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Low-density lipoprotein cholesterol lowering by adding ezetimibe to statin is associated with improvement of postprandial hyperlipidemia in diabetic patients with coronary artery disease

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ABSTRACT

Objective and methods: We investigated the hypothesis that serum low-density lipoprotein cholesterol (LDL-C) reduction by ezetimibe is associated with the improvement in postprandial hyperlipidemia by performing an oral fat loading test before and 24 weeks after ezetimibe treatment in diabetic (n = 29) and non-diabetic (n = 30) male patients with coronary artery disease (CAD).

Results: Serum LDL-C levels were significantly reduced by ezetimibe in both groups (diabetic, from 120.3 ± 39.4 to 79.5 ± 23.2 mg/dL, $p < 0.001$; non-diabetic, from 98.2 ± 41.7 to 76.7 ± 29.2 mg/dL, $p < 0.001$), and the mean reduction in serum LDL-C was greater in diabetic than non-diabetic patients (−32.0 vs. −19.0%, $p = 0.004$). The area under the curve (AUC) for triglyceride (TG) and remnant-like particle cholesterol (RLP-C) decreased significantly in both groups. When compared with the reduction before and after treatment in AUC of TG ($\Delta AUC_{0-6\ h}$ TG) and RLP-C ($\Delta AUC_{0-6\ h}$ RLP-C), they were significantly greater in diabetic than non-diabetic patients (ΔAUC_{0-6h} TG, −28.9 vs. −12.2%, $p = 0.028$; ΔAUC_{0-6h} RLP-C, −27.8 vs. −12.3%, $p = 0.007$). In diabetic patients, $\Delta AUC_{0-6\ h}$ TG and $\Delta AUC_{0-6\ h}$ RLP-C in the highest tertile of serum LDL-C reduction were significantly greater than those in the lowest tertile (ΔAUC_{0-6h} TG, −34.1 vs. −20.9%, $p = 0.012$; ΔAUC_{0-6h} RLP-C, −34.5 vs. −15.1%, $p = 0.024$).

Conclusions: These findings suggest that serum LDL-C reduction by ezetimibe might be associated with the improvement of postprandial hyperlipidemia in diabetic patients with CAD.

1. Introduction

Both diabetes mellitus (DM) and hyperlipidemia play important roles in the development of atherosclerosis and are strong risk factors for cardiovascular events. There is a strong association between glucose and lipid metabolism, and an increase of intestinal cholesterol absorption has been reported in DM patients [1]. Postprandial hyperlipidemia characterized by the accumulation of excess triglyceride (TG)-rich lipoproteins and their hydrolyzed products in a non-fasting state, has been shown to play an important role in the progression or vulnerability of coronary arterial plaque [2–4]. Lipid metabolism is significantly impaired in DM patients with coronary artery disease (CAD) compared with non-DM patients with CAD [5]. Ezetimibe is a lipid-lowering drug that selectively inhibits intestinal cholesterol absorption by binding to Niemann–Pick C1-like 1 (NPC1L1) protein [6]. The administration of this cholesterol transporter inhibitor has been shown to reduce the serum levels of low-density lipoprotein cholesterol (LDL-C) and fasting TG, especially when used in combination with other drugs, such as statins [7]. Ezetimibe also improves postprandial hyperlipidemia in patients with hyperlipidemia [8–10].

It has been reported that the addition of ezetimibe to statin therapy can induce a greater reduction in serum LDL-C levels in DM patients compared with non-DM patients [11,12]. However, the mechanism for this more effective response in DM patients is not clearly understood. To investigate the hypothesis that the serum LDL-C level reduction induced by combining ezetimibe and statin therapy is associated with improvement of postprandial hyperlipidemia, we performed an oral fat loading test before and 24 weeks after ezetimibe treatment and

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compared the changes in the lipid profiles of DM and non-DM male patients with CAD.

2. Materials and methods

This study was a 24- week, prospective, open-label, single-center study to examine the effects of ezetimibe on LDL-C reduction and the relationship with postprandial hyperlipidemia in DM and non-DM male patients with CAD who were also receiving statin therapy. The study was conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent was obtained from the patients and the study protocol was approved by the ethics committee of the Iwate Prefectural Central Hospital.

2.1. Study subjects

A total of 65 consecutive type 2 DM and non-DM male patients (DM group, n = 33; non-DM group, n = 32) with stable angina pectoris, who were receiving atorvastatin (10 mg, once daily) had angiographically confirmed CAD, and who did not meet the exclusion criteria, were enrolled in the study. The exclusion criteria were: 1) type 1 DM; 2) type 2 DM with insulin therapy; 3) body mass index (BMI) ≥ 25.0; 4) gastrointestinal disease limiting drug absorption or partial ileal bypass; 5) major surgery within six months prior to enrollment or concomitant inflammatory disease or malignant tumors; 6) congestive heart failure, active liver disease, or hepatic dysfunction defined as alanine aminotransferase or aspartate aminotransferase exceeding the normal range; 7) concurrent therapy with long-term immunosuppressants; 8) familial hypercholesterolemia; and 9) taking lipid lowering medications without statins (e.g., cholestyramine, niacin, or fibrates) and/or eicosapentaenoic acid or docosahexaenoic acid therapy.

2.2. Definitions

Patients with stable angina pectoris were defined as cardiac ischemic patients who had a history of myocardial infarction, coronary artery bypass, percutaneous coronary intervention with or without stenting, or a previous angiographically confirmed stenotic lesion (≥75%) in a major epicardial coronary artery. They were also in stable condition when chest pain was brought on by exertion, which was resolved under nitrate-therapy and had unchanged characteristics (frequency, severity, duration, time of appearance, and precipitating factors) for the previous 60 days [13]. Diagnosis of type 2 DM was made according to the criteria in the 2010 American Diabetes Association Guidelines [14]: fasting plasma glucose (FPG) ≥ 126 mg/dL, hemoglobin A1c (HbA1c) ≥ 6.5%, or current use of hypoglycemic agents. Non-DM patients were defined as patients with FPG < 100 mg/dL and HbA1c < 5.7% without use of any hypoglycemic agents. There were no additions or changes to any of the hypoglycemic or lipid-lowering agents during the period of this study.

2.3. Study design

Patients were given one high-fat meal between June 2015 and March 2016 to collect the baseline values. For fat loading, all patients were given an oral high-fat meal (the “cake sále test”) [5,10,15] before and 24 weeks after ezetimibe treatment (10 mg, once daily). This “cake sale” consisted of high-fat and high-glucose food (1003 kcal; protein, 28.6 g {11.4%}; lipids, 62.4 g {56.0%}; carbohydrate, 80.7 g {32.2%}; cholesterol, 320.5 mg {0.4%}). The ingredients were similar to those of an American fast-food meal (Big Mac® cheeseburger with French fries and Coca-Cola®), which is one of the most popular meals in the world. Patients were asked to eat this high-fat meal (“cake sale”) in 30 min. In all patients, the test was performed for breakfast after overnight fasting for at least 12 h, and when the patient was in stable condition.

2.4. Measurements

The changes in the lipid profile in the DM and non-DM groups were compared. Blood samples were obtained by venipuncture during the fasting state just before the meal and 0, 2, 4, and 6 h after the meal. Sera were separated immediately after blood collection by low-speed centrifugation (3000 rpm for 15 min at 4 °C) and stored at −80 °C until laboratory analysis was conducted. Serum TG levels were determined by an enzymatic method, serum LDL-C and high-density lipoprotein cholesterol (HDL-C) levels by a direct method, serum apolipoprotein A-I (Apo A-I) and apolipoprotein B (Apo B) levels by an immunoturbidity method, and serum remnant-like particle cholesterol (RLP-C) levels by an immunoaffinity isolation method at a contract laboratory (SRL Co., Ltd., Tokyo, Japan). Serum LDL-C levels were determined by direct measurement, not by calculation using the Friedewald formula, since the postprandial TG levels were expected to exceed 400 mg/dL. Plasma glucose and HbA1c levels were also measured before and 24 weeks after ezetimibe treatment. HbA1c levels were determined by a high-performance liquid chromatography method at the laboratory in our hospital. The area under the curve (AUC) of each parameter was calculated by the trapezoidal method and was compared to an estimate of the postprandial integrated response of each group during the test.

2.5. Statistical analysis

All values were expressed as mean ± standard deviation for continuous variables and as numbers and percentages for categorical variables. Differences between two groups were assessed using the Student's unpaired *t*-test or Mann–Whitney's U test for continuous variables, and the chi-square test or Fisher's exact test for categorical variables. One-way analysis of variance, followed by Tukey's honestly significant difference test, was used to examine differences among multiple groups. A two-sided p-value of ≤0.05 was considered statistically significant. All statistical analyses were performed with SPSS version 14.0 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics in the DM and non-DM groups

Three patients in the DM group and two patients in the non-DM group did not want to do the oral fat loading test after 24 weeks of ezetimibe treatment, and one patient in the DM group had restricted oral intake due to a stroke during the study period. After exclusion of these patients, 59 patients (DM group, n = 29; non-DM group, n = 30) were included to this analysis, and their baseline characteristics are shown in Table 1. The levels of HbA1c and FPG were 7.6 ± 1.7%, 127.9 ± 6.1 mg/dL in the DM group; and 5.4 ± 0.2%, 91.8 ± 9.2 mg/dL in non-DM group, respectively. All patients received the statin therapy (atorvastatin 10 mg). There were several significant differences between the lipid profiles of the DM and non-DM groups. The serum RLP-C and Apo B levels in the DM group were significant higher than those in the non-DM group (RLP-C: 7.2 ± 3.5 vs. 4.5 ± 2.0 mg/dL, p = 0.008; Apo B: 120.3 ± 23.5 vs. 98.2 ± 15.4 mg/dL, p = 0.003). The serum LDL-C levels in the DM group were higher compared with the non-DM group, but the difference was not statistically significant (120.3 ± 39.4 vs. 98.2 ± 41.7 mg/dL, p = 0.052). Patients with BMI ≥ 25.0 were excluded from this study, and there was no significant difference in body size. There were also no significant differences in age, blood pressure, smoking, and the incidence of hypertension between the groups.

Table 1
Baseline characteristics in patients.

Variable	Overall (n = 59)	DM group (n = 29)	Non-DM group (n = 30)	p value
Age (years)	66.5 ± 7.7	67.4 ± 7.3	65.8 ± 8.2	0.540
Weight (kg)	62.9 ± 5.8	63.4 ± 5.9	62.0 ± 5.8	0.448
Height (cm)	164.8 ± 4.5	165.3 ± 3.0	164.2 ± 4.9	0.456
Body mass index (kg/m^2)	22.9 ± 1.5	23.1 ± 1.4	22.7 ± 1.6	0.745
Hypertension	41 (69%)	21 (72%)	20 (67%)	0.632
Blood pressure				
Systolic (mm Hg)	132.8 ± 15.8	137.3 ± 14.4	129.5 ± 16.5	0.333
Diastolic (mm Hg)	73.8 ± 10.7	68.5 ± 11.9	75.6 ± 10.3	0.217
Current or ex-smokers	41 (69%)	22 (76%)	19 (63%)	0.296
Glucose markers				
HbA1c (%)	6.5 ± 1.6	7.6 ± 1.7	5.4 ± 0.2	<0.001
Fasting plasma glucose (mg/dL)	109.9 ± 7.8	127.9 ± 6.1	91.8 ± 9.2	<0.001
Lipid markers				
Triglyceride (mg/dL)	143.4 ± 74.9	150.5 ± 77.3	121.4 ± 72.5	0.096
LDL cholesterol (mg/dL)	115.0 ± 42.7	120.3 ± 39.4	98.2 ± 41.7	0.052
HDL cholesterol (mg/dL)	48.7 ± 12.6	47.8 ± 11.8	49.6 ± 13.4	0.696
RLP cholesterol (mg/dL)	5.9 ± 3.1	7.2 ± 3.5	4.5 ± 2.0	0.008
Apolipoprotein A-I (mg/dL)	134.9 ± 23.9	140.7 ± 25.1	128.5 ± 17.8	0.139
Apolipoprotein B (mg/dL)	109.4 ± 20.1	120.3 ± 23.5	98.2 ± 15.4	0.003

Values are expressed as either mean ± SD or number (percentage).
DM = diabetes mellitus; HbA1c = hemoglobin A1c; LDL = low-density lipoprotein; HDL = high-density lipoprotein; RLP = remnant lipoprotein.

3.2. Changes in the serum LDL-C levels after ezetimibe treatment

There were no changes in lipid- or glucose-lowering medications or any other medications during the study period. Neither group showed a significant change in the body weight from the baseline to the 24 week follow-up examination (DM group, 63.4 ± 5.9 kg at baseline vs. 63.2 ± 5.7 kg at 24 weeks, p = 0.372; non-DM group, 62.0 ± 5.8 kg vs. 62.3 ± 5.5 kg at 24 weeks, p = 0.218). The levels of HbA1c were not significantly different between baseline and the 24 week follow-up in either group (DM group, 7.6 ± 1.7% at baseline vs. 7.7 ± 1.5% at 24 weeks, p = 0.537; non-DM group, 5.4 ± 0.2% vs. 5.5 ± 0.4% at 24 weeks, p = 0.604). Serum LDL-C levels were significantly reduced by ezetimibe treatment in both groups (DM group, 120.3 ± 39.4 mg/dL at baseline vs. 79.5 ± 23.2 mg/dL at 24 weeks, p < 0.001; non-DM group, 98.2 ± 41.7 mg/dL at baseline vs. 76.7 ± 29.2 at 24 weeks, p < 0.001) (Fig. 1A), and the percent reduction in serum LDL-C levels was significantly greater in the DM group than in the non-DM group (−32.0 ± 13.4% vs. −19.0 ± 19.1%, p = 0.004) (Fig. 1B).

3.3. Postprandial lipid metabolism before and after ezetimibe treatment in the DM and non-DM groups

The changes in the lipid profile during the oral fat loading test before and after ezetimibe treatment in the DM and non-DM groups are summarized in Table 2. Serum TG and RLP-C levels showed significant changes during the study. Other lipid parameters did not show any meaningful changes from the baseline. Fig. 2A and B shows the changes in the serum TG and RLP-C levels before and after the treatment in the DM and non-DM groups. Serum TG and RLP-C levels before the treatment continued to rise for 6 h after the high fat meal in both groups. After 24 weeks of treatment, ezetimibe significantly decreased the baseline and peak levels for serum TG and RLP-C, and AUC for both markers between 0 and 6 h decreased significantly in both groups (AUC of TG in DM group, from 2669.9 ± 745.3 to 1302.9 ± 377.3 mg/dL at 6 h, p < 0.001; AUC of TG in non-DM group, from 1876.8 ± 445.3 to 1109.2 ± 352.1 mg/dL at 6 h, p = 0.005; AUC of RLP-C in DM group, from 91.9 ± 28.3 to 44.2 ± 14.6 mg/dL at 6 h, p < 0.001; AUC of RLP-C in non-DM group, from 62.4 ± 20.4 to 36.2 ± 10.9 mg/dL at 6 h, p = 0.007). The percent reductions in AUC of serum TG ($\Delta AUC_{0-6\ h}$ TG) and RLP-C ($\Delta AUC_{0-6\ h}$ RLP-C) during the study period were significantly greater in the DM group than in non-DM group ($\Delta AUC_{0-6\ h}$ TG, −28.9 ± 20.5% vs. −12.2 ± 22.0%, p = 0.028; ΔAUC_{0-6h} RLP-C, −27.8 ± 15.5% vs. −12.3 ± 16.0%, p = 0.007) (Fig. 2C and D).

3.4. Association between reduction of the serum LDL-C levels and improvement in postprandial hyperlipidemia after ezetimibe treatment in the DM group

When the patients in the DM group were divided into tertiles according to the percent reduction of serum LDL-C level before and after the treatment, the $\Delta AUC_{0-6\ h}$ TG and $\Delta AUC_{0-6\ h}$ RLP-C in the highest tertile (from −36.0 to −61.9%, respectively, n = 10) were significantly greater than those in the lowest tertile (from −6.7 to −22.3%,

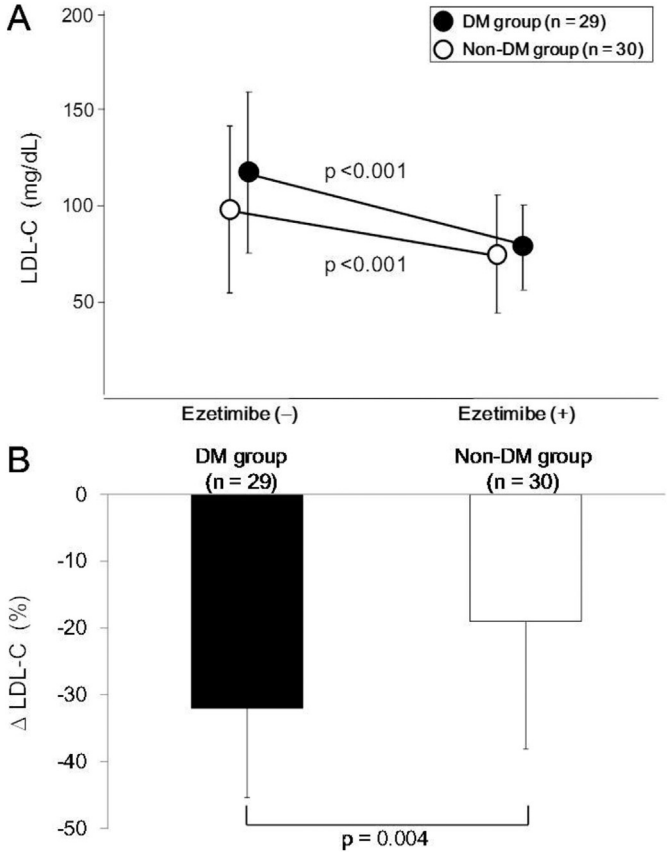

Fig. 1. Changes (A) and percentage reduction (B) in serum LDL levels after ezetimibe treatment. Data are expressed as mean ± SD.

Table 2
Changes of lipid parameters after the oral fat loading test.

	Before	After			
		0 h	2 h	4 h	6 h
Triglyceride (mg/dL)					
DM group; ezetimibe (−)	150.5 ± 77.3	154.8 ± 92.7	234.7 ± 75.6	375.9 ± 113.2‖	394.1 ± 117.6‖
DM group; ezetimibe (+)	121.8 ± 73.3	125.3 ± 45.2	165.7 ± 66.4	235.2 ± 75.2†	225.8 ± 54.7†
Non-DM group; ezetimibe (−)	121.4 ± 72.5	125.8 ± 75.7	195.3 ± 81.5	267.4 ± 105.8‡	271.2 ± 126.7‡
Non-DM group; ezetimibe (+)	89.5 ± 32.8	90.4 ± 32.8	136.4 ± 45.8	203.4 ± 75.6†	173.2 ± 79.7†
RLP cholesterol (mg/dL)					
DM group; ezetimibe (−)	7.2 ± 3.5	7.0 ± 3.3	11.1 ± 4.0	18.3 ± 5.8‖	22.7 ± 7.4‖
DM group; ezetimibe (+)	3.2 ± 0.9	3.2 ± 0.9	6.0 ± 1.9	9.2 ± 3.6‡	8.9 ± 3.9†
Non-DM group; ezetimibe (−)	4.5 ± 2.0	4.5 ± 1.9	8.0 ± 3.0	12.5 ± 4.0§	14.4 ± 6.4§
Non-DM group; ezetimibe (+)	2.6 ± 0.6	2.7 ± 0.8	4.9 ± 1.5	7.5 ± 2.7†	7.3 ± 3.5†
LDL cholesterol (mg/dL)					
DM group; ezetimibe (−)	120.3 ± 39.4	122.5 ± 40.3	119.5 ± 37.5	117.8 ± 30.9	120.4 ± 36.2
DM group; ezetimibe (+)	79.5 ± 23.2	78.9 ± 22.8	75.3 ± 21.5	72.6 ± 22.7	73.7 ± 21.8
Non-DM group; ezetimibe (−)	98.2 ± 41.7	100.6 ± 40.6	95.5 ± 38.8	92.3 ± 38.5	93.7 ± 37.9
Non-DM group; ezetimibe (+)	76.7 ± 29.2	76.1 ± 27.3	71.4 ± 25.7	70.7 ± 25.5	71.4 ± 26.8
HDL cholesterol (mg/dL)					
DM group; ezetimibe (−)	47.8 ± 11.8	49.3 ± 11.8	46.0 ± 11.4	44.4 ± 10.9	45.1 ± 12.1
DM group; ezetimibe (+)	51.9 ± 12.8	52.4 ± 11.9	48.9 ± 12.0	47.3 ± 12.2	47.3 ± 12.3
Non-DM group; ezetimibe (−)	49.6 ± 13.4	50.7 ± 13.0	46.4 ± 12.3	45.3 ± 12.9	45.8 ± 13.7
Non-DM group; ezetimibe (+)	50.2 ± 11.3	51.2 ± 11.6	47.2 ± 10.5	46.3 ± 10.7	46.8 ± 11.0
Apolipoprotein A-I (mg/dL)					
DM group; ezetimibe (−)	140.7 ± 25.1	144.8 ± 23.8	137.8 ± 24.6	135.1 ± 22.5	137.2 ± 23.8
DM group; ezetimibe (+)	139.6 ± 24.8	143.5 ± 24.1	139.2 ± 23.8	137.3 ± 24.1	139.3 ± 23.6
Non-DM group; ezetimibe (−)	128.5 ± 17.8	129.4 ± 18.9	122.9 ± 17.9	123.5 ± 18.6	125.6 ± 20.1
Non-DM group; ezetimibe (+)	128.1 ± 18.9	131.2 ± 17.9	124.8 ± 18.1	125.4 ± 19.3	127.7 ± 20.5
Apolipoprotein B (mg/dL)					
DM group; ezetimibe (−)	120.3 ± 23.5	122.7 ± 21.3	117.9 ± 25.3	117.4 ± 21.6	118.2 ± 20.9
DM group; ezetimibe (+)	103.0 ± 22.1	105.4 ± 19.3	101.9 ± 20.3	102.4 ± 19.7	103.0 ± 23.1
Non-DM group; ezetimibe (−)	98.2 ± 15.4	99.1 ± 16.4	95.0 ± 15.1	95.7 ± 14.0	97.5 ± 14.6
Non-DM group; ezetimibe (+)	88.3 ± 15.8	88.1 ± 15.6	85.5 ± 17.8	85.6 ± 15.1	87.7 ± 16.3

Values are expressed as mean ± SD.
†$p < 0.05$, ‡$p < 0.01$, §$p < 0.005$, ‖$p < 0.001$ comparing with the value before the loading test in the same group.
DM = diabetes mellitus; RLP = remnant lipoprotein; LDL = low-density lipoprotein; HDL = high-density lipoprotein.

respectively, n = 10) ($\Delta AUC_{0-6\ h}$ TG, −34.1 ± 13.2 vs. −20.9 ± 6.9%, p = 0.012; $\Delta AUC_{0-6\ h}$ RLP-C, −34.5 ± 23.1 vs. −15.1 ± 14.6%, p = 0.024) (Fig. 3A and B). In comparison $\Delta AUC_{0-6\ h}$ TG and RLP-C were not significantly different between the highest (from −29.0 to −51.8%, respectively, n = 10) and lowest (from +24.8 to −10.3%, respectively, n = 10) tertiles in the non-DM group ($AUC_{0-6\ h}$ TG, −17.0 ± 19.8 vs. −11.8 ± 8.3%, p = 0.225; $\Delta AUC_{0-6\ h}$ RLP-C, −17.1 ± 30.1vs. −13.7 ± 13.8%, p = 0.406).

4. Discussion

There are three major findings of this study. First, diabetic CAD patients experienced a greater reduction in serum LDL-C levels after ezetimibe treatment than non-diabetic CAD patients. Secondly, there was greater improvement in postprandial hyperlipidemia after ezetimibe treatment in diabetic compared with non- diabetic CAD patients. Thirdly, the highest tertile of LDL reduction after ezetimibe treatment showed a significant improvement in postprandial hyperlipidemia compared with the lowest tertile in diabetic CAD patients, but not in non-diabetic CAD patients. These findings suggested that the enhanced LDL-C reduction by ezetimibe in diabetic CAD patients might be associated with the improvement in postprandial hyperlipidemia.

It is well known that the addition of ezetimibe to statin therapy can achieve a greater reduction in serum LDL-C levels compared to statin monotherapy [16,17]. However, the potential effects of ezetimibe have not been extensively evaluated, and little information is available about diabetic patients with hyperlipidemia. Nakajima et al. [11] reported the effect of the addition of ezetimibe to a statin on coronary plaque regression, estimated by intravascular ultrasound in patients with acute coronary syndrome (ZEUS trial). They found that the reduction of both serum LDL-C levels and plaque volume were significantly greater in diabetic patients compared with non-diabetic patients. We also found that the addition of ezetimibe to statin therapy induced a greater reduction in serum LDL-C levels in diabetic CAD patients compared with non-diabetic CAD patients. Thus, diabetic patients may be more likely to benefit from the addition of ezetimibe to statin therapy.

Postprandial hyperlipidemia is characterized by the accumulation of excess TG-rich lipoproteins and their partially hydrolyzed products such as chylomicron (CM) remnant and very low-density lipoprotein (VLDL) remnant during the postprandial period, and is a predisposing factor in cardiovascular events [4,18]. Therefore, the inhibition of increased cholesterol not only in a fasting state but also in a postprandial state is an additional strategy for serum LDL-C reduction for patients in whom the therapeutic effect of statin monotherapy is insufficient. Although endogenous and exogenous cholesterol pathways can induce postprandial lipid accumulations, the activated exogenous pathway seems to be more strongly related with postprandial hyperlipidemia. Masuda et al. [19] measured Apo B-48 and Apo B-100 levels separately in the fasting and postprandial states to assess the endogenous and exogenous pathways independently. They reported that the postprandial increase in serum TG and RLP-C levels was mainly due to increases of CM and CM remnant, but not VLDL and VLDL remnant. In diabetic patients, the following have been demonstrated: 1) increased expression of NPC1L1, which facilitates cholesterol absorption in the small intestine; 2) decreased expression of adenosine triphosphate (ATP-) binding cassette transporters G5 and G8 (ABCG5, ABCG8), which bring cholesterol to the small intestinal lumen from small intestinal epithelial cells; and 3) increased microsomal TG transfer protein (MTP), which packages the CM particle by assembling cholesterol, TG, phospholipids and Apo B48 [20]. These alterations to the expression of intestinal genes could result in increased cholesterol absorption and lead to elevation of serum LDL-C levels in diabetic patients. Consistent with previous reports [2,21], our study indicates that the magnitude of postprandial

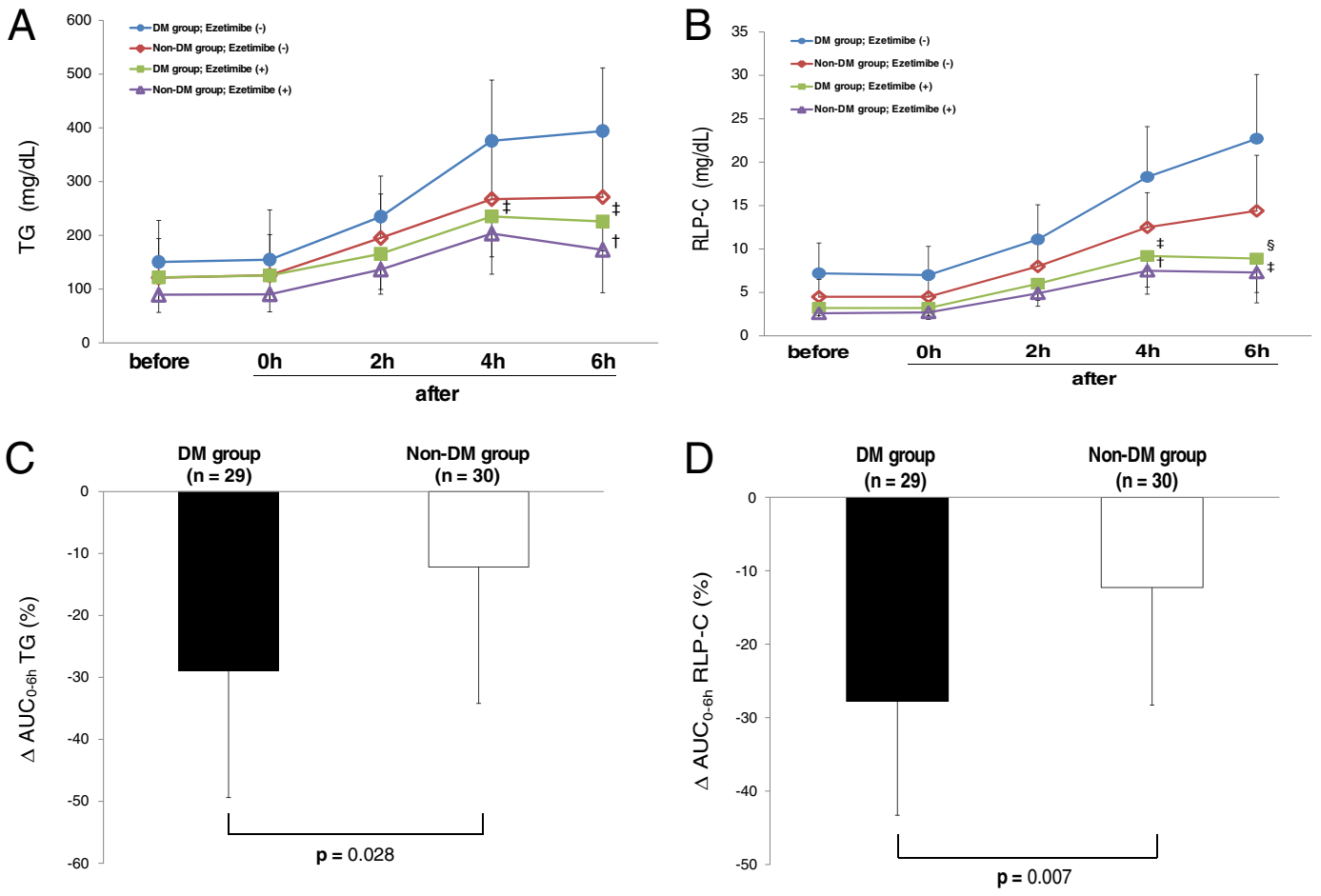

Fig. 2. Postprandial changes in serum TG (A), RLP-C (B) levels and reductions in AUC for postprandial serum TG (C), RLP-C (D) levels after ezetimibe treatment. Data are expressed as mean ± SD. †$p < 0.05$, ‡$p < 0.01$, §$p < 0.005$ comparing with the value at the same time before ezetimibe treatment.

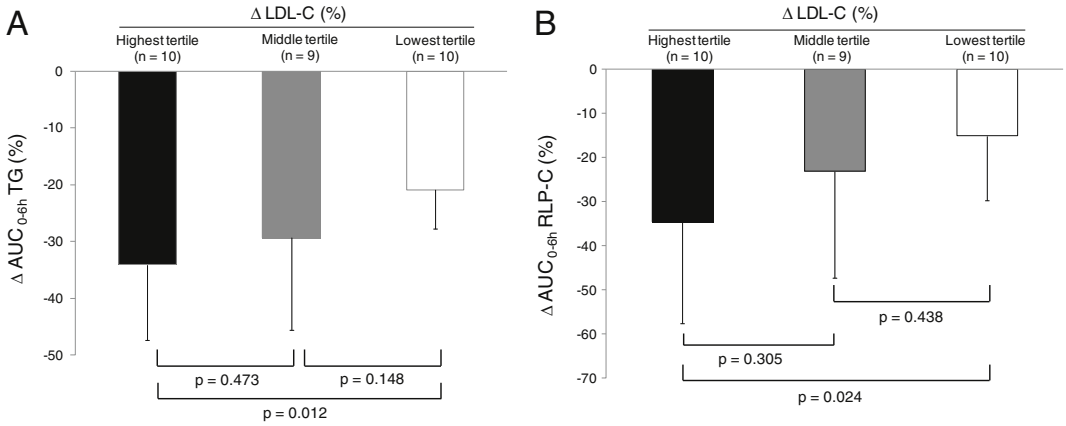

Fig. 3. Reductions in AUC for postprandial serum TG (A), RLP-C (B) levels in the high, middle, and low tertiles of LDL-C reduction after ezetimibe treatment. Data are expressed as mean ± SD.

serum TG or RLP-C accumulation, which was measured as the AUC of TG or RLP-C, respectively, was greater in diabetic CAD patients than in non-diabetic CAD patients.

Recently, some studies have reported that the addition of ezetimibe, a NPC1L1 protein inhibitor, to statin therapy improved postprandial hyperlipidemia [8,9]. However, little is known about the differences in ezetimibe treatment in diabetic patients compared with non-diabetic patients. One purpose of this study was to investigate whether the improvement of postprandial hyperlipidemia by ezetimibe treatment was greater in CAD patients with DM compared with those without DM. Our study showed significantly greater postprandial TG or RLP-C reduction after ezetimibe treatment in diabetic CAD patients compared with non-diabetic CAD patients. To the best of our knowledge, this is the first study to investigate the effectiveness of combination therapy with ezetimibe and a statin (atorvastatin) for the management of postprandial hyperlipidemia in CAD patients with DM.

Another important finding of this study was that CAD patents in the highest tertile of LDL-C reduction by ezetimibe treatment demonstrated a greater reduction in AUC for TG and RLP-C in the diabetic group, but not in the non-diabetic group. In non-diabetic patients, in whom the expression of NPC1L1 protein has not been enhanced in the intestine, the possibility exists that ezetimibe reduces hepatic cholesterol by inhibition of NPC1L1 protein activity not only in the intestine, but also in the liver [22]. Measurement of lipid markers associated with the endogenous pathway, such as VLDL cholesterol, VLDL remnant, and Apo B-100, would contribute to a better understanding of the differences in the effect of ezetimibe between diabetic and non-diabetic CAD patients.

5. Study limitations

There were several limitations to this study. First, the study only included males to exclude the hormonal effect of estrogen on postprandial lipid metabolism. Second, this study did not include patients taking insulin therapy to eliminate the effects of exogenous insulin. The effect of ezetimibe on postprandial lipid metabolism remains unknown in these patients. Third, all patients had CAD and were treated with the same dose of atorvastatin with ezetimibe. It remains unknown whether similar results would be obtained with other statins or different doses of atorvastatin.

6. Conclusions

The addition of ezetimibe to statin therapy induced a greater reduction in the serum LDL-C levels in diabetic compared with non-diabetic CAD patients. This enhanced LDL-C lowering effect by ezetimibe treatment might be accomplished with the improvement of postprandial hyperlipidemia in diabetic CAD patients.

Conflict of interest

We have no conflicts of interest.

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