Japanese ACS patients. These findings could not be fully detected by fasting blood examination and HbA1c levels. An OGTT should be included in the diagnostic routine for ACS patients without previously known DM.

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