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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.