Original Article

Improved Lipid Profiles are Associated with Reduced Incidence of Coronary Vascular Events in Asymptomatic Patients with Type 2 Diabetes and Impaired Myocardial Perfusion

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Aim: Individuals with type 2 diabetes are at high risk for cardiovascular events; however, a modality that could reduce risk has not been fully evaluated. We examined the annual incidence rate of cardiovascular events in asymptomatic Japanese diabetic patients who underwent gated myocardial perfusion single-photon computed tomography (SPECT).

Methods: Asymptomatic patients ($n=485$) aged ≥ 50 years and with either a maximal carotid artery intima-media thickness of ≥ 1.1 mm, or urinary albumin ≥ 30 mg/g creatinine, or at least two of abdominal obesity, low HDL cholesterol, high triglyceride levels and hypertension were evaluated at 50 institutions using gated SPECT with the stress-rest protocol and were followed up for three years. In the patients with summed stress scores (SSS) of ≥ 9 , the initial high cardiovascular incidence rate in the first year declined significantly ($p<0.001$) from 21% to 2% during the second and third year.

Results: The incident rate was consistent among diabetics with low SSS during follow-up. Baseline LDL and non-HDL cholesterol levels significantly reduced (123 ± 6.4 to 99 ± 6.1 mg/dL; $p<0.05$) during the first year in diabetic patients with high SSS, but did not significantly change in diabetic patients with low (<9) SSS.

Conclusion: The immediate improvement of lipid levels within one year correlated with the significant reduction in CVD events arising in diabetic patients with moderate or severe myocardial ischemia. Thus, rapidly lowering hyperlipidemia is very effective for patients with type 2 diabetes at high risk for cardiac events.

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Key words; Cardiovascular events, ^{99m}Tc -tetrofosmin, Prognosis, Estimated glomerular filtration rate

Introduction

Coronary stenosis, myocardial ischemia and baseline cardiac functions are important factors for the risk stratification of cardiac events and thus to predict patient prognosis. Among various clinical factors, dia-

betes mellitus promotes atherosclerosis, a major pathophysiological cause of cerebral and myocardial infarction (MI)¹. The risk for diabetic patients without prior MI is 2-4-fold higher than that for non-diabetic patients and is comparable with the risk for non-diabetic patients with prior MI^{2, 3}; however, since atherosclerosis can progress even in asymptomatic diabetic patients, diagnosing ischemic heart diseases at an early subclinical stage is vital⁴.

The role of single-photon emission computed tomography (SPECT) in detecting myocardial ischemia and evaluating prognosis has been validated^{1, 3, 5-7}. We

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designed the J-ACCESS (Japanese-Assessment of Cardiac Event and Survival Study by Quantitative Gated SPECT) 2 prospective cohort study of asymptomatic patients with type 2 diabetes⁸⁾ and the first year interim report clarified the value of gated SPECT for such patients⁹⁾. The final report then evaluated the prognostic value of gated SPECT to a more detailed stratification of ischemic cardiovascular events in diabetic patients¹⁰⁾. Patients with considerable myocardial ischemia had a significantly higher incidence of cardiac vascular events than those without ischemia. In addition, multivariate regression analysis showed that the significant variables were myocardial ischemia, a low estimated glomerular filtration rate and current smoking; however, the annual rate of cardiovascular events considerably differed after the first year among diabetic patients with moderate or severe myocardial ischemia. The present study retrospectively evaluates the clinical parameters and treatment modalities that might correspond to this observation.

Methods

Patients

The J-ACCESS 2 prognostic registry is a prognostic cohort study of 513 patients from 50 institutions⁸⁾ who were registered between June 2004 and September 2005; the protocol has been described in detail⁸⁻¹⁰⁾. Physicians specializing in diabetes with a high risk of cardiovascular events at all 50 institutions participated in a 3-year follow-up study. The inclusion criteria comprised age ≥ 50 years with type 2 diabetes and either a maximal carotid artery intima-media thickness (max IMT) of ≥ 1.1 mm¹¹⁾ or a urinary albumin level of ≥ 30 mg/g creatinine^{12, 13)}, or at least two of abdominal obesity (BMI ≥ 25 and abdominal circumference ≥ 85 cm for men, and ≥ 90 cm for women); hypo-HDL-cholesterolemia (HDL-cholesterol < 40 mg/dL); hypertriglyceridemia (triglyceride ≥ 150 mg/dL) and hypertension (blood pressure $\geq 130/85$ mmHg). The abdominal circumference criteria conformed to Japanese guidelines for obesity. Individuals with previous cardiovascular events were excluded.

The institutional review board of each hospital approved the study, which complied with the Ethics Guidelines for Epidemiological Research in Japan. Written informed consent was obtained from all participants before starting the study.

Myocardial Perfusion Imaging

The protocol for acquiring stress-rest myocardial perfusion SPECT images and the evaluation of images has been described in detail^{9, 10)}. All SPECT images

were interpreted by experienced physicians using a 20-segment model as in the J-ACCESS study³⁾. The results of the segmentation were comparable with estimations based on the 17-segment model¹⁴⁾. Each of the myocardial segments was visually scored using a 5-point system as 0, normal; 1, mildly reduced; 2, moderately reduced; 3, severely reduced and 4, absent. Totals were calculated as summed stress, rest and difference scores (SSS, SRS and SDS) as validated by precedent prognostic studies⁷⁾. The maximum score was 80 points (20 segments $\times$ 4 points/segment). Risk-based groups were determined from the SSS severity categories of < 9 (normal or mildly abnormal), and ≥ 9 (moderately or severely abnormal) as categorized in the J-ACCESS study³⁾.

Quantitative gated SPECT proceeded as described^{3, 15)}. SPECT slices were reconstructed using the standard software provided by the manufacturer. Gated SPECT images were analyzed at each institution using QGS software (Cedars Sinai Medical Center, CA, USA) with automated processing. Inappropriate edge tracing was manually adjusted. Values for left ventricular ejection fraction (LVEF, %), end-diastolic volume (EDV, mL) and end-systolic volume (ESV, mL) were obtained.

Follow-Up Survey

Cardiovascular events were investigated 1, 2, and 3 years after registration and the final prognostic analysis herein was based on 3-year follow-up data from 485 of the 513 patients because seven underwent revascularization within 30 days of registration, seven died due to non-cardiac causes and 14 who did not attend the hospital were excluded. The end-point of the follow-up was hard events defined as sudden or cardiac death and acute coronary syndrome. Total events also included heart failure severe enough to require hospitalization, percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), *de novo* stable angina, unstable angina, non-severe heart failure, transient ischemic attack of the brain (TIA), as well as stroke and peripheral artery disease (PAD).

Statistics

Continuous variables are expressed as the means $\pm$ standard deviation. We applied the χ^2 test to categorical data. Changes in blood lipid concentrations were compared using two-way ANOVA. Statistical significance was defined as $p < 0.05$.

Results

Diabetic patients with a high SSS (≥ 9) included

Fig. 1. Total (Panel A) and initial (Panel B) cardiac event rates among patients during years 1, 2, 3 and 2 plus 3.

Black and white bars, cardiac event rates among patients with high and low SSS, respectively. Significance indicates difference between high and low SSS. NS, no significant difference.

a significantly higher prevalence of subjects with ACE inhibitor, aspirin and wall motion abnormality, and significantly higher levels of blood urea nitrogen and urinary albumin. Diabetic patients with total events included a significantly higher prevalence of insulin- and ticlopidine-administered subjects as well as a high prevalence of current smokers and high SSS, as well as significantly higher total cholesterol and systolic blood pressure, and a lower estimated glomerular filtration rate than those without events.

The sum of total events was significantly higher

among diabetic patients with high than low SSS during the first year of follow-up (36.2%, 17/47 vs. 7.8%, 34/438, $p < 0.0001$). The total number of events that occurred during the second and third years of follow-up among diabetic patients with high SSS was significantly lower than that during the first year (5 events, 5.3% per patient-year; $p < 0.0001$). In contrast, the total event rate was consistent among diabetic patients with low SSS during the second and third years (6.4% per patient-year; **Fig. 1A**).

The incident rate of initial total events during

Fig. 2. Non-HDL, HDL, total and LDL cholesterol at baseline and follow-up.

Data are shown as the means $\pm$ standard deviation. Solid and broken lines, patients with high and low SSS, respectively.

the first year of follow-up was significantly higher among diabetic patients with high than low SSS (21.2%, 10/47 vs. 4.0%, 17/438, $p < 0.0001$). Diabetic patients with high SSS had one initial event during the second and third years of follow up, which was significantly lower than that during the first year (1.0% per patient-year; $p < 0.0001$). In contrast, the initial event rate was consistent throughout the second and third years among diabetic patients with low SSS (4.0% per patient-year; **Fig. 1B**).

Neither the baseline numbers of patients given hypoglycemic drugs such as sulphonylurea, metformin or insulin, nor baseline levels of glycated hemoglobin significantly differed from those during the second and third years. The number of diabetic patients with high SSS administered pioglitazone significantly decreased from the baseline to the second and third years of the follow-up period.

Baseline LDL cholesterol and non-HDL cholesterol significantly reduced from 123 ± 6.4 to 99 ± 6.1 mg/dL during the first year in diabetic patients with high SSS ($p < 0.05$), but did not significantly change in those with low SSS (< 9 ; **Fig. 2**). Without a lipid-

lowering drug, subjects with high SSS showed an increase in LDL cholesterol. With lipid-lowering drugs, subjects with high SSS showed a decrease in LDL cholesterol. The baseline estimated glomerular filtration rate did not significantly change during the first year in both diabetic patients with high SSS and low SSS.

Discussion

Coronary artery disease is a leading cause of death among American and European patients with diabetes. The prevalence of diabetes in the Japanese population is rapidly increasing as the lifestyle becomes more Americanized; therefore, the cardiovascular event rate among asymptomatic diabetic Japanese patients is a matter of considerable concern.

The rate of cardiac deaths and cardiovascular events among patients with type 2 diabetes in the J-ACCESS 2 population during a three-year follow-up was 13%. Asymptomatic patients with type 2 diabetes were enrolled in the J-ACCESS 2 study and we validated markers of high risk, such as a maximal carotid artery intima-media thickness of > 1.1 mm¹¹), urinary

albumin >30 mg/g creatinine¹²⁾, and at least two of the four relevant conditions to ensure the registration of those with appropriate diagnostic yields. Considering the substantial difference in cardiovascular event rates among American, European, and Japanese diabetic patients, we consider that these conditions for enrolment into J-ACCESS 2 might have specifically selected diabetic patients at high-risk for cardiovascular diseases.

The role of SPECT in detecting myocardial ischemia has been validated^{5, 6)} and a general consensus has also been reached regarding prognostic evaluation. Since the risk of cardiac death and MI increases with increasing degrees of scan abnormalities, the summed score is now widely accepted as described in the guidelines of the American Cardiology Society⁷⁾. The rate of sudden or cardiac death and cardiovascular events in the J-ACCESS 2 population with asymptomatic type 2 diabetes was 1.9-fold higher among individuals with high than low SSS.

Thus, the J-ACCESS 2 study has proven that asymptomatic myocardial ischemia stratified a high risk of coronary vascular events in asymptomatic patients with diabetes. Such patients with high SSS had a sum of 22 events during the three-year follow-up. The high annual incident rate of 36% in the first year was significantly ($p < 0.0001$) reduced to 5.3% during the second and third years; however, diabetic patients with low SSS had 34 events in the first year and 56 events thereafter (**Fig. 1A**). J-ACCESS 2 was designed as a follow-up study, but the involved physicians could modify treatment modalities; therefore, the present study evaluated whether changes in modality or clinical parameters correlated with the significant reduction in the coronary vascular event rate in diabetic patients with high SSS.

Neither the baseline numbers of patients given hypoglycemic drugs, such as sulphonylurea, metformin or insulin, nor baseline levels of glycated hemoglobin significantly differed from those during the second and third years of follow-up. The number of diabetic patients with high SSS given pioglitazone significantly decreased from baseline to the second and third years of follow-up. The baseline frequency of pioglitazone administration did not differ between diabetic patients with high and low SSS (data not shown). Because pioglitazone is contraindicated for diabetic patients with coronary cardiac insufficiency, the significant reduction in the rate of pioglitazone administration to diabetic patients with high SSS might be the result of moderate or severe myocardial perfusion impairment rather than the possibility that it was a leading cause of the reduction in CVD events.

Due to the design of the J-ACCESS 2 study, lipid profiles but not modalities for treating dyslipidemia were compared between the baseline and the first year of follow up. Baseline levels of LDL and non-HDL cholesterol significantly reduced during the first year in diabetic patients with high SSS (123 ± 6.4 to 99 ± 6.1 mg/dL; $p < 0.05$). These values did not significantly change in diabetic patients with low (<9) SSS. Because of the study design, insufficient numbers of subjects given anti-platelet drugs, lipid-lowering drugs, and current smoking were addressed to examine statistical significance.

Two possibilities could explain the rapid change in the annual rate of cardiovascular events in diabetic patients with high SSS. One is that a considerable portion of diabetic patients at high risk for CVD developed a coronary vascular event during the first year and this considerably decreased the likelihood of another developing thereafter; however, the J-ACCESS study³⁾ found that event rates among diabetic patients with previous coronary heart disease were consistently high during a 3-year follow-up period. Thus, the high incidence rate in the first year might not have been reduced after CVD events in the J-ACCESS 2 population.

The second possibility is that some risk reduction in the first year might be responsible for decreasing the rate of CVD events. Levels of LDL cholesterol and non-HDL cholesterol significantly decreased in the first year only among patients with high SSS. This improved lipid profile might partially account for the subsequent decrease in the event rate. A retrospective survey to examine the possible lipid-lowering medication was performed using the 47 subjects with high SSS and indicated that 6 subjects not taking a lipid-lowering drug showed an increase in LDL cholesterol, 2 subjects taking statins showed a decrease, and the remaining 39 subjects gave no response because of absence or personnel changes of the responsive doctors. These data are comparable with the speculation that a significant reduction of LDL cholesterol in subjects with high SSS might result from the initiation of lipid-lowering medication rather than the reinforcement of diet or exercise therapy.

The immediate reduction in the CVD event rate was associated with improved lipid profiles in diabetic patients with high SSS and an average LDL cholesterol level of 123 mg/dL. This finding was partially comparable with the results of the CARDS study¹⁶⁾; however, intensive lipid lowering was not associated with an immediate reduction in the rate of CVD events in diabetic patients without high LDL cholesterol in the CARDS study.

The J-ACCESS 2 study design precluded a full investigation into which treatment strategy would improve the lipid profile among diabetics with high SSS; however, the present findings suggest that intensively lowering lipid levels might immediately reduce the likelihood of CVD events arising in diabetic patients with moderate or severe myocardial ischemia and near-normal LDL cholesterol levels.

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Conflicts of Interest

None.

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