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Original article

The effect of ezetimibe on lipid and glucose metabolism after a fat and glucose load

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ABSTRACT

Objectives: The clinical benefit of ezetimibe, an intestinal cholesterol transporter inhibitor, for treatment of postprandial hyperlipidemia was assessed in subjects who ingested a high-fat and high-glucose test meal to mimic westernized diet.
Methods: We enrolled 20 male volunteers who had at least one of the following: waist circumference ≥ 85 cm, body mass index ≥ 25 kg/m^2, or triglycerides (TG) from 150 to 400 mg/dL. After 4 weeks of treatment with ezetimibe (10 mg/day), the subjects ingested a high-fat and high-glucose meal. Then changes in serum lipid and glucose levels were monitored after 0, 2, 4, and 6 h, and the area under the curve (AUC) was calculated for the change in each parameter.
Results and conclusion: At 4 and 6 h postprandially, TG levels were decreased ($p < 0.01$) after 4 weeks of ezetimibe treatment, and the AUC for TG was also decreased ($p < 0.01$). Apolipoprotein B48 (apo-B48) levels at 4 and 6 h postprandially were significantly decreased after ezetimibe treatment ($p < 0.01$ and $p < 0.001$, respectively), and the AUC for apo-B48 was also significantly decreased ($p < 0.01$). Blood glucose and insulin levels at 2 h postprandially were significantly decreased by ezetimibe ($p < 0.05$). The AUCs for blood glucose and insulin were also significantly decreased ($p < 0.05$ and $p < 0.01$, respectively). Since ezetimibe improved postprandial lipid and glucose metabolism, this drug is likely to be beneficial for dyslipidemia in patients with postprandial metabolic abnormalities.

Introduction

Fat intake of the Japanese population has been increasing sharply because of westernization of their diet since the 1970s. Consequently, the prevalence of dyslipidemia in Japan has increased approximately 8-fold [1,2]. The increased fat intake results in enhancement of chylomicron secretion and causes postprandial metabolic abnormalities. Postprandial hyperlipidemia is characterized by pronounced and prolonged hypertriglyceridemia. It is commonly seen in obese individuals, patients with metabolic syndrome, and patients with abnormalities of glucose metabolism, including those with glucose intolerance. Postprandial hyperlipidemia results from an increase in remnant lipoproteins and small dense low-density lipoprotein (LDL) that are highly atherogenic and closely linked to insulin resistance, fatty liver, and vascular endothelial dysfunction [3,4]. Postprandial hyperlipidemia has been also shown to be a risk factor that is independent of the cholesterol level [5,6].

To achieve improvement in postprandial hyperlipidemia, diet and exercise therapy for lifestyle modification is most important. However, patients usually fail to complete diet and exercise regimens because of temptation to overeat, irregular mealtimes, and limits on performing exercise due to insufficient time and fatigue. This represents an "unmet medical need" for the modern Japanese population and effective pharmacotherapy should therefore be established for persons with insufficient improvement of their lifestyle.

In recent years, the cholesterol transporter protein Niemann–Pick C1-like 1 (NPC1L1), which is expressed by small intestinal epithelial cells, has been cloned, and its function has been elucidated [7]. Ezetimibe selectively inhibits cholesterol absorption by binding to NPC1L1, and this drug has become available in Japan for clinical use. Ezetimibe decreases LDL cholesterol (LDL-C) levels by about 20% and also improves both hypertriglyceridemia and low high-density lipoprotein cholesterol (HDL-C) levels [8]. The Fujita Ezetimibe Study Assembly (FESTA) previously revealed that ezetimibe treatment improves hyperinsulinemia as well as

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adiponectin level [9]. However, the mechanism by which ezetimibe modifies glucose and lipid metabolism is not well understood. Ezetimibe has been documented to prevent lipid-related increase of chylomicrons and to improve insulin resistance and hepatic lipid accumulation in a rat model of metabolic syndrome [10]. Ezetimibe has also been known to prevent the increase in triglycerides (TG), remnant lipoproteins, and fatty acids after a lipid load in patients with mixed dyslipidemia. Therefore, improvement in postprandial lipid metabolism by ezetimibe is thought to account for its effects on glucose and fat metabolism [11]. That is, ezetimibe is suggested to not only improve circulating lipid levels, but also modify glucose and fat metabolism by alleviating various postprandial lipid abnormalities.

In previous studies [11], however, the influence of ezetimibe on postprandial metabolic abnormalities was assessed after loading with fat alone, although fats are ingested together with carbohydrates in ordinary meals. It is therefore necessary to investigate the efficacy of ezetimibe in a more normal dietary environment.

Accordingly, we investigated the effects of ezetimibe on postprandial lipid and glucose metabolism by giving a simultaneous fat and glucose load to obese individuals, who commonly have postprandial metabolic abnormalities, and patients with hypertriglyceridemia.

Methods

Japanese men aged 20–65 years who had not received lipid-lowering agents or oral antidiabetic agents for at least 12 weeks were eligible for participation in this study if they had at least one of the following: (1) a waist circumference ≥85 cm; (2) a body mass index (BMI) ≥25 kg/m^2; and (3) a TG level from 150 to 400 mg/dL. Persons with a history of hypersensitivity to ezetimibe and patients with serious hepatic disease, renal disease, or atherosclerosis were excluded from the study, as were individuals who were judged by the investigator to be inappropriate for the study for other reasons. Before entering the study, all subjects gave written informed consent to participation.

After fasting for at least 12 h, subjects were given a high-fat and high-glucose meal for breakfast on Day 1. Then they received oral ezetimibe (10 mg/day) once daily for 4 weeks. After completing ezetimibe treatment, the subjects again ate a high-fat and high-glucose meal for breakfast. A fast-food meal (a hamburger with sausage and egg, apple pie, and Coca-Cola®, which are widely available and have stable major ingredients) was chosen as the high-fat and high-glucose test meal (1001 kcal; protein, 31.6 g; lipids, 61.4 g; carbohydrate, 79.8 g; cholesterol, 299 mg). Subjects were requested to eat the test meal in 20–30 min.

At 0, 2, 4, and 6 h after the test meal, blood was sampled to evaluate the changes in serum lipid levels and glucose metabolism. The serum lipids measured were TG, HDL-C, LDL-C, apolipoprotein B, and apolipoprotein B48, which is specifically contained in dietary lipoprotein. LDL-C levels were determined by direct measurement and not by calculation, since the postprandial TG level was predicted to exceed 400 mg/dL. Blood glucose and insulin levels were measured for the assessment of glucose metabolism. Measurement of parameters was performed by a contract laboratory (SRL).

Changes in lipid and glucose parameters after ingestion of the test meal and the area under the concentration vs. time curve (AUC) of each parameter were compared before and after treatment with ezetimibe to evaluate its effects on lipid and glucose metabolism.

To assess changes in each laboratory parameter after the test meal, the *Z* test was initially performed to confirm a normal distribution. The Bonferroni multiple comparison test was performed if a normal distribution was confirmed, while Dunnet's test was employed if the distribution was not normal. The postprandial change in each laboratory parameter and the AUC of the change were compared between baseline and after ezetimibe treatment using the paired *t*-test, with significance being accepted at $p < 0.05$.

The present study was conducted after being approved by the Ethics Committee of Fujita Health University School of Medicine and under the supervision of this committee.

Table 1
Profile of the subjects.

Number of subjects	20
Age	40.5 ± 5.1 years
Height	171.7 ± 5.5 cm
Weight	74.4 ± 7.6 kg
Body mass index	25.6 ± 2.9 kg/m^2
Waist circumference	87.2 ± 6.0 cm
Triglycerides	186.0 ± 89.8 mg/dL
HDL-cholesterol	53.5 ± 11.0 mg/dL
LDL-cholesterol	141.3 ± 29.0 mg/dL
Fasting blood glucose	100.7 ± 12.1 mg/dL
Fasting insulin	10.2 ± 5.2 μIU/mL

Results

Informed consent was obtained from 20 volunteers with a mean age of 40.5 ± 5.1 years, BMI of 25.6 ± 2.9 kg/m^2, and fasting TG level of 186.0 ± 89.8 mg/dL (Table 1).

Fasting lipid and glucose metabolism

Baseline fasting TG level was 186.0 ± 89.8 mg/dL and decreased to 140.3 ± 55.2 mg/dL after 4 weeks of treatment with ezetimibe ($p < 0.01$) (Table 2); meanwhile, HDL-C level was unchanged from baseline after treatment. LDL-C decreased from 141.3 ± 29.0 mg/dL at baseline to 112.1 ± 22.6 mg/dL after ezetimibe treatment ($p = 0.001$), with the percent change being −19.2 ± 15.3%. Apolipoprotein B decreased from 118.0 ± 23.9 mg/dL at baseline to 94.5 ± 19.7 mg/dL after ezetimibe treatment ($p < 0.01$), with the percent change being −19.1 ± 11.7%. The apolipoprotein B48 level was 6.5 ± 4.5 μg/mL at baseline and it declined to 4.6 ± 2.4 μg/mL after treatment ($p < 0.05$). The fasting glucose level decreased from 100.7 ± 12.1 mg/dL at baseline to 97.7 ± 10.6 mg/dL after treatment ($p < 0.01$), but the fasting insulin level showed no significant change after ezetimibe treatment.

Changes in lipid and glucose metabolism after the test meal

The baseline TG level was 186.0 ± 89.8 mg/dL before the high-fat and high-glucose meal, and it gradually increased after ingestion of the meal to 257.3 ± 102.5 mg/dL ($p < 0.001$) at 2 h, 417.1 ± 174.4 mg/dL ($p < 0.001$) at 4 h, and 415.7 ± 231.2 mg/dL ($p < 0.001$) at 6 h postprandially. HDL-C and LDL-C decreased slightly after ingestion of the meal (Fig. 1). The apolipoprotein B level showed no significant change after ingestion of the meal (Fig. 2). The baseline apolipoprotein B48 level was 6.5 ± 4.5 μg/dL, and it gradually increased to 12.5 ± 5.3 μg/mL ($p < 0.001$) at 2 h, 15.3 ± 6.2 μg/mL ($p < 0.001$) at 4 h, and 14.6 ± 6.5 μg/mL ($p < 0.001$) at 6 h postprandially (Fig. 2). The baseline blood glucose level showed a significant decrease at 2 and 4 h postprandially (Fig. 1, both $p < 0.05$). The blood insulin level was 10.1 ± 5.2 μU/mL before the test meal, while it was 32.8 ± 22.9 μU/mL ($p < 0.05$) at 2 h, 16.9 ± 9.3 μU/mL ($p < 0.05$) at 4 h, and 10.1 ± 5.6 μU/mL at 6 h postprandially (Fig. 1).

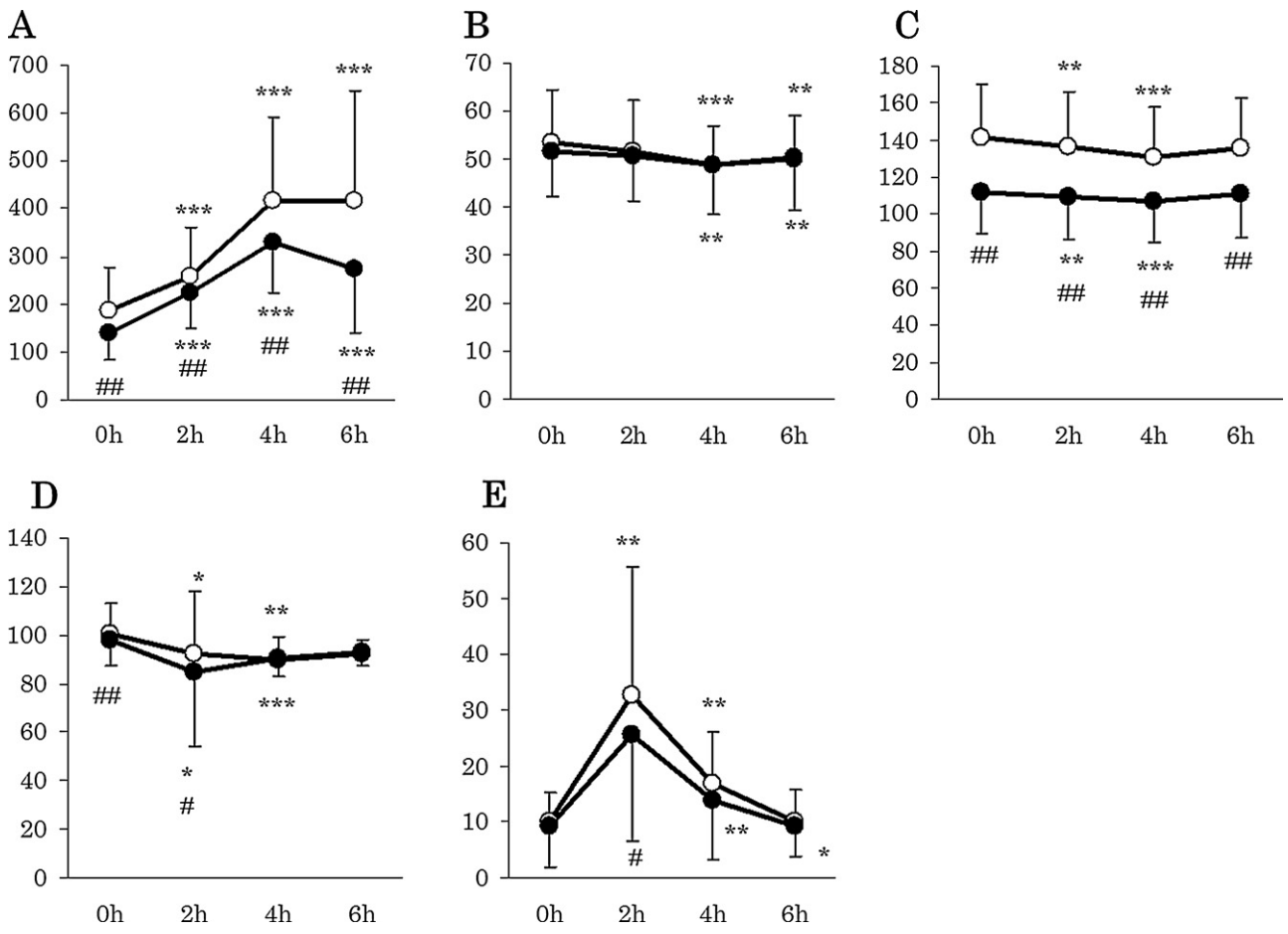

Fig. 1. Effects of the test meal before (open circles) and after (solid circles) ezetimibe treatment. The subjects ($n = 20$) received a high-fat and high-glucose meal (1001 kcal, protein 31.6 g, fat 61.4 g, carbohydrate 79.8 g, cholesterol 299 mg) before and after the treatment with ezetimibe. Blood samples were obtained while fasting and 2, 4, and 6 h after the test meal. (A) Triglycerides; (B) high-density lipoprotein cholesterol; (C) low-density lipoprotein cholesterol; (D) blood glucose; and (E) insulin. The Bonferroni *t*-test was used to compare before and after the test meal ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$). The paired *t*-test was employed to compare before and after treatment with ezetimibe (#$p < 0.05$; ##$p < 0.01$; ###$p < 0.001$).

Table 2
Parameters of lipid and glucose metabolism before and after ezetimibe treatment.

	Before ezetimibe	After ezetimibe	Percent change	*p* Value
Body weight (kg)	74.4 ± 7.6	74.4 ± 7.7	−0.1 ± 1.3	0.6727
BMI (kg/m$^{2)}$	25.6 ± 2.9	25.6 ± 2.9	0.01 ± 1.2	0.9580
Waist circumference (cm)	87.2 ± 6.0	87.0 ± 6.3	−0.3 ± 1.3	0.3935
Triglycerides (mg/dL)	186.0 ± 89.8	140.3 ± 55.2	−16.7 ± 31.0	0.0075
HDL-cholesterol (mg/dL)	53.5 ± 11.0	51.7 ± 10.6	−2.1 ± 11.6	0.2082
LDL-cholesterol (mg/dL)	141.3 ± 29.0	112.1 ± 22.6	−19.2 ± 15.3	0.001
Apolipoprotein B (mg/dL)	118.0 ± 23.9	94.5 ± 19.7	−19.1 ± 11.7	<0.001
Apolipoprotein B48 (μg/m)	6.5 ± 4.5	4.6 ± 2.4	−19.7 ± 28.4	0.007[a]
Fasting blood glucose (mg/dL)	100.7 ± 12.1	97.7 ± 10.6	−2.8 ± 4.4	0.0094
Fasting insulin (μIU/mL)	10.2 ± 5.2	9.3 ± 7.4	−9.9 ± 39.1	0.4473

Parameters are shown as the mean ± SD for 20 patients. Statistical analysis was done with the paired *t*-test.
[a] Wilcoxon signed rank test.

Table 3
Area under the curve for parameters of lipid and glucose metabolism before and after ezetimibe treatment.

	Before ezetimibe	After ezetimibe	Percent change	*p* Value
Triglycerides	1950.3 ± 843.1	1522.6 ± 486.6	−13.8 ± 30.4	0.009
LDL-cholesterol	811.0 ± 168.0	654.3 ± 133.4	−17.8 ± 16.0	$p < 0.001$
HDL-cholesterol	303.9 ± 62.7	300.7 ± 52.8	0.0 ± 10.6	0.635
Apolipoprotein B	695.3 ± 139.0	566.2 ± 112.8	−17.6 ± 11.8	$p < 0.001$
Apolipoprotein B48	76.7 ± 31.9	59.9 ± 19.2	−17.2 ± 21.0	$p < 0.001$[a]
Blood glucose	556.9 ± 66.6	540.4 ± 82.4	−3.1 ± 5.7	0.043
Insulin	119.7 ± 61.3	97.7 ± 53.9	−16.6 ± 27.7	0.008

Parameters are shown as the mean ± SD for 20 patients. Statistical analysis was done by the paired *t*-test.
[a] Wilcoxon signed rank test.

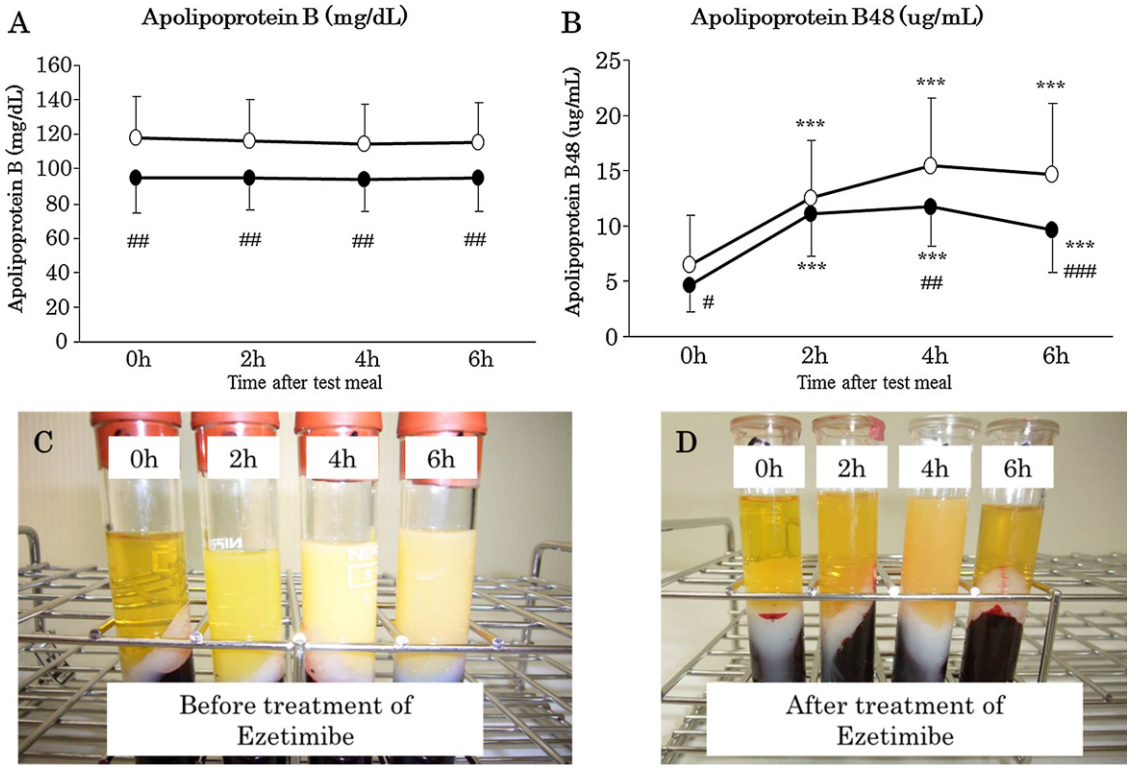

Fig. 2. Fat and glucose loading test before (open circles) and after (solid circles) ezetimibe treatment. The subjects ($n = 20$) received a high-fat and high-glucose meal (1001 kcal, protein 31.6 g, fat 61.4 g, carbohydrate 79.8 g, cholesterol 299 mg) before and after the treatment with ezetimibe. Blood samples were obtained while fasting and 2, 4, and 6 h after the test meal. (A) Apolipoprotein B and (B) apolipoprotein B48. (C and D) Photos of blood samples from a typical case are shown. The color of the sample changes from clear while fasting to white (lipemia) after the fat and glucose load before treatment with ezetimibe (C). Then the sample obtained after the fat and glucose load changes from white (lipemia) to normal after treatment with ezetimibe (D). Statistical analysis was done with the Bonferroni t-test to compare before and after the test meal ($^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$), and was done with the paired t-test to compare before and after the treatment with ezetimibe (#$p < 0.05$; ##$p < 0.01$; ###$p < 0.001$).

Effect of ezetimibe on lipid and glucose metabolism after the test meal

The TG level at 4 h after ingestion of the high-fat and high-glucose meal was 417.1 ± 174.4 mg/dL before treatment and it decreased to 329.6 ± 107.0 mg/dL ($p < 0.01$) after 4 weeks of ezetimibe treatment. The baseline TG level at 6 h postprandially was 415.7 ± 231.2 mg/dL and this decreased to 272.8 ± 131.8 mg/dL ($p < 0.01$) after ezetimibe treatment (Fig. 1). The AUC for the postprandial change in TG decreased from 1950.3 ± 843.1 before treatment to 1522.6 ± 486.6 after ezetimibe treatment (Table 3, $p < 0.01$). LDL-C levels at 2 and 4 h postprandially were significantly decreased after ezetimibe treatment and were similar to the preprandial levels (Fig. 1), with LDL-C showing a similar reduction at each time of measurement. The AUC for the change in LDL-C was also significantly decreased by ezetimibe treatment (Table 3, $p < 0.001$). HDL-C showed no significant changes at any time of assessment, and no significant change in the AUC for HDL-C was noted either (Fig. 1 and Table 3). The apolipoprotein B level was significantly decreased at 2, 4, and 6 h postprandially, and the decrease was similar at all times of assessment, as it was for LDL-C. The AUC for the postprandial change of apolipoprotein B was also significantly decreased by ezetimibe treatment (Fig. 2 and Table 3, $p < 0.001$). The apolipoprotein B48 level at 4 h postprandially decreased from 15.3 ± 6.2 μg/mL before treatment to 11.8 ± 3.6 μg/mL ($p < 0.01$) after ezetimibe treatment, while the level at 6 h decreased from 14.6 ± 6.5 μg/mL to 9.7 ± 3.9 μg/mL ($p < 0.001$). The AUC for the postprandial change of apolipoprotein B48 showed a significant decrease from 76.7 ± 31.9 mg/dL before treatment to 59.9 ± 19.2 mg/dL after ezetimibe treatment (Fig. 2 and Table 3, $p < 0.001$). At 2 h postprandially, blood glucose was 92.4 ± 25.9 mg/dL before treatment versus 84.7 ± 31.0 mg/dL after ezetimibe treatment (Fig. 1, $p < 0.05$). The AUC for the postprandial change of blood glucose showed a significant decrease from 556.9 ± 66.6 before treatment to 540.4 ± 82.4 after treatment (Table 3, $p < 0.05$). At 2 h postprandially, the blood insulin level was 32.8 ± 22.9 μU/mL before treatment as compared with 25.7 ± 19.1 μU/mL after ezetimibe treatment (Fig. 1, $p < 0.05$). The AUC for the postprandial change of insulin was significantly decreased from 119.7 ± 61.3 before treatment to 97.7 ± 53.9 after treatment (Table 3, $p < 0.01$).

Also the incremental area under the curve (IAUC) for postprandial change of TG, apolipoprotein B48, glucose, and insulin were significantly decreased after ezetimibe treatment (Table 4).

No adverse events or laboratory abnormalities of clinical relevance were observed during the study period.

Discussion

In recent years, the selective cholesterol-absorption inhibitor ezetimibe has been available for clinical use, allowing the regulation of cholesterol absorption as an option for the treatment of hyperlipidemia. Restriction of dietary fat intake is of vital importance for modern Japanese people, who have an increased cholesterol intake because of westernization of their diet. However, if sufficient efficacy is not obtained by diet alone, cholesterol absorption inhibitors like ezetimibe may provide an effective treatment option. Since this drug undergoes enterohepatic circulation, once-daily administration of ezetimibe achieves considerable improvement in serum lipid levels [12]. In the Japanese clinical study, ezetimibe monotherapy achieved an approximately 20% reduction in serum LDL-C level [8]. Previously, FESTA evaluated

Table 4
Incremental area under the curve for parameters of lipid and glucose metabolism before and after ezetimibe treatment.

	Before ezetimibe	After ezetimibe	Percent change	*p* Value
Triglycerides	1117.6 ± 454.5	920.3 ± 281.7	−9.7 ± 32.0	0.0280
Apolipoprotein B48	46.7 ± 20.0	38.5 ± 12.8	−8.3 ± 13.5	0.0133
Blood glucose	193.1 ± 33.7	182.4 ± 37.9	−5.7 ± 5.8	0.0012
Insulin	43.0 ± 25.2	35.0 ± 22.8	−13.6 ± 35.9	0.0176

Triglycerides and apo-48 (0–4 h), blood glucose and insulin (0–2 h).

the effect of ezetimibe (10 mg once daily) on serum lipids, glucose metabolism, and lipid metabolism in 120 patients with dyslipidemia during treatment for 12 weeks, and demonstrated a decrease in LDL-C by about 20% along with a decrease in the fasting insulin level and an increase in adiponectin [9]. That is, ezetimibe seemed to not only improve serum lipid levels but also metabolic abnormalities, including those of glucose metabolism and lipid metabolism. Ezetimibe is expected to be useful in Japan because patients with the combination of obesity, metabolic syndrome, and/or glucose intolerance [13] have been increasing in number due to progressive westernization of the diet. In recent years, there have been some reports about the mechanisms by which ezetimibe may improve metabolism. Masuda et al. [11] administered ezetimibe (10 mg once daily) for 2 months to patients with type IIb hyperlipidemia and gave them a lipid load before and after the treatment to evaluate influence of ezetimibe on postprandial lipid abnormalities. They reported that ezetimibe inhibited increase of serum apolipoprotein B48 and also inhibited increase in fatty acids. It was also reported that ezetimibe blocks the postprandial increase of chylomicrons due to inhibition of chylomicron secretion from the small intestines [14]. These postprandial effects of ezetimibe are thought to have a favorable impact on glucose and lipid metabolism. However, the effects of ezetimibe on postprandial metabolism have only been investigated after a fat load, and no investigation has assessed the effect of ezetimibe on postprandial glucose metabolism after a glucose load. People ingest both fat and carbohydrate during normal meals, so studies simulated with usual diet were required. Therefore, we investigated the effects of ezetimibe on postprandial lipid and glucose metabolism in patients with obesity or hypertriglyceridemia, who are likely to have postprandial metabolic abnormalities, after a simultaneous fat and glucose load. A fast-food meal was used as loading so that its nutritional content was both known and reproducible. The increase in serum TG at 4 and 6 h after ingestion of the test meal was significantly inhibited as a result of ezetimibe treatment, and the increase in apolipoprotein B48 was similarly inhibited at 4 and 6 h. In addition, the AUCs for both TG and apolipoprotein B48 were significantly decreased, suggesting an improvement in postprandial hyperlipidemia. Since HDL-C and LDL-C levels tended to decrease after a fat load, it was suggested that lipoprotein metabolism was delayed. This finding showed little change after treatment with ezetimibe. It is therefore suggested that ezetimibe treatment resulted in inhibition of chylomicron production rather than acceleration of lipoprotein metabolism. In fact, Nakamura et al. reported that the combination of ezetimibe and statin therapy significantly reduced remnant lipoproteinemia, which correlates chylomicron, compared with doubling of statin dose therapy [14].

Tremblay et al. [15] investigated the effect of ezetimibe on serum apolipoprotein B48 levels after a fat load in patients with mixed dyslipidemia. Their study showed that metabolism of apolipoprotein B48 was little changed while its production was enhanced, and the results of the present study are consistent with their results. In addition, we found that the blood glucose level at 2 h after the test meal was significantly decreased, resulting in a significant reduction in the AUC for glucose. The serum insulin level also showed a significant reduction at 2 h postprandially ($p < 0.05$), as did the AUC of insulin ($p < 0.01$). That is, an increase of glucose was inhibited even though the circulating insulin level was decreased as a result of ezetimibe treatment, suggesting that insulin sensitivity was improved by ezetimibe. A study in obese rats conducted by Yoshida et al. [10,16] showed that ezetimibe inhibited expression of the gene for sterol regulation element binding protein-1c (SREBP1c), which is a transcription factor involved in hepatic fatty acid synthesis, and that it improved chylomicrons, serum lipids (including fatty acids), and insulin resistance. It was also reported that ezetimibe decreased small intestinal expression of the gene for fatty acid transfer protein-4 (FATP-4) and inhibited fatty acid absorption [17]. The mechanism by which the supposedly selective cholesterol absorption inhibitor ezetimibe also inhibits fatty acid absorption is not well understood. However, inhibition of chylomicron formation due to depletion of cholesterol in small intestinal cells after treatment with ezetimibe may lead to an excess of triglycerides and secondary inhibition of fatty acid absorption and triglyceride synthesis. Moreover, a clinical study has revealed that ezetimibe is effective for improvement in non-alcoholic fatty liver disease (NAFLD). Yoneda et al. [18] conducted a study in 10 NAFLD patients receiving ezetimibe (10 mg/day) for 6 months, and carried out liver biopsy for histopathological examination before and after treatment. They reported that the ezetimibe treatment significantly decreased the amount of fat droplets in the liver. Furthermore, a study employing magnetic resonance imaging showed that ezetimibe combined with dietary therapy significantly reduced the hepatic fat area compared with dietary therapy alone [19]. Fatty liver is closely associated with insulin sensitivity. Therefore, it is expected that a decrease in lipid accumulation in the liver due to ezetimibe treatment would have a favorable impact on hepatic insulin sensitivity. That is, the improvement in postprandial glucose metabolism is suggested to be secondary to improvement in fatty acid metabolism and reduced hepatic lipid accumulation resulting from inhibition of chylomicron secretion by ezetimibe.

In our present study, glucose and insulin levels at 30 min and 60 min after meal were not measured because multiple blood sampling is invasive for our study subjects (healthy volunteers) excluding patients with diabetes. Although our preliminary data suggested a possible involvement of ezetimibe in glucose metabolism, measurements of glucose and insulin levels at 30 min and 60 min after a meal are required to confirm this correlation.

The prevalence of dyslipidemia is increasing in modern Japan because of westernization of the diet and ezetimibe is a reasonable etiologic therapy for dyslipidemia. Since this drug also improves postprandial metabolism, ezetimibe could be a beneficial treatment option for patients who have dyslipidemia accompanied by obesity or metabolic syndrome. The present study had no control group and a limited sample size, as well as investigating relatively few laboratory parameters. It is difficult to establish that ezetimibe treatment itself improved postprandial lipid and glucose metabolism. A randomized controlled trial should therefore be conducted in the future.

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