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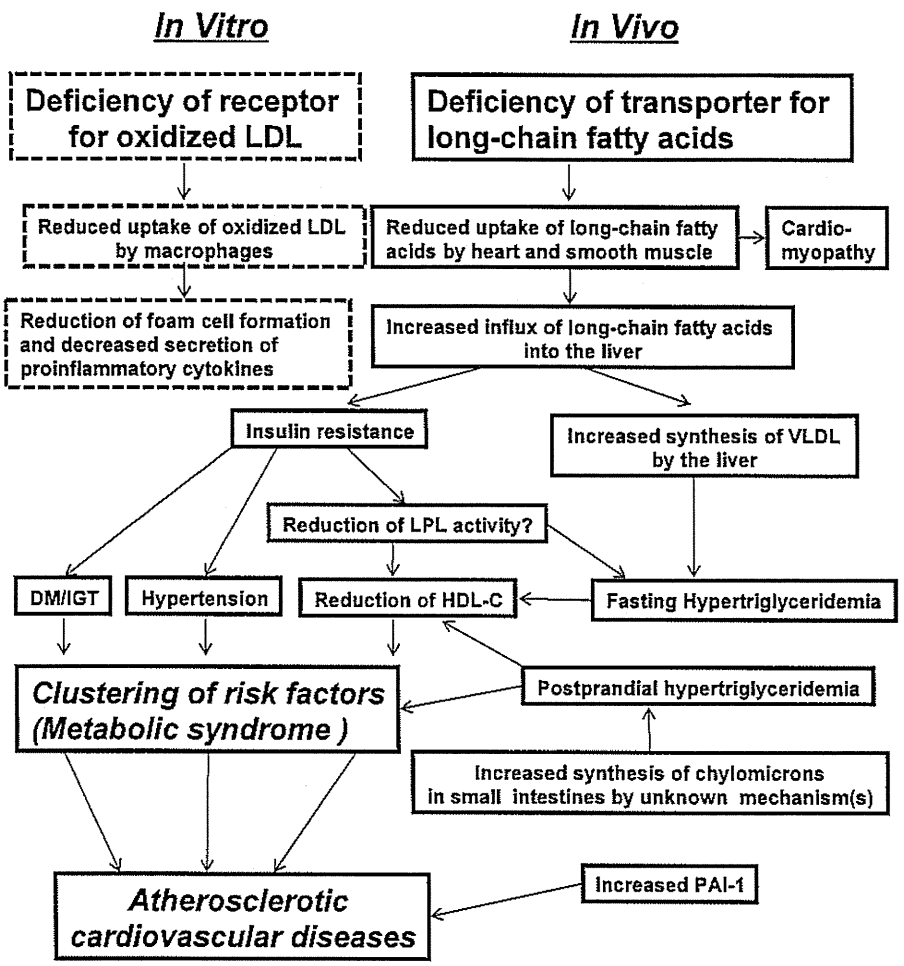

Fig. 5. Possible molecular mechanisms for enhanced atherosclerosis in human CD36-D

In vitro, CD36 deficiency causes the reduced uptake of oxidized LDL by macrophages, leading to decreased foam cell formation and secretion of proinflammatory cytokines; however, *in vivo*, CD36 deficiency results in reduced uptake of long-chain fatty acids (LCFA) by the heart and skeletal muscles, causing impaired metabolism of LCFA by the liver and circulation. These abnormalities as a whole may eventually lead to atherosclerotic cardiovascular diseases.

be linked with an increased risk of atherosclerotic cardiovascular diseases in obesity, insulin resistance and diabetes mellitus[46]. The increase of PAI-I was partly attributed to the accumulation of abdominal visceral fat[47]. Yanai *et al.*[48] reported elevated PAI-I levels in patients with CD36-D, although the mechanism was speculated to be linked to abnormal fatty acid metabolism.

Taken together, as illustrated in **Fig. 5**, despite the anti-atherosclerotic aspects of monocyte-derived macrophages from CD36-D patients due to the reduced uptake of oxidized LDL and decreased secretion of proinflammatory cytokines *in vitro*, the pro-atherogenic profiles *in vivo* may exceed the anti-atherosclerotic properties, thus enhancing the development of atherosclerosis. These pro-atherogenic profiles of CD36-D patients include: 1) increased lipoprotein remnants and postprandial hyperlipidemia, 2) reduced serum HDL-C levels, 3) increased FFA levels because of deficiency of LFCA transporter, 4) insulin resistance and impaired glucose metabolism, 5) hypertension, and 6) increased levels of PAI-I. These risk parameters may cluster and interact, finally leading to the marked enhancement of atherosclerosis; therefore, early screening and detection of CD36-D patients and assessment of atherosclerotic cardiovascular diseases are essential, especially in a population such as the Japanese in which their frequency is extremely high. Fur-

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ther investigations into the molecular and vascular biological mechanisms of the progression of atherosclerosis in patients with CD36-D may be necessary in future studies.

Conclusions

Patients with CD36-D are associated with severe and enhanced atherosclerotic diseases. The morbidity of CAD is significantly higher in patients with CD36-D than in healthy subjects, and the frequency of CD36-D is significantly higher in patients with CAD than in healthy subjects. The clustering of atherogenic metabolic profiles such as dyslipidemia, including the accumulation of FFA and remnants, hypertension and insulin resistance, may enhance atherogenicity in patients with CD36-D.

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Conflicts of Interest

S. Yamashita has received consultancy fees from Otsuka Pharmaceutical Company and Skylight Biotech Co. The other co-authors have nothing to disclose.

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Original Article

Fasting Serum Apolipoprotein B-48 Can be a Marker of Postprandial Hyperlipidemia

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Aim: Postprandial hyperlipidemia (PH) is thought to be caused by the impaired postprandial metabolism of triglycerides (TG)-rich lipoproteins in both endogenous and exogenous pathways; however, there is no consensus. It is difficult to estimate the presence of PH without performing a time-consuming oral fat loading (OFL) test, so postprandial lipoprotein metabolism was analyzed by measuring the postprandial levels of apolipoprotein (apo) B-48 and apo B-100, and the correlation between postprandial TG increase and fasting apoB-48 levels was assessed to establish a good marker of PH without performing an OFL test.
Methods: Ten male normolipidemic subjects were loaded with a high-fat (HF, 1045 kcal) or standard (ST, 566 kcal) meal, and the lipids, apolipoproteins and lipoprotein profiles were analyzed after each meal.
Results: TG, apo B-48, remnant-like particles (RLP)-cholesterol and RLP-TG levels were increased and their levels were significantly higher after intake of the HF meal than the ST meal; however, there was no postprandial increase in apo B-100 and LDL-C levels. Postprandial increases in TG levels of CM, VLDL, LDL and HDL were significantly higher after intake of the HF meal than the ST meal. Fasting apo B-48 levels were strongly correlated with the incremental area under the curve of TG after intake of the HF meal, but not the ST meal.
Conclusion: Postprandial TG increase was mainly due to increased CM and CM-R, but not VLDL. Measurement of fasting serum apo B-48 may be a simple and useful method for assessment of the existence of PH.

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Key words; Apolipoproteins, Atherosclerosis, Chylomicrons, Postprandial hyperlipidemia, Remnants

Introduction

Several epidemiological studies have recently demonstrated that both fasting and non-fasting hypertriglyceridemia are closely related to the development of atherosclerosis[1,2]. Non-fasting hypertriglyceridemia is partially associated with postprandial hyperlipidemia (PH) in patients with dyslipidemia, which is characterized by the postprandial accumulation of excess TG-rich lipoproteins (TRLs) and their partially hydrolyzed product, remnants or remnant lipoprotein particles. The atherogenicity of postprandial accumu-

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lation of TRLs and their remnants was predicted by Zilversmit over 30 years ago[3], and has been demonstrated in numerous subsequent studies[4-6]. For the quantitative evaluation of remnant lipoprotein particles, two methods for measuring remnant lipoprotein cholesterol levels have been developed. Remnant-like particle cholesterol (RLP-C) is determined by measuring cholesterol concentrations in remnant-like particles (RLP), the unbound fraction of serum via immunoaffinity columns attaching monoclonal antibodies against apo B-100 and apo A-I[7]. Remnant lipoprotein cholesterol (RemL-C) is assessed by directly measuring the cholesterol level in a mixture of CM remnants and VLDL remnants[8]. These serum remnant lipoprotein cholesterol levels are a very useful marker related to atherosclerosis because they correlate with the morbidity of coronary heart disease (CHD)[9, 10].

In the postprandial state, serum TG levels increase rapidly around 3-4 hours after the meal because of the prompt production of TRLs. TRLs and their remnants are heterogeneous and originate from two different organs, that is, the small intestines (CM and CM remnants) and liver (VLDL and VLDL remnants), respectively; however, it is unclear whether the increase in TRLs is mainly due to the increase in CM or VLDL in the postprandial state and whether the postprandial increase in remnant lipoprotein particles is due to the increase in CM-R or VLDL-R. For quantitative analysis of postprandial lipoprotein profiles, the development of new methods for analyzing fasting serum levels and postprandial changes in the levels of CM-R and VLDL-R separately and stably has long been awaited.

For accurate analysis of fasting and postprandial changes in the levels of CM and CM-R, we previously developed a novel sandwich enzyme-linked immunosorbent assay (ELISA) system to measure serum apolipoprotein B-48 (apo B-48) concentrations[11]. Both CM and CM-R continue to possess one apo B-48 molecule at a time until they are cleared by the liver; therefore, serum apo B-48 concentrations represent the number of CM and CM-R. Fasting apo B-48 levels were distributed over a wide range (mean ± SD was 5.2 ± 3.8 μg/mL) in normolipidemic and hyperlipidemic subjects[11]. Fasting apo B-48 was significantly higher in patients with supposed accumulation of CM and CM-R[11] and in patients with metabolic syndrome (MetS)[12] compared with normolipidemic subjects. Fasting apo B-48 levels may be influenced by postprandial changes of CM and CM-R derived from the last meal; however, there have been no report on whether fasting apo B-48 is correlated with postprandial changes of CM and CM-R and whether it can be a good marker of these lipoproteins. Many clinical studies have reported the relationship between high serum apo B-48 and atherosclerosis[13, 14], and emerging evidence suggests that CM-R might be responsible for the initiation of atherogenesis in the arterial wall[6]. If the correlation between fasting and postprandial levels of apo B-48 could be clarified, it would become very easy to speculate the existence of PH by a single measurement of fasting apo B-48.

In the current study, we attempted to investigate whether apo B-48-containing lipoproteins or apo B-100-containing lipoproteins were the main lipoproteins that increased in the postprandial state and whether the fasting serum level of apo B-48 might be a simple and useful marker of PH, using a crossover study in healthy subjects loaded with an HF meal.

Subjects and Methods

Subjects

Ten healthy young male volunteers were enrolled and hospitalized at Kitasato University Research Center for Clinical Pharmacology. None of the subjects had obesity (body mass index, BMI ≥25), dyslipidemia (fasting serum total cholesterol (TC) ≥200 mg/dL and/or fasting serum TG ≥150 mg/dL), abnormal renal or hepatic functions, symptoms of illness, family history of premature CHD (before 60 years of age) or hypertension (systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg). None of the subjects was taking any medications known to affect carbohydrate or lipoprotein metabolism. Their mean age was 23.9 ± 3.1 years (mean ± SD) and the mean BMI was 21.3 ± 1.6 kg/m^2. Written informed consent was obtained from the subjects and the study design was approved by the ethics committee of the university.

Oral Meal Loading Test

Subjects were divided into two groups (group A and group B; each, n=5) and these groups were matched for age and BMI. We prepared two kinds of meals. The ST meal contained 566 kcal, consisting of 20.1 g fat (32% of the total calories), 16.4 g protein (12%) and 81.2 g carbohydrate (56%), respectively, while the HF meal contained 1,045 kcal, consisting of 62.6 g fat (54%), 36.2 g protein (14%) and 80.9 g carbohydrate (32%), respectively. On day 1 and 3 of hospitalization, both groups were loaded with the ST meal and directed not to eat after supper. Group A was loaded with the HF meal in the morning on day 2 and the ST meal on day 4. For a cross-over study, group B was loaded with the ST meal on day 2 and the HF meal on day 4. Blood was collected during

fasting and 1, 2, 3, 4, 5, 6 and 8 hours after meal loading. Sera were separated immediately by low-speed centrifugation (15 minutes, 2,000 g at 4℃) and stored at −80℃ until measurements.

Measurements

Serum TC and TG levels were determined by enzymatic methods, serum apo B-100 levels by an immunoturbidity method, serum LDL-C and HDL-C levels by a direct method (Sekisui Medical Co., Ltd., Tokyo, Japan), and serum RLP-C and RLP-TG levels by the immunoaffinity isolation method (Jimro-II; Japanese Immunoresearch Laboratories Co., Tokyo, Japan), respectively. Serum apo B-48 levels were determined by a chemiluminescent enzyme immunoassay (CLEIA) system (Fuji Rebio Inc., Tokyo, Japan) which was modified from a sandwich ELISA system which we developed in a previous study[11]. Cholesterol and TG levels of CM, VLDL, LDL and HDL were measured by the densitometry method after being separated by electrophoresis (CholeTriCombo, Helena Laboratories, Tokyo, Japan). All samples were treated in accordance with the Helsinki Declaration. The areas under the curve (AUC) of these parameters were calculated by the trapezoidal method and the incremental AUC (iAUC) values were also calculated by ignoring the area beneath the fasting level.

Statistical Analysis

The statistical significance of differences between the subjects on the HF meal and ST meal was estimated by Mann-Whitney's *U* test and Wilcoxon's test. The correlation coefficients (r) and statistical significance of differences were analyzed between the lipid profiles and iAUC-TG, between fasting apo B-48 and the postprandial peak of apo B-48, and between fasting apo B-48 and AUC-apo B-48 by Spearman's rank-order correlation coefficient analysis. All statistical assessments were conducted using StatView statistical software (Hulinks Inc., Tokyo, Japan).

Results

Postprandial Changes of Serum Lipoprotein and Apolipoprotein Profiles

All subjects were loaded with the ST and HF meals and postprandial changes of lipoprotein and apolipoprotein profile were analyzed. There was no significant postprandial increase in TC, LDL-C, HDL-C or apo B-100 after the intake of either meal (**Fig. 1A**). In contrast, TG, apo B-48, RLP-C and RLP-TG increased after intake of each meal in a time-dependent manner and decreased after their peak at 3 to 5 hours (**Fig. 1A**). The postprandial levels of these parameters were significantly higher after intake of the HF meal than the ST meal, and their peaks were delayed at 4 to 5 hours after intake of the HF meal (**Fig. 1A**). The iAUC-TG and iAUC-apo B-48 values, which indicated the net postprandial increase in TG and apo B-48, were about 2-fold higher after the intake of the HF meal than the ST meal (**Fig. 1B**).

Postprandial Changes of Serum Lipoprotein Profiles

For the analysis of postprandial changes of lipoproteins, the cholesterol and TG contents of CM, VLDL, LDL and HDL were measured before and after the intake of each meal. There were no significant increases in LDL-C and HDL-C in the postprandial state after the intake of each meal (**Fig. 2**). CM-C and CM-TG levels were significantly higher after intake of the HF meal than the ST meal. VLDL-C increased after the intake of each meal but there was no significant difference in postprandial VLDL-C levels between the ST and HF meals. VLDL-TG, LDL-TG and HDL-TG increased after the intake of each meal, and were significantly higher after intake of the HF meal than the ST meal (**Fig. 2**).

Correlations between the Serum iAUC-TG and Fasting Lipid Levels

We assessed the correlations between iAUC-TG levels and fasting/postprandial lipid parameters. The correlation coefficients between the iAUC-TG and fasting levels of TC, TG, HDL-C, LDL-C, apo B-48, apo B, RLP-C and RLP-TG were estimated after intake of the ST meal ($n=10$), HF diet ($n=10$) or a combination of the two meals (ST + HF meal; $n=20$) (**Table 1**). Significant correlation was observed only between the iAUC-TG and fasting serum apo B-48 level after intake of the HF meal (**Table 1** and **Fig. 3**). Between the iAUC-TG and postprandial peaks of TG, RLP-C, RLP-TG and apo B-48, the significant correlations were observed most prominently 5 hours after intake of the HF meal (TG; $r=0.950$, $p<0.0001$, RLP-C; $r=0.811$, $p<0.01$, RLP-TG; $r=0.926$, $p<0.001$, apo B-48; $r=0.775$, $p<0.01$). Moreover, the fasting apoB-48 level was significantly correlated with AUC-apo B-48 and the postprandial peak level of apo B-48 after intake of the HF meal, but not the ST meal (**Fig. 3**).

Discussion

The current study has demonstrated for the first time that the postprandial increase in TG was mainly due to the increase in apo B-48-containing lipopro-

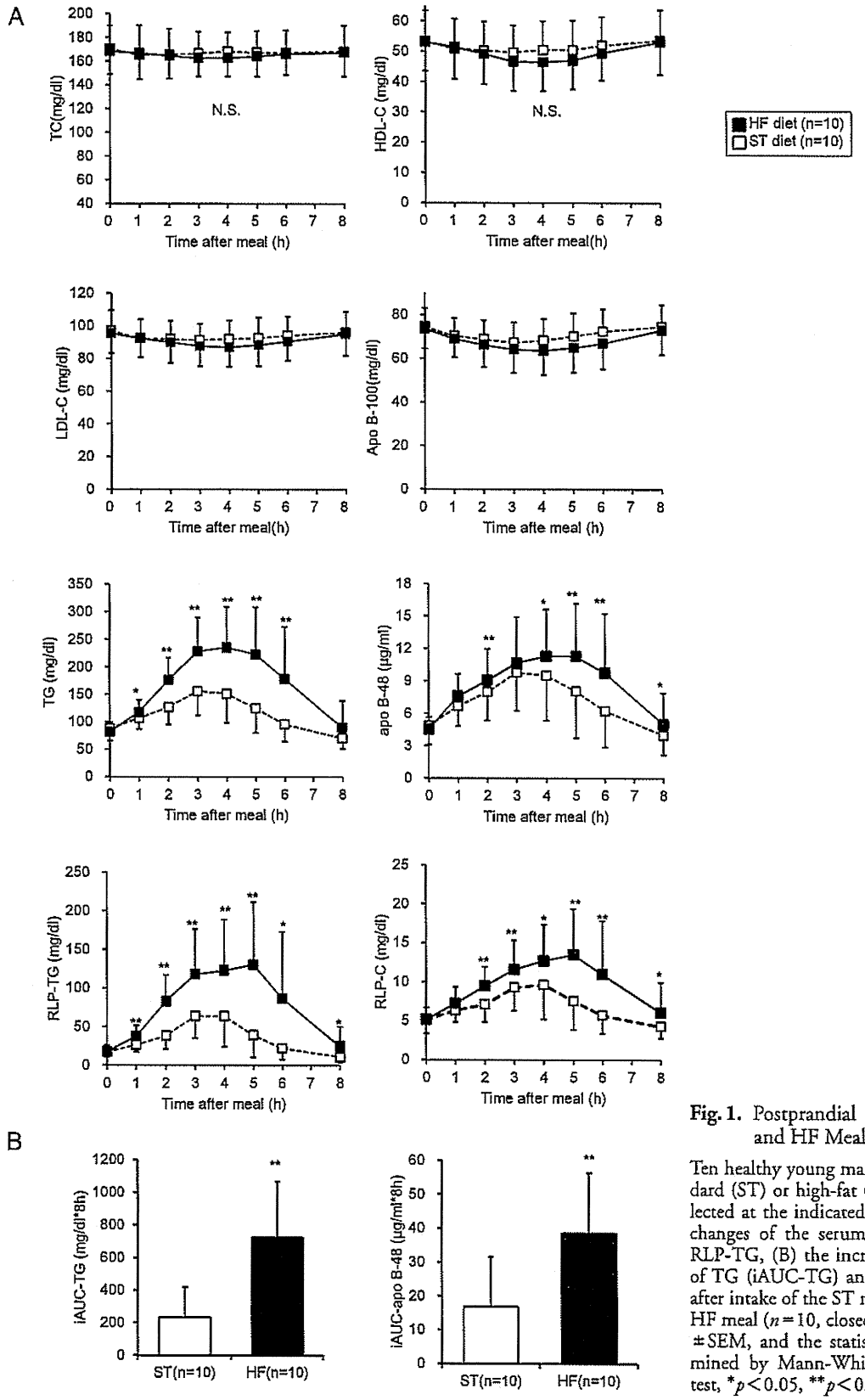

Fig. 1. Postprandial Lipid Profiles after the ST and HF Meals.

Ten healthy young male subjects consumed the standard (ST) or high-fat (HF) meal and blood was collected at the indicated time-points. (A) Postprandial changes of the serum TG, apo B-48, RLP-C and RLP-TG, (B) the incremental area under the curve of TG (iAUC-TG) and apo B-48 (iAUC-apo B-48) after intake of the ST meal ($n=10$, open squares) and HF meal ($n=10$, closed squares). Values are the mean ±SEM, and the statistical significances were determined by Mann-Whitney's U test and Wilcoxon's test, $^{*}p<0.05$, $^{**}p<0.01$ vs. the ST diet.

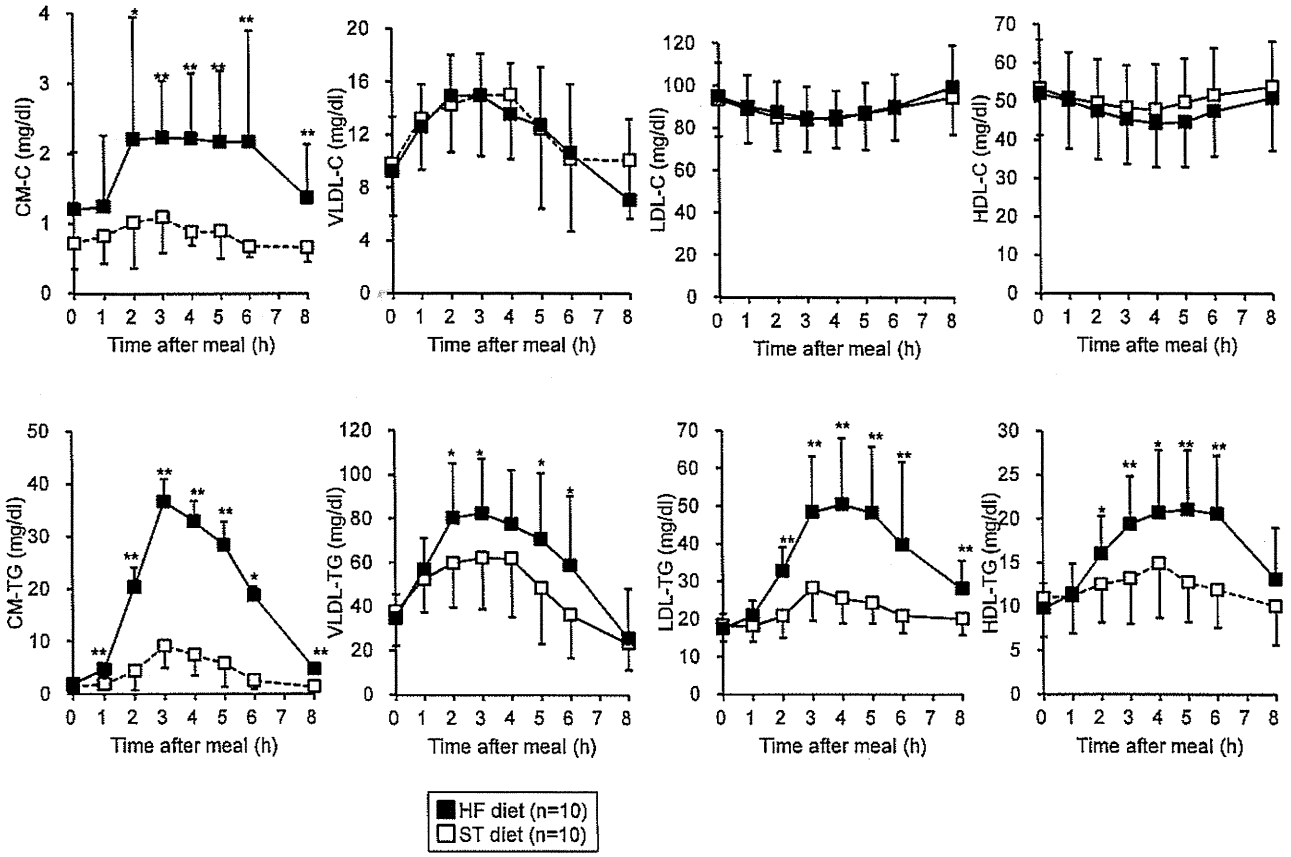

Fig. 2. Postprandial Lipoprotein Profiles after the ST and HF Meals.

Postprandial changes in cholesterol and TG of CM, VLDL, LDL and HDL after the intake of each meal were measured by the densitometry method after being separated by agarose gel electrophoresis (CholeTriCombo; Helena Laboratories, Tokyo, Japan). Values are the mean ± SEM, and statistical significances were determined by Mann-Whitney's *U* test and Wilcoxon's test, $^{*}p<0.05$, $^{**}p<0.01$ vs. ST.

teins, but not due to the increase in apo B-100-containing lipoproteins. Fasting serum apo B-48 levels are most strongly associated with iAUC-TG levels.

Measurement of Serum ApoB-48

In the current study, we evaluated fasting and postprandial CM and CM-R metabolism by measuring apo B-48 concentrations using a CLEIA system, which is suitable for automatic quantitative statistical analyses in clinical settings. Retinyl palmitate (RP) and SDS-PAGE coupled with Western blotting were previously acceptable for the analysis of CM metabolism; however, these two methods are not suitable for exact quantitative analysis for the following reasons: uniform labeling of CM by RP is disrupted in the presence of CM-R[15], the quantity of apo B-48 assessed by SDS-PAGE is variable and unstable for repeated measurements[16-18] and many samples cannot be handled at the same time. The ELISA system using

Table 1. Correlation coefficients (r) between iAUC-TG and Various Fasting Parameters

	ST diet ($n=10$)	HF diet ($n=10$)	ST+HF ($n=20$)
TC	0.028	−0.061	−0.052
TG	−0.142	0.505	0.047
HDL-C	0.286	0.017	0.081
LDL-C	0.011	0.111	−0.084
Apo B-48	0.162	0.809*	0.238
Apo B-100	−0.781	−0.455	−0.314
RLP-C	−0.175	0.144	0.035
RLP-TG	0.151	0.608	0.345

The incremental area the curve of TG (iAUC-TG) was calculated in both groups and correlation coefficients (r) were calculated.
*$p=0.0046$

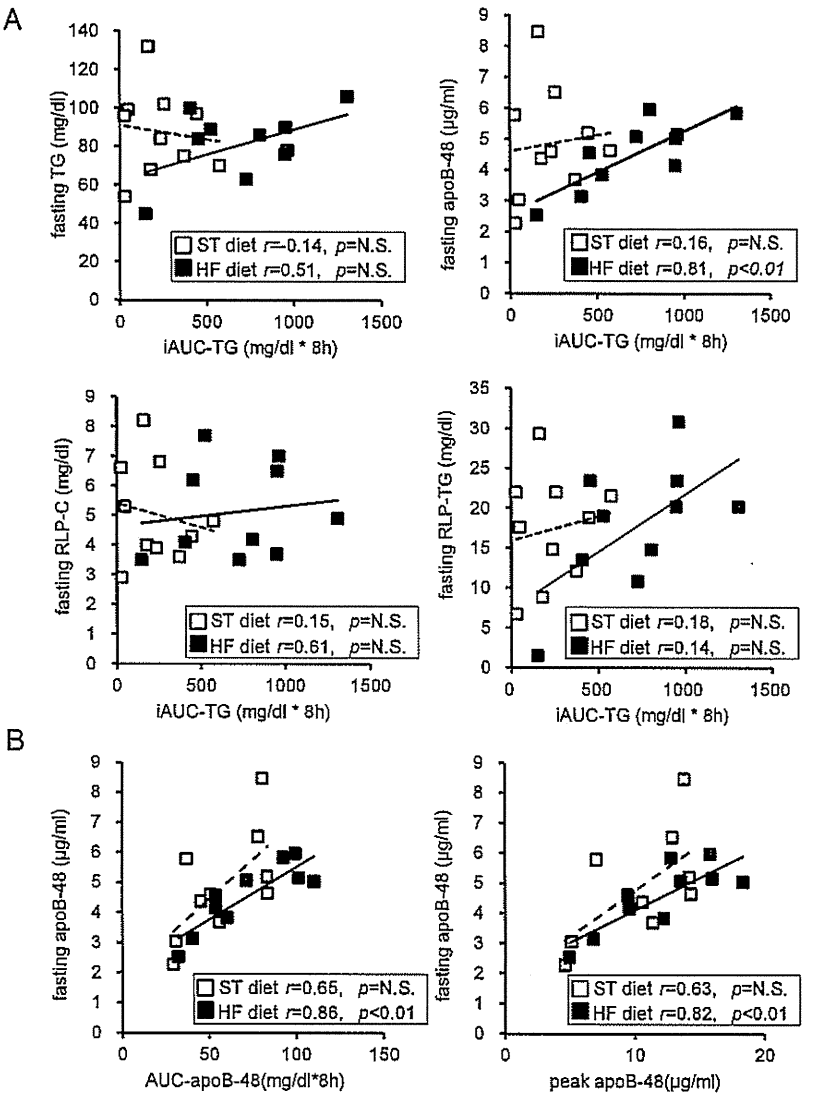

Fig. 3. Correlations between the iAUC-TG and Fasting Lipid Parameters.

(A) Correlations of iAUC-apo B-48 with fasting TG, apo B-48, RLP-C and RLP-TG, (B) correlations of fasting apo B-48 with AUC-apo B-48 or peak apo B-48, were determined after intake of the ST meal ($n=10$, open squares and dotted line) or the HF meal ($n=10$, closed squares and continuous line). The correlation coefficients (r) and the statistical significances of differences (p) were calculated using Spearman's rank-order correlations. Significance was assumed at $p<0.01$.

polyclonal antibody against apo B-48 has been used for stable and kinetic studies of CM/CM-R[11, 19, 20]; however, polyclonal antibodies are not reproducible for strict statistical analysis with high specificity compared with monoclonal antibodies[18, 19, 21]. Therefore, our CLEIA system, which uses monoclonal antibodies against apo B-48 molecule and could be used with an autoanalyzer (results within 2 hours), is suitable for strict statistical analyses related to apo B-48-containing lipoprotein metabolism. In the present study, we could measure apo B-48 both in the fasting and postprandial states for use in accurate statistical analysis with high quality and reproducibility.

ApoB-48-Containing Lipoproteins But Not Apo B-100-Containing Lipoproteins Are Increased in the Postprandial State

After meal loading, serum TG levels gradually

increased because of the postprandial increase in TRLs. These TRLs might consist of both apo B-48-containing lipoproteins, which are produced in the intestine, and apo B-100-containing lipoproteins from the liver. In the present study, we focused on which lipoproteins were increased in the postprandial state. After the intake of each meal, TG and apo B-48 increased, but LDL-C and apoB-100 did not (**Fig. 1A**), which clearly indicated that apo B-48-containing lipoproteins were increased in postprandial serum, but apo B-100-containing lipoproteins were not. Karpe *et al.* showed that the percentage of VLDL in TRLs was 96-97% in the fasting state and 91-96% in the postprandial state, respectively, and suggested that both VLDL and CM particles increased in the postprandial state, but VLDL particles were mainly increased because the lipoprotein lipase (LPL)-induced hydrolysis of VLDL was halted by competitive hydrolysis of CM/CM-R[5]; however, no postprandial increase in apo B-100 and LDL-C levels indicates the absence of postprandial increase in apo B-100-containing lipoproteins and the postprandial increase in apo B-48-containing lipoproteins can decrease the VLDL/whole TRLs ratio. It was thus suggested that postprandial increase in TRLs was mainly due to the progressive accumulation of CM and CM-R, not due to that of VLDL or LDL.

Postprandial increases in TG and apo B-48 (iAUC-TG and iAUC-apoB-48) were higher after intake of the HF meal than the ST meal, indicating that intestinal absorption of a high fat meal promoted more abundant CM production from the intestine (**Fig. 1B**). Intake of the HF meal caused higher postprandial increases in CM-C and CM-TG levels (**Fig. 2**), suggesting that the proportion of fat which was contained in the meal directly affected the quantity of CM from the intestine. VLDL-TG, LDL-TG and HDL-TG levels were increased after the intake of each meal, and postprandial increases in these levels were higher after intake of the HF meal than the ST meal (**Fig. 2**). In our previous study, we demonstrated that the particle size of CM-R in patients with PH varied from large CM to small LDL, using fractionated flow-through by HPLC[22]. Since there was little postprandial increase in LDL-C and apo B-100, it was suggested that postprandial increases in VLDL-C, VLDL-TG and LDL-TG were mainly due to the increase in CM-R, which might be related to the increase in CM production after intake of the HF meal. The postprandial increase in HDL-TG was higher when subjects were loaded with the HF meal than the ST meal (**Fig. 2**), which might be due to postprandial TG exchanges between CM and HDL; the TG contained in CM are transferred to HDL in exchange for cholesteryl esters from HDL to CM by the action of plasma cholesteryl ester transfer protein (CETP).

Fasting Serum Apo B-48 is a Good Marker of Postprandial Increases in CM and CM-R

Previously, the oral fat loading (OFL) test or the stable isotope study was used to evaluate postprandial dynamic changes in the lipid and lipoprotein profile; however, the study subjects must tolerate overnight fasting and restraint for over 8 hours before 7 collections of blood samples after administration of the fatty meal or a stable isotope[23]. Therefore, these tests are not suitable for routine studies of the postprandial lipoprotein metabolism. In the current study, we assessed the correlation coefficients of the fasting serum apo B-48 and postprandial lipid and lipoprotein metabolism. As we have clearly shown in **Table 1**, among other lipid parameters, only the apo B-48 level was demonstrated to have a significant correlation with iAUC-TG after intake of the HF meal. This appears quite reasonable because the fasting apo B-48 indicates the particle number of residual CM-R produced by the last meal and remaining in the fasting serum. Intake of the HF meal causes higher CM production and CM-R accumulation than the ST diet. As shown in **Fig. 3**, the correlations between fasting apo B-48 and iAUC-TG, between fasting apo B-48 and AUC-apo B-48, and fasting apo B-48 and peak apo B-48, were significant after intake of the HF meal but not significant after intake of the ST meal. High levels of iAUC-TG, AUC-apo B-48 and peak apo B-48 may indicate that postprandial CM production was enhanced after meal loading and/or CM-R accumulation might have occurred due to the impaired catabolism of CM-R; therefore, increased fasting apo B-48 was significantly reflected by the postprandial increases in CM and CM-R. Recently, Sato *et al.* also reported that fasting TG and RemL-C were significantly higher and fasting apo B-48, RLP-C and RLP-TG were relatively higher in subjects with healthy, but high postprandial TG than in subjects with normal postprandial TG using TEST MEAL A[24]. In the current study, using HF and ST meals as a control, we found a significant correlation between fasting apoB-48 and postprandial increases of CM and CM-R. These results clearly suggest that fasting apo B-48 correlated with the postprandial accumulation of TRLs, mainly CM and CM-R, and fasting apo B-48 was the best explanatory variable for the impaired accumulation of TRLs and their remnants.

Many reports have suggested that not only oxi-

dized LDL, but also CM-R are associated with atherogenicity[6]. The accumulation of CM-R was associated with insulin resistance and the prevalence of type II diabetes mellitus[25]. Plasma apo B-48 was inversely correlated with plasma adiponectin and leptin levels and positively associated with plasma insulin, HOMA, and visceral, subcutaneous and total adipose tissue areas[26]. High fasting serum apoB-48 should be reduced carefully by a variety of nutritional and pharmacological approaches along with clinical interventions for the improvement of other impaired metabolic diseases and atherosclerotic cardiovascular diseases. Since PH has been established as one of the risk factors for CHD, its detection is very important for the prevention of CHD. The measurement of fasting serum apo B-48 may lead to straightforward detection of PH in a variety of patients at risk without a time-consuming meal test. Taken together, the current apo B-48 assay may have a number of applications in future studies.

Limitations of the Current Study

In the present study, we investigated study subjects who were young (23.9 ± 3.1 years old), lean (mean BMI; 21.3 ± 1.6 kg/m^2) and healthy males. In further investigations, we would also examine postprandial lipoprotein metabolism in females, normolipidemic obese, aged, diabetic and hyperlipidemic subjects.

Conclusion

In conclusion, postprandial high TG is mainly caused by the postprandial accumulation of CM and CM-R in subjects with normolipidemia after ingesting the HF meal. Fasting serum apo B-48 is a simple and useful marker of postprandial high TG and the accumulation of CM-R.

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Disclosures

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ORIGINAL ARTICLE
Preventive Medicine

Longitudinal Risk of Cardiovascular Events in Relation to Depression Symptoms After Discharge Among Survivors of Myocardial Infarction

– Osaka Acute Coronary Insufficiency Study (OACIS) –

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Background: The purpose of this study was to investigate the association between depression symptoms 1 year after onset and subsequent cardiovascular events among survivors of myocardial infarction (MI).

Methods and Results: The participants were recruited from respondents to a district-based survey known as the Osaka Acute Coronary Insufficiency Study. Of 4,271 eligible MI patients, 1,951 completed the Zung Self-Rating Depression Scale (SDS) at their 1-year follow-up examination. After excluding patients who experienced cardiovascular events within 1 year, the data for the remaining 1,307 male patients and 280 female patients were analyzed. Among male patients, depression status at 1 year after onset of MI was significantly related to risk of subsequent cardiovascular events throughout the follow-up period (median 2.9 years). The male patients in the top vs. bottom tertiles of SDS scores (top tertile being ≥42) had a multivariable-adjusted hazard ratio (HR) of 1.67 (95% confidence interval (CI) 1.01–2.77, P=0.04), and a 1-SD increment in SDS score was significantly related to a heightened risk of cardiovascular events, with a multivariable-adjusted HR of 1.30 (95%CI 1.07–1.58, P=0.01). There were no significant associations between SDS scores and cardiovascular events among female patients.

Conclusions: Depression symptoms 1 year after onset of MI are a significant predictor of subsequent cardiovascular events for male patients. (*Circ J* 2011; **75:** 2878–2884)

Key Words: Cardiovascular events; Depression; Long-term prognosis; Myocardial infarction

Depression symptoms develop in approximately 20–25% of patients following myocardial infarction (MI)[1–3] and several studies have emphasized that depression symptoms following MI are associated with worse prognosis, reinfarction, and other cardiac events.[4,5] Most of the previous studies[6–8] have focused on the relationship between depression symptoms at the time of hospitalization and cardiac outcomes during the high-risk period associated with recurrence and death (ie, the initial 6 months after acute MI).[6–8]

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However, the prognosis for the acute phase of MI has improved dramatically because of new diagnostic aids and advanced treatment techniques,[9,10] so the issues of concern about patients with MI have changed gradually from the acute phase only to both the acute and chronic phases. We previously reported that depression symptoms within 3 months after onset were related to cardiac outcomes during the first year.[11] However, only a few other studies have documented the relationship between depression symptoms after hospital discharge and cardiovascular outcomes.[12,13] One study suggested that reassessment of depression symptoms at 1 year might not be useful for identifying additional patients at risk, because the level of depression symptoms during admission was more closely linked to long-term survival than the level at 1 year, although the depression symptoms both during admission and at 1 year post-MI were significantly related to long-term prognosis.[12] The more recent study assessed the time course of depression symptoms at hospitalization and 3, 6, and 12 months post-MI,

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Table 1. Clinical Characteristics According to Tertile of Depression Score

	Total	Tertile of SDS score			P value
		≤33	34–41	≥42	
Male patients (n)	1,307	403	446	458	
Sociodemographic characteristics					
Age (mean±SD)	61.4±10.2	62.8±9.7	60.8±10.3	60.6±10.4	0.002
Living alone (%)	13.6	12.8	10.7	17.3	0.06
Unemployed (%)	33.0	32.2	29.1	37.6	0.03
Medical history and risk factors					
Hyperlipidemia (%)	49.0	51.9	46.0	49.2	0.24
Hypertension (%)	51.4	50.8	49.9	53.6	0.52
Diabetes mellitus (%)	29.8	27.1	27.7	34.2	0.04
Smoking status (%)	76.2	71.1	77.1	79.9	0.009
Drinking status (%)	57.1	59.4	56.0	56.0	0.52
Prior MI (%)	10.2	10.1	10.0	10.6	0.95
Medical status					
Killip class >1 (%)	10.4	10.7	9.1	11.4	0.51
Q-wave MI (%)	73.5	72.5	74.0	73.9	0.87
β-blockers at discharge (%)	10.4	10.4	8.4	12.6	0.35
	Total	**Tertile of SDS score**			**P value**
		≤35	**36–43**	**44**	
Female patients (n)	280	82	101	97	
Sociodemographic characteristics					
Age (mean±SD)	67.8±11.9	66.4±11.6	68.0±11.3	68.9±11.9	0.36
Living alone (%)	20.9	13.0	26.8	22.6	0.19
Unemployed (%)	78.4	73.3	76.9	83.9	0.24
Medical history and risk factors					
Hyperlipidemia (%)	51.3	56.6	49.5	48.9	0.55
Hypertension (%)	57.5	57.0	63.3	52.1	0.29
Diabetes mellitus (%)	29.0	31.2	27.8	28.4	0.87
Smoking status (%)	27.8	23.8	26.7	32.3	0.43
Drinking status (%)	28.3	25.0	29.0	30.4	0.72
Prior MI (%)	5.1	6.2	5.0	4.3	0.84
Medical status					
Killip class >1 (%)	14.4	13.3	11.5	18.5	0.57
Q-wave MI (%)	63.0	67.9	63.9	57.9	0.38
β-blockers at discharge (%)	12.8	12.8	13.0	12.5	0.99

SDS, Self-Rating Depression Scale; MI, myocardial infarction.

and found that patients with advancing depression symptoms during 1 year post-MI showed a particularly high risk of cardiac events during the average follow-up period of 2.5 years.[13] Therefore, cardiac events after MI are likely to be affected by depression not only at the time of hospitalization but also after discharge.

The typical Japanese MI patient has a more favorable prognosis after onset than patients in Europe and America,[14] related to low-fat dietary habits and the small proportion of cases of non-Q-wave or prior MI, or multivessel disease.[15] Not only physical mechanisms but also psychosocial mechanisms may influence long-term convalescence. The depression status during convalescence of survivors with MI may be an important marker reflecting physical status, health-related behaviors and life-styles.[6,16,17] However, little is known about the relationship between depression after the onset of MI and long-term outcomes. The purpose of this study was to investigate the association between depression symptoms within 1 year after onset of MI and subsequent cardiovascular events.

Methods

Patient Sample

The participants were recruited from among respondents to a district-based survey known as the Osaka Acute Coronary Insufficiency Study (OACIS),[18,19] which was conducted to assess clinical variables, therapeutic procedures, and subsequent clinical events involving patients with acute MI in Osaka. This study comprised consecutive patients admitted directly or transferred to 1 of the 25 collaborating hospitals between April 1998 and April 2006 within 1 week of the onset of acute MI. Acute MI was diagnosed if 2 of the following 3 criteria were met: (1) clinical history of central chest pressure, pain, or tightness lasting ≥30 min, (2) ST segment elevation >0.1 mV in at least one standard or 2 precordial leads, and (3) a rise in serum creatine kinase concentration to more than twice the normal laboratory value. Participants provided written informed consent for long-term follow-up, which was approved by the respective hospital's ethics review committee, before discharge from the hospital. Patients who died in hospital, were unable to

Table 2. Age-Adjusted HRs of Total Cardiovascular Events Associated With Baseline Clinical Characteristics

	HR for cardiovascular events	P value
Male patients (n=1,307)		
Sociodemographic characteristics		
Living alone	1.06 (0.50–2.24)	0.89
No occupation	1.26 (0.82–1.94)	0.29
Medical history and risk factors		
Hyperlipidemia	0.95 (0.63–1.43)	0.79
Hypertension	1.78 (1.16–2.74)	0.010
Diabetes mellitus	2.03 (1.35–3.04)	<0.001
Smoking status	1.29 (0.79–2.11)	0.32
Drinking status	1.08 (0.72–2.11)	0.70
Prior MI	2.39 (1.46–3.91)	<0.001
Medical status		
Killip class >1	1.43 (0.82–2.50)	0.21
Q-wave MI	1.07 (0.68–1.70)	0.77
β-blockers at discharge	1.30 (0.55–3.50)	0.56
Female patients (n=280)		
Sociodemographic characteristics		
Living alone	3.04 (0.82–11.32)	0.09
No occupation	0.99 (0.29–3.43)	0.99
Medical history and risk factors		
Hyperlipidemia	0.43 (0.16–1.13)	0.09
Hypertension	2.26 (0.80–6.42)	0.13
Diabetes mellitus	1.56 (0.61–3.95)	0.35
Smoking status	0.25 (0.06–1.12)	0.07
Drinking status	0.30 (0.07–1.31)	0.11
Prior MI	1.04 (0.14–7.75)	0.97
Medical status		
Killip class >1	2.75 (0.36–20.65)	0.34
Q-wave MI	1.57 (0.56–4.35)	0.39
β-blockers at discharge	0.93 (0.12–7.34)	0.94

HR, hazard ratio; MI, myocardial infarction.

communicate verbally with attending physicians, had a major psychological disease, or refused entry into this study were excluded. The present study was approved by the Institutional Review Board of Osaka University Hospital.

Initially, 4,271 successive cases were registered in the present study, but we excluded 1,038 patients with missing data for baseline risk factors such as blood pressure, anthropometrics, and the Zung Self-Rating Depression Scale (SDS).[20] Of 3,233 patients who returned the questionnaire within 1 year after onset of MI, 1,282 responses were excluded because of missing data for follow-up SDS. Of the remaining 1,951 patients, 364 patients (302 male patients, 62 female patients) were excluded because of an onset of cardiovascular events within 1 year. The data for the remaining 1,587 patients (1,307 male patients, 280 female patients) were used for the analysis.

Baseline Characteristics

To determine baseline characteristics and depression symptom status over time, data on the following clinical variables were extracted from the OACIS registry database: age, sex, living arrangements, employment status, hypertension, hyperlipidemia, diabetes mellitus, smoking status, drinking status, history of previous MI, Killip class, Q-wave MI, and β-blocker use at discharge. Hypertension was defined as a history of systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg, and/or administration of antihypertensive therapy. Hyperlipidemia was defined as a fasting total cholesterol level >5.7 mmol/L, a fasting triglyceride level >1.7 mmol/L, and/or administration of antilipidemia therapy. Diabetes mellitus was defined as a fasting plasma glucose level >126 mg/dl and/or utilization of antidiabetic therapy. Smoking status and drinking status were determined according to whether the patient was a current smoker or drinker at the baseline time point.

Assessment of Depression Status

Depression symptoms were assessed with SDS, which comprises 20 items describing depression symptoms.[20] This self-completed questionnaire is in wide use and has been shown to have satisfactory reliability and validity. The SDS tests were mailed out by research assistants within 3 months after onset of MI and within 1 year after onset of MI, and respondents described how frequently they experienced each symptom on a 4-point scale: 'little of the time', 'some of the time', 'good part of the time', or 'most of the time'. The frequency was converted to an integer between 1 and 4, and the total SDS score was the sum of the numbers obtained in response to the 20 questions.

Follow-up

For ethical reasons, all patients without exception received the usual in-hospital and post-discharge care independent of

Table 3. Profiles of Cardiovascular Events During Each Follow-up Period According to Depression Score

	Outcome among male patients				Outcome among female patients			
	Tertile of SDS score			Total	Tertile of SDS score			Total
	≤33	34–41	≥42		≤35	36–43	≥44	
N	403	446	458	1,307	82	101	97	280
Total CVD events	25 (6.2)*	30 (7.4)	42 (10.4)	97	7 (1.7)	5 (1.2)	7 (1.7)	19
Fatal CVD events	4 (1.0)	3 (0.7)	5 (1.2)	12	1 (0.2)	0 (0)	0 (0)	1
Cardiac deaths	2 (0.5)	3 (0.7)	5 (1.2)	10	1 (0.2)	0 (0)	0 (0)	1
Stroke deaths	2 (0.5)	0 (0)	0 (0)	2	0 (0)	0 (0)	0 (0)	0
Non-fatal CVD events	21 (5.2)	27 (6.7)	37 (9.2)	85	6 (1.5)	5 (1.2)	7 (1.7)	18
Angina	3 (0.7)	0 (0)	3 (0.7)	6	0 (0)	0 (0)	0 (0)	0
Myocardial reinfarction	3 (0.7)	2 (0.5)	3 (0.7)	8	0 (0)	0 (0)	1 (0.2)	1
Heart failure	1 (0.2)	1 (0.2)	4 (1.0)	6	2 (0.5)	1 (0.2)	2 (0.5)	5
Arrhythmia	2 (0.5)	0 (0)	5 (1.2)	7	0 (0)	0 (0)	0 (0)	0
PTCA	11 (2.7)	19 (4.7)	18 (4.5)	48	3 (0.7)	4 (1.0)	1 (0.2)	8
Coronary artery bypass surgery	1 (0.2)	2 (0.5)	2 (0.5)	5	0 (0)	0 (0)	1 (0.2)	1
Stroke	0 (0)	3 (0.7)	2 (0.5)	5	1 (0.2)	0 (0)	2 (0.5)	3

*Frequency (%) in parentheses.
SDS, Self-Rating Depression Scale; CVD, cardiovascular disease; PTCA, percutaneous transluminal coronary angioplasty.

their SDS score. The follow-up data from the OACIS database were collected at 3, 6, and 12 months after onset of MI and annually thereafter until January 1, 2008. Data concerning cardiovascular events were obtained from hospital records and interviews with patients or their family members by telephone. The primary outcome of this study was related to cardiovascular events (predefined as cardiac death, stroke death, nonfatal myocardial reinfarction, coronary angioplasty or bypass, readmission for heart failure, unstable angina, stroke or uncontrolled arrhythmia). Survival time was defined as the date from 1 year after the onset of MI to the date of the event or final follow-up period. The median follow-up period was 3.9 years after onset.

Statistical Analysis

SPSS for Windows (version 16) was used for statistical analyses. Continuous baseline and outcome variables are expressed as mean±SD, and discrete variables as absolute values, percentages, or both. The ANOVA test was used for comparing continuous variables and the Pearson chi-square test or Fisher exact test for comparing discrete outcome variables, and their trends were tested using linear regression for continuous variables and logistic regression for dichotomous variables. In order to determine dose-dependent relationships between SDS scores and cardiovascular events, we analyzed the association by using the tertile of the SDS score. A Cox proportional-hazards model was used to assess hazard ratios (HRs) of cardiovascular events for patients in relation to baseline clinical characteristics and depression symptoms within 1 year after the onset of MI adjusting for age and traditional cardiovascular risk factors including hyperlipidemia, hypertension, diabetes mellitus, smoking status, and prior MI. The median follow-up period in the survival analysis was 2.9 years. Because a SDS score ≥40 is a well-accepted standard cutoff for the identification of clinically significant depressive symptoms,[20] SDS scores were also examined dichotomously (SDS <40 as referent). The analysis was also done by further adjustment for the presence of depression symptoms (SDS score ≥40) within 3 months after the onset of the initial MI. For all analyses, statistical significance was set at $P<0.05$ using a 2-tailed procedure.

Results

Participants' Characteristics

The average score on the depression symptoms scale (potential range 20–80) 1 year after MI was 38.9 (SD=8.7, range 20–73) for the 1,587 patients who had not experienced a cardiovascular event within 1 year, and 39.8 (SD=9.1, range 20–72) for the 364 patients who were excluded because of the onset of events within 1 year ($P=0.08$ between groups). Compared with male patients (average score=38.5, SD=8.6), female patients (average score=40.8, SD=8.9) had a significantly higher depression score ($P<0.001$ between sexes).

Table 1 shows the prevalence of baseline clinical characteristics grouped according to tertile of depression score. The depression score at 1 year after MI in male patients was significantly related to age, employment status (being unemployed), diabetes mellitus, and smoking at baseline (P for trend <0.05, respectively). There were no significant differences among tertiles of depression score for other baseline characteristics. The depression score of female patients was not significantly related to any baseline characteristic.

Table 2 shows the age-adjusted HRs of total cardiovascular events associated with baseline clinical characteristics, including sociodemographic variables, medical history and medical status. Among male patients, hypertension, diabetes mellitus, and prior MI were significant risk factors for total number of cardiovascular events. Among female patients, living alone, hyperlipidemia, and smoking status were risk factors for total number of cardiovascular events, although the trend did not reach statistical significance. In the subanalysis, compared with 364 patients who were excluded because of the onset of cardiovascular events within 1 year, the 1,587 patients who had not experienced such events within 1 year were less likely to have diabetes mellitus [$\chi^2(1)=4.93$, $P=0.03$] or hypertension [$\chi^2(1)=6.34$, $P=0.01$], be classified as Killip class >1 [$\chi^2(1)=2.84$, $P=0.09$], or have had a prior MI [$\chi^2(1)=2.89$, $P=0.09$].

Associations Between Depression Symptoms and Long-Term Prognosis

Table 3 shows the profiles of cardiovascular events accord-

Table 4. Multivariate Model for Total Cardiovascular Events During Follow-up Period

	Male				Female			
	Tertile of SDS score			1-SD** increment of SDS score	Tertile of SDS score			1-SD** increment of SDS score
	≤33	34–41	≥42		≤35	36–43	≥44	
Patients, n	403	446	458	1,307	82	101	97	280
No. at risk	403	446	458	1,307	82	101	97	280
No. of events	24	30	42	96	7	5	7	19
Age-adjusted HR	1	1.23	1.72	1.29	1	0.56	0.86	1.08
95%CI		0.72–2.09	1.05–2.82	1.06–1.56		0.18–1.77	0.30–2.49	0.69–1.68
P value		0.44	0.03	0.01		0.32	0.79	0.75
Multivariable HR*	1	1.26	1.67	1.30	1	0.50	0.97	1.17
95%CI		0.74–2.17	1.01–2.77	1.07–1.58		0.15–1.61	0.33–2.87	0.74–1.83
P value		0.39	0.04	0.01		0.25	0.97	0.51

*Adjusted for age, hyperlipidemia, hypertension, diabetes mellitus, smoking status and prior myocardial infarction.
**One SD: male, 8.6 points; female, 8.9 points.
SDS, Self-Rating Depression Scale; HR, hazard ratio; CI, confidence interval.

Table 5. Multivariate Model for Non-Fatal Cardiovascular Events During Follow-up

	Male				Female			
	Tertile of SDS score			1-SD** increment of SDS score	Tertile of SDS score			1-SD** increment of SDS score
	≤33	34–41	≥42		≤35	36–43	≥44	
Patients, n	403	446	458	1,307	82	101	97	280
No. at risk	403	446	458	1,307	82	101	97	280
No. of events	21	27	37	85	6	5	7	18
Age-adjusted HR	1	1.29	1.74	1.29	1	0.64	0.97	1.14
95%CI		0.73–2.28	1.02–2.98	1.05–1.59		0.19–2.12	0.32–2.93	0.73–1.79
P value		0.39	0.04	0.01		0.47	0.96	0.57
Multivariable HR*	1	1.30	1.64	1.29	1	0.55	1.07	1.24
95%CI		0.73–2.33	0.95–2.84	1.04–1.59		0.17–1.84	0.35–3.28	0.78–1.97
P value		0.38	0.08	0.02		0.33	0.90	0.37

*Adjusted for age, hyperlipidemia, hypertension, diabetes mellitus, smoking status and prior myocardial infarction.
**One SD: male, 8.6 points; female, 8.9 points.
Abbreviations see in Table 4.

ing to tertile of depression score 1 year after onset. For male patients, approximately 88%, and for female patients, approximately 95% of total cardiovascular events were non-fatal and half of the non-fatal cases received percutaneous transluminal coronary angioplasty (PTCA) during the follow-up period. The number of total cardiovascular events in male patients increased with higher tertile of the SDS score.

Depression status 1 year after onset of MI was significantly related to risk of cardiovascular events during the follow-up period for male patients (Table 4). The male patients in the top tertile of SDS scores had a multivariable-adjusted HR of 1.67 (95% confidence interval (CI), 1.01–2.77, P=0.04) during the follow-up, compared with those in the bottom tertile. Furthermore, a 1-SD increment in SDS score was significantly related to risk of cardiovascular events, with a multivariable-adjusted HR of 1.30 (95%CI, 1.07–1.58, P=0.01). This relation remained statistically significant after further adjustment for the presence of depression symptoms within 3 months after onset of initial MI: the multivariable-adjusted HR=1.25 (95%CI, 1.00–1.56, P=0.046). There were no significant associations between SDS score and cardiovascular events among female patients. Age-adjusted and multivariable-adjusted HRs of cardiovascular events for patients with depression (SDS ≥40) vs. those without depression (SDS <40) were 1.48 (95%CI, 0.99–2.21, P=0.05) and 1.44 (95%CI, 0.96–2.16, P=0.08), respectively for male patients, and 0.66 (95%CI, 0.26–1.64, P=0.37) and 0.89 (95%CI, 0.34–2.32, P=0.82), respectively for female patients.

Also, the depression status 1 year after the onset of MI was significantly related to only the risk of non-fatal cardiovascular events during the follow-up period (Table 5). The patients in the top tertile of SDS scores had an age-adjusted HR of 1.74 (95%CI, 1.02–2.98, P=0.04) during the follow-up, compared with those in the bottom tertile. Also, a 1-SD increment of SDS score was significantly related to risk of events, with a respective age-adjusted HR of 1.29 (95%CI, 1.06–1.59, P=0.01). The patients classified as having depression symptoms (SDS >40) had an approximately 50% higher risk of cardiovascular events than patients without depression symptoms, although this association did not reach statistical significance; the age-adjusted HR of non-fatal cardiovascular events for male patients with depression (SDS ≥40) vs. those without depression (SDS <40) was 1.46 (95%CI, 0.96–2.24, P=0.08).

Discussion

The purpose of this study was to investigate the association between depression symptoms at 1 year after onset of MI and subsequent cardiovascular events during the follow-up period (median, 2.9 years) among survivors of MI. We found that depression symptoms observed 1 year after onset were a signifi-

cant predictor of subsequent long-term cardiovascular events for male patients. Our findings extend the evidence from our previous study indicating that the presence of depression symptoms within 3 months after the onset of MI is a significant predictor of 1-year cardiac events.[11] Further, the predictions by depression symptoms within 1 year after onset remain independent of the presence of depression symptoms within 3 months after onset of MI.

Several studies examining the role of depression symptoms in patients with MI have emphasized the importance of depression symptoms at hospitalization compared with after discharge.[6,7] Depression symptoms among survivors of MI after discharge have not been well documented.[12–14,21] Although an association between the severity of depression symptoms at 1 year and long-term cardiac mortality has been found, it was not independent of baseline depression levels.[12] That study emphasized that depression symptoms during admission for MI were more closely linked to long-term mortality than depression symptoms at 1 year. However, the risk of non-fatal cardiac events was better predicted by depression symptoms at 1 year than depression symptoms during admission.[12] In the present study (in which approximately 90% of total cardiovascular events were non-fatal), depression symptoms after 1 year better predicted the risk of non-fatal than fatal cardiovascular events among male patients, which supports previous findings.[12] Thus, the assessment of depression symptoms at 1 year may be useful for predicting non-fatal events among survivors. Healthcare providers therefore should pay attention to patient's depressive symptoms not only in the few months after onset of MI but also over a long-term period in order to prevent future cardiovascular events.

Although there is no established mechanism linking depression symptoms and cardiovascular events, considerable evidence indicates that depression has both pathophysiological and behavioral effects.[11] For instance, the effects of depression on increased sympathoadrenal and platelet activity,[22] autonomic tone such as low heart rate variability,[23,24] or poor compliance with risk-reducing recommendations[25] may contribute to an increase in cardiovascular disease risk among post-MI patients.

In the present study, patients who were unemployed, had diabetes mellitus or a smoking history tended to be in the top tertile of SDS scores. There were no significant intergroup differences for the other patient characteristics. Our data suggest that possible mechanisms linking depression symptoms and cardiovascular events may comprise both biological (diabetes mellitus) and psychosocial (smoking, unemployment) factors. In a controlled study, the odds of depression in the diabetic group were twice that of the non-diabetic comparison group and did not differ by sex, type of diabetes, subject source, or assessment method.[26] Thus, possible factors responsible for the association between depression symptoms and adverse cardiovascular events include poor metabolic control and/or occurrence of diabetes mellitus after onset, because diabetes mellitus is an established strong risk factor for cardiac events.[27,28] Also, many reports have indicated that smoking and unemployment are also associated with depression.[7,16,25,29–31] Depression in turn is associated with several behavioral risk factors for the secondary progression of coronary heart disease, including smoking, unfavorable dietary patterns, physical inactivity, and non-adherence to cardiovascular medication regimens.[29]

Some observational studies have indicated that improvement in depression symptoms is associated with lower cardiovascular mortality.[7] However, according to the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study, the treatment of depression and enhancement of social support for MI patients had no beneficial effect in terms of reducing cardiac events and mortality.[32,33] Because most programs for the treatment for depression and enhancement of social support for MI patients, such as the ENRICH study, have been conducted during the initial 6 months after onset,[32] depression intervention for long-term survivors who have not experienced cardiovascular events during the high-risk period is highly warranted.

Study Limitations

The main limitation of our study was that we did not examine changes in clinical characteristics and antidepressant use after onset. The mechanism by which the relationship between depression and long-term cardiovascular events can be best explained thus remains unclear. Second, the number of female patients might be too small for a meaningful analysis of the association between cardiovascular events and depression symptoms 1 year after onset of MI for this sex. In the present study, although female patients had significantly higher depression scores than males, depressive symptoms were associated with subsequent cardiovascular events among men, but not women. This may be led in part by the small sample size and small number of events in women. Hence, this finding needs to be replicated in other settings before any conclusions are drawn. Finally, in the present study, 1,282 (39.7%) of patients did not evaluate depressive symptoms 1 year after onset of MI, and this may lead to a selection bias. However, there were no significant differences in baseline characteristics such as hypertension, diabetes, smoking and drinking status between responders and non-responders of the 1-year follow-up survey. Therefore, we think that representativeness of the study participants is acceptable. This study also has several strengths, including the large number of male survivor patients with MI and a long duration of follow-up for cardiovascular endpoints, compared with previous studies.[6,7,12,13]

In conclusion, depression at 1 year after onset of MI is a significant predictor of subsequent long-term cardiovascular events among male patients. Our findings suggest that the assessment of depression status after onset may be important in the prediction of long-term prognosis for male survivors of MI.

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