Double-Blind Randomized Clinical Trial of the Effects of Ezetimibe on Postprandial Hyperlipidaemia and Hyperglycaemia

Kaori Kikuchi¹, Uru Nezu¹, Koji Inazumi¹, Takashi Miyazaki¹, Kanako Ono¹, Kazuki Orime¹, Jun Shirakawa¹, Koichiro Sato¹, Hirofumi Koike², Tadashi Wakasugi², Misako Sato², Chihiro Kawakami³, Shinichiro Watanabe⁴, Tadashi Yamakawa⁵ and Yasuo Terauchi¹

¹Department of Endocrinology & Metabolism, Yokohama City University Graduate School of Medicine, Kanagawa, Japan
²Pharmaceutical Department, Yokohama City University Hospital, Kanagawa, Japan
³Department of Epidemiology and Public Health, Yokohama City University Graduate School of Medicine, Kanagawa, Japan
⁴Clinical Laboratory Department, Yokohama City University Hospital, Kanagawa, Japan
⁵Department of Endocrinology & Metabolism, Yokohama City University Hospital Medical Center, Kanagawa, Japan

Aim: Ezetimibe selectively blocks intestinal cholesterol absorption by inhibiting Niemann-Pick C1-like 1 (NPC1L1) and reducing LDL cholesterol (LDL-C). In animals, ezetimibe reversed diet-induced obesity, liver steatosis, and insulin resistance. In humans, its potential effects on liver steatosis and insulin resistance have been suggested. We investigated the effects of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia in obese subjects with dyslipidaemia in a double-blind randomized crossover trial.

Methods: Twenty obese men with hypertriglyceridaemia were assigned randomly to an ezetimibe- or a placebo-precedence-treated group. Subjects in the ezetimibe group were treated with ezetimibe (10 mg/day) for the first 4 weeks, followed by a 4-week interval and then treated with placebo for another 4 weeks. The placebo group received these treatments in reverse order. Subjects were requested to fast for at least 12 hours and then received a standard meal. Blood samples were collected at 0, 30, 60, 120, 240, 360 and 480 minutes after the meal on Days 0, 28, 56 and 84 and were used to measure the lipid and glucose metabolism markers.

Results: Ezetimibe significantly decreased the postprandial serum triglyceride excursion ($p=0.01$) and fasting serum LDL-C, remnant-like particles (RLP) and ApoB48 levels ($p<0.05$). Postprandial glucose excursion, serum insulin levels, serum glucose-dependent insulinotropic polypeptide (GIP) and active glucagon-like peptide-1 (GLP-1) were not significantly affected by ezetimibe treatment.

Conclusion: Ezetimibe restored the postprandial dysregulation of lipid but did not affect glucose metabolism in a double-blind randomized crossover trial.


Key words; Ezetimibe, Hyperlipidaemia, Hyperglycaemia
Postprandial hyperglycaemia and hypertriglyceridaemia are also recognized as the risk for cardiovascular events related to postprandial endothelial dysfunction, in addition to classical risk factors. Lipoprotein particles undergo partial hydrolysis predominantly through the action of lipoprotein lipase (LPL), forming smaller and denser particles known as remnants that are believed to be more atherogenic than larger triglyceride-rich lipoproteins (TRL). In the postprandial state, the blood levels of chylomicrons (CM) and chylomicron remnants (CM-R) quickly rise to reflect the increased exogenous lipid supply. This subsequently activates endogenous lipid synthesis in the liver by increased hepatic lipid inflow, leading to the augmented hepatic production of very low-density lipoproteins (VLDL). Postprandial hypertriglyceridaemia is caused by the overproduction and/or impaired clearance of TRL and TRL remnants, leading to rapid accumulation and sustained blood levels after dietary intake. Insulin resistance, often observed in metabolic syndrome, is associated with elevated TRL in the VLDL-1 fraction and remnants in the postprandial state.

Ezetimibe selectively blocks intestinal cholesterol absorption by inhibiting Niemann-Pick C1-like 1 (NPC1L1). Clinically, the administration of ezetimibe has been shown to reduce fasting levels of total cholesterol (TC) and LDL-C in patients with primary hypercholesterolemia in both Japan and the United States. In addition, ezetimibe has been reported to reduce postprandial hypertriglyceridaemia and inflammation and to improve insulin sensitivity. In animals experiments, ezetimibe reversed diet-induced obesity, liver steatosis, and insulin resistance. In humans, in addition to the effect of ezetimibe on lowering serum LDL-C, its potential effects on liver steatosis and insulin resistance have been reported. In contrast, ezetimibe reportedly affected the secretion of the incretin hormones as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Thus, ezetimibe significantly reduced the secretion of both GIP and GLP-1 into the lymph after the infusion of Ensure; however, these effects have not been fully confirmed in human subjects.

In the present study, we investigated the effects of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia in obese subjects with dyslipidaemia in a double-blind randomized crossover trial.

Research Design and Methods

Subjects
Twenty obese Japanese men (body mass index \( \geq 25 \text{ kg/m}^2 \) or waist circumference \( \geq 85 \text{ cm} \)) whose triglyceride (TG) levels were between 150 and 400 mg/dL were randomly assigned to an ezetimibe- or a placebo-precedence-treated group. The exclusion criteria were treatment with anti-dyslipidaemic and/or anti-diabetic agents within the last 3 months, a history of macrovascular disease, or the presence of thyroid, hepatic, or renal diseases, as identified using a standardized health questionnaire. The clinical study was approved by our Institutional Ethics Review Committee, and subjects were recruited between November 2009 and February 2010. The objective and design of the study were explained to all the subjects, and written informed consent was obtained from each of the study participants.

Study Design
In this prospective, randomized, crossover, double-blind trial, subjects in the ezetimibe precedence-group were treated with ezetimibe (10 mg/day) for the first 4 weeks, followed by a 4-week interval and then treated with placebo for another 4 weeks. The placebo group received these treatments in reverse order. At the beginning and end of each 4-week treatment period, the subjects were requested to fast for more than 12 hours and then underwent a physical examination, including measurement of the patient’s height, weight, waist circumference, and blood pressure. All the subjects received a model meal (frozen commercial food, 1,300 kcal; protein, 48 g; fat, 50 g; carbohydrates, 170 g) and were prohibited from consuming any further food for 480 minutes after eating the model meal. Blood samples were collected at 0, 30, 60, 120, 240, 360 and 480 minutes after the start of the meal on Days 0, 28, 56 and 84; these samples were used to measure clinical parameters related to lipid and glucose metabolism. During the study, other medications for the treatment of dyslipidaemia and diabetes were prohibited.

Ezetimibe was encapsulated with lactose. The placebo was encapsulated with only lactose. Only the pharmacist was aware of the drug allocation.

The protocol for this study was registered with the UMIN Clinical Trial Registry as UMIN000002954, based on the World Medical Association Declaration of Helsinki. The examination period was from January 2010 to June 2010.

Measurement of Serum Samples
The primary endpoints were the lipid metabolism markers. The secondary endpoints were glucose metabolism markers, inflammatory markers, and the serum adiponectin level. For the lipid metabolism
Effects of Ezetimibe on Hyperlipidaemia and Hyperglycaemia

measures ANOVA were used for comparisons of values obtained before and after the administration of ezetimibe and the placebo. A value of $p < 0.05$ was considered significant. All data were analyzed using SPSS software, ver. 18.

Results

Among the 22 men who were initially screened, two were excluded because of severe hypertriglyceridaemia (TG > 1,000 mg/dL) or an underlying disease; thus, 20 men were enrolled in the present study (Fig. 1). These subjects were randomly allocated to two treatment groups using a blocked randomization method.

The demographic, clinical, and laboratory characteristics of the subjects at baseline are provided in Table 1. The mean age was 43.7 ± 8.1 years. The mean body mass index was 26.0 ± 2.6 kg/m². The mean waist circumference was 92.0 ± 4.4 cm. The mean systolic and diastolic blood pressures were slightly elevated: the mean systolic blood pressure was 133.7 ± 10.5 mmHg, and the mean diastolic blood pressure was 86.8 ± 9.3 mmHg. Furthermore, the mean serum TC, TG, RLP-C and malondialdehyde modified low-density lipoprotein cholesterol (MDA-LDL) levels were also elevated (TC: 222.3 ± 38.4 mg/dL, TG: 226.6 ± 110.6 mg/dL, RLP-C: 11.8 ± 6.7 mg/dL, MDA-LDL: 138.3 ± 39.2 U/L). No carryover effects or period effects between the two treatments periods were observed.

Statistical Analyses

All the data were disclosed after the termination of the trial and were analyzed by an investigator in the Department of Endocrinology & Metabolism, Yokohama City University Graduate School of Medicine. The results are expressed as the mean ± SD. The post-prandial variations were integrated as the area under the curve (AUC). Student’s paired $t$-test and repeated measures ANOVA were used for comparisons of values obtained before and after the administration of ezetimibe and the placebo. A value of $p < 0.05$ was considered significant. All data were analyzed using SPSS software, ver. 18.

Rate-of-Change Analysis for Fasting Period

Table 2 shows the fasting serum biomarker levels before and after the administration of ezetimibe for 4 weeks. The fasting levels of serum TC, LDL-C, MDA-

---

**Table 1. Baseline characteristics of the subjects**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (year)</td>
<td>43.7 ± 8.1</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>26.0 ± 2.6</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133.7 ± 10.5</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>86.8 ± 9.3</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>92.0 ± 4.4</td>
</tr>
<tr>
<td>Past cardiovascular disease</td>
<td>0%</td>
</tr>
<tr>
<td>Family history of cardiovascular disease</td>
<td>42.9%</td>
</tr>
<tr>
<td>Smoking</td>
<td>75.0%</td>
</tr>
<tr>
<td>Alcohol</td>
<td>90.0%</td>
</tr>
<tr>
<td>Exercise habits</td>
<td>50.0%</td>
</tr>
<tr>
<td>Eating between meals</td>
<td>50.0%</td>
</tr>
<tr>
<td>Body weight gain: 3 kg/year or more</td>
<td>55.0%</td>
</tr>
</tbody>
</table>

All data are shown as the mean ± SD, $n=20$.  

---

**Fig. 1. CONSORT diagram of the study.**

Twenty-two men were screened, of which 2 were excluded. Consequently, 20 men were enrolled in this study and were randomly assigned to two groups.
Table 2: Rate-of-change analysis for fasting period

<table>
<thead>
<tr>
<th></th>
<th>Ezetimibe</th>
<th>Placebo</th>
<th>Rate of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>After treatment</td>
<td>Baseline</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>76.2±8.3</td>
<td>76.0±8.6</td>
<td>76.4±7.9</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>91.9±4.5</td>
<td>92.2±5.0</td>
<td>92.3±5.1</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>133.1±9.4</td>
<td>132.4±8.5</td>
<td>133.5±10.3</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>85.4±8.2</td>
<td>88±6.9</td>
<td>86.3±9.6</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>223.1±37.2</td>
<td>189.4±32.7</td>
<td>224.8±38.0</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>135.5±40.8</td>
<td>111.1±30.1</td>
<td>136.0±40.2</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>46.2±8.0</td>
<td>46.7±11.1</td>
<td>46.5±9.2</td>
</tr>
<tr>
<td>MDA-LDL (U/L)</td>
<td>135.2±41.2</td>
<td>111.2±44.6</td>
<td>150.2±55.7</td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>254.8±128.6</td>
<td>202.1±166.0</td>
<td>277.4±227.1</td>
</tr>
<tr>
<td>FFA (μEq/L)</td>
<td>386.2±137.5</td>
<td>408.4±175.4</td>
<td>394.3±137.5</td>
</tr>
<tr>
<td>RLP-C (mg/dL)</td>
<td>14.4±8.8</td>
<td>6.8±3.3</td>
<td>13.4±16.0</td>
</tr>
<tr>
<td>ApoA1 (mg/dL)</td>
<td>135.2±16.6</td>
<td>134.4±23.6</td>
<td>134.6±17.7</td>
</tr>
<tr>
<td>ApoA2 (mg/dL)</td>
<td>33.0±3.9</td>
<td>32.5±5.2</td>
<td>32.7±4.5</td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>115.9±25.7</td>
<td>96.2±21.2</td>
<td>116.6±26.2</td>
</tr>
<tr>
<td>ApoB48 (μg/mL)</td>
<td>11.4±7.2</td>
<td>7.4±5.2</td>
<td>10.8±10.0</td>
</tr>
<tr>
<td>ApoC2 (mg/dL)</td>
<td>6.5±2.1</td>
<td>5.1±1.8</td>
<td>6.4±2.2</td>
</tr>
<tr>
<td>ApoC3 (mg/dL)</td>
<td>13.6±4.1</td>
<td>11.3±4.5</td>
<td>13.4±4.6</td>
</tr>
<tr>
<td>ApoE (mg/dL)</td>
<td>5.4±1.8</td>
<td>4.6±1.7</td>
<td>5.5±1.8</td>
</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>106.0±10.0</td>
<td>105.1±9.6</td>
<td>105.9±10.9</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>5.0±0.3</td>
<td>5.0±0.3</td>
<td>5.0±0.3</td>
</tr>
<tr>
<td>IRI (μU/mL)</td>
<td>11.4±6.0</td>
<td>9.6±4.4</td>
<td>10.7±5.2</td>
</tr>
<tr>
<td>GIP (pg/mL)</td>
<td>75.7±51.7</td>
<td>73.9±48.7</td>
<td>60.5±30.6</td>
</tr>
<tr>
<td>Active GLP-1 (pmol/L)</td>
<td>2.7±2.5</td>
<td>2.8±2.9</td>
<td>3.1±3.2</td>
</tr>
<tr>
<td>Adiponectin (μg/mL)</td>
<td>5.5±1.9</td>
<td>5.2±2.0</td>
<td>5.3±2.2</td>
</tr>
<tr>
<td>TNFa (pg/mL)</td>
<td>1.7±3.3</td>
<td>1.5±2.9</td>
<td>1.4±1.9</td>
</tr>
<tr>
<td>hsCRP (mg/mL)</td>
<td>792.5±450.5</td>
<td>828±552.0</td>
<td>1730.5±3768.9</td>
</tr>
</tbody>
</table>

All data are shown as the mean±SD, n=20, paired t-test. TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; MDA-LDL, malondialdehyde modified low-density lipoprotein cholesterol; TG, triglyceride; FFA, free fatty acid; RLP-C, remnant-like particle cholesterol; IRI, immunoreactive insulin; HbA1c, haemoglobin A1c (JDS); GIP, glucose-dependent insulino tropic polypeptide; active GLP-1, active glucagon-like peptide-1; TNFa, tumor necrosis factor α; hsCRP, high sensitivity C-reactive protein.

LDL-C and RLP-C excursions were significantly lower after ezetimibe treatment; however, the rate-of-change of serum TG, HDL-C and FFA levels remained stable. ApoB, ApoB48, ApoC2, ApoC3 and ApoE excursions were significantly reduced. Glucose metabolism markers and inflammatory markers were unaltered. The serum adiponectin concentration was slightly, but significantly, reduced. Weight, waist circumference, and blood pressure remained stable during the 4-week treatment with ezetimibe or the placebo.

Postprandial Changes in Clinical Markers Related to Lipid and Glucose Metabolism

Levels and AUCs of serum TC and LDL-C were reduced after ezetimibe treatment (Fig. 2a, b). Peak serum TG excursion was seen around 240 minutes after the meal. Of note, ezetimibe significantly decreased postprandial serum TG excursions at 120, 240, 360 and 480 minutes after consumption of the model meal and significantly decreased the AUC of TG (−26.9%) (Fig. 2d). By contrast, the serum HDL-C level remained essentially stable after the meal (Fig. 2c). Ezetimibe also decreased the AUC of RLP-C and ApoB48 (−37.4% and −22.1%) (Fig. 2e, f). Serum FFA decreased similarly in both groups after the meal (Fig. 2g).

Ezetimibe had no impact on fasting and postprandial glucose levels and had no impact on incretin (GIP and active GLP-1) concentrations in response to the model meal (Fig. 2j, k). The AUC for the serum insulin levels tended to reduce but was not statistically significant (p = 0.08 (Fig. 2h, i).
Effects of Ezetimibe on Hyperlipidaemia and Hyperglycaemia

at 120, 240, 360 and 480 min after the model meal and significantly decreased the AUC of TG (Fig. 3d).

Ezetimibe also decreased postprandial RLP-C excursions at 360 and 480 min and postprandial ApoB48 excursions at 480 min after the model meal (Fig. 3e, f).

In addition, ezetimibe significantly decreased the AUC

Differences in Postprandial Changes of Clinical Markers Related to Lipid and Glucose Metabolism when Administering Ezetimibe or Placebo

Ezetimibe reduced postprandial changes in serum TG, RLP-C and ApoB48 levels. Thus, ezetimibe significantly decreased postprandial serum TG excursions at 120, 240, 360 and 480 min after the model meal and significantly decreased the AUC of TG (Fig. 3d).

Ezetimibe also decreased postprandial RLP-C excursions at 360 and 480 min and postprandial ApoB48 excursions at 480 min after the model meal (Fig. 3e, f). In addition, ezetimibe significantly decreased the AUC
of RLP-C. By contrast, postprandial changes in serum TC, LDL-C, HDL-C and FFA were not affected by ezetimibe treatment (Fig. 3a, b, c, g).

Ezetimibe had no impact on the difference in the postprandial change of glucose metabolism markers in response to the model meal (Fig. 3h, i, j, k).

Safety and Tolerability

Treatment was well tolerated. No significant increases in serum creatine phosphokinase and trans-
aminase levels were observed.

**Discussion**

Previous studies have revealed a potential effect of ezetimibe on insulin sensitivity and glucose metabolism. Here, we investigated the effects of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia in obese subjects with dyslipidaemia in a double-blind randomized crossover trial. We report three findings regarding the effect of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia. First, ezetimibe significantly decreased postprandial serum TG excursion at 120, 240, 360 and 480 minutes after the model meal (Fig. 2d, 3d). Second, postprandial glucose and insulin excursions were not affected by ezetimibe (Fig. 2h, i, 3h, i), raising the possibility that ezetimibe does not contribute to glucose tolerance aggravation. Third, postprandial incretin excursions were not affected by ezetimibe.

In the present study, ezetimibe significantly decreased postprandial serum TG excursion at 120, 240, 360 and 480 minutes after the model meal (Fig. 2d, 3d). Postprandial serum TG excursion after oral fat loading is reportedly reduced by ezetimibe in patients with type IIb hyperlipidaemia. Our results were essentially consistent with this previous report. It should be noted, however, that while the previous study used fat cream, the present study used a typical daily meal. Another study indicated that ezetimibe combined with simvastatin decreased postprandial hypertriglyceridaemia; however, the effect of ezetimibe alone has not examined. We determined that ezetimibe was effective in inhibiting postprandial hypertriglyceridaemia in this study. The reductions in LDL-C and RLP were thought to have resulted from the inhibition of cholesterol absorption (Table 2, Fig. 2b, e). RLP-C is composed of CM-R and VLDL-R. During meal loading, the major part of RLP-C is derived from CM-R. The reduction of serum RLP-C by ezetimibe might indicate that the inhibition of cholesterol inflow into the liver might cause the upregulation of remnant receptors, which would improve the clearance of CM-R and reduce the serum CM-R level. The reduction of ApoB48 may be associated with a decrease in chylomicron generation (Fig. 2f, 3f); however, the reduction in postprandial serum TG excursion by ezetimibe was not fully explained by the minimally decreased chylomicron level, since the TG peak occurred 240 minutes after the start of the meal. The release of VLDL from the liver may also be involved in this alteration. Iso et al. reported that postprandial hypertriglyceridaemia was associated with cardiovascular disease. The results of our study suggested that ezetimibe might modify postprandial TG metabolism after meals and reduce the risk of cardiovascular disease by decreasing the postprandial serum TG level. On the other hand, postprandial serum FFA excursion, a risk factor for cardiovascular disease, was unaffected by ezetimibe administration and showed a J-curve in this study. Whenever serum insulin and plasma glucose increase during OGTT, serum FFA decreases in the opposite direction; however, a previous study reported that serum FFA increased after a lipid-rich meal and that ezetimibe inhibited the increment of serum FFA excursion. The discrepancy between our study and the previous study may be explained by insulin-stimulated lipoprotein lipase (LPL) activity derived from the presence or absence of carbohydrates, although we did not measure LPL activity in this study. Another possibility is that our model meal contained more carbohydrates than the meal in the previous study.

Postprandial glucose and insulin excursion and serum incretin levels were not affected by ezetimibe significantly (Fig. 2h, i, j, k, 3h, i, j, k). These results suggested that glucose tolerance was not exacerbated by ezetimibe. Several studies in humans showed that HbA1c was decreased by ezetimibe. The results of our animal study supported the concept that ezetimibe ameliorates hepatic insulin resistance as well as dyslipidaemia and hepatic steatosis in high-fat diet-induced obese subjects. However, our results suggest that glucose tolerance was not exacerbated by ezetimibe, but the present study failed to confirm the effects of ezetimibe on the improvement of glucose metabolism markers. Because diabetic patients were excluded from this study, a similar clinical study of subjects with diabetes is needed. A previous clinical study in which liver biopsy were performed revealed a role of ezetimibe in the improvement of hepatic steatosis in humans. Because the design of the present study had an intervention period of only 4 weeks, we did not focus on this issue.

Ezetimibe was previously reported to reduce or increase active GLP-1 excursion, but ezetimibe did not affect active GLP-1 excursion in response to the model meal in this study (Fig. 2j, k, 3j, k). Li Yang et al. reported that lymphatic incretin was significantly decreased by ezetimibe in a Sprague-Dawley rat model. In contrast, Soo Jin Yang et al. reported a reduction in serum dipeptidyl peptidase-4 activity, increased serum active GLP-1, and improved glucose metabolism after ezetimibe treatment in OLETF rats. The mechanism responsible for these effects was not clear in these animal studies. The reasons why
ezetimibe did not affect serum active GLP-1 excursion in the present study might be explained by the fact that the subjects of the study were humans with dyslipidaemia and that serum samples, and not lymphatic samples, were measured. Nevertheless, because this clinical study was a double-blind, randomized trial, we concluded that postprandial serum incretin excursions were not affected by ezetimibe in human obese subjects with dyslipidaemia.

Our findings in this study suggested some treatment options for patients with combined hyperlipidaemia. Ezetimibe administration may be a favourable option for the treatment of patients with elevated VLDL, LDL and RLP-C levels. Several studies have shown that ezetimibe improved lipid metabolism in obese patients with dyslipidaemia and in animal models of metabolic syndrome. Moreover, ezetimibe reportedly inhibits the elevation of hs-CRP and improves endothelium-dependent acetylcholine-induced vasodilatation in patients with metabolic syndrome, although we were unable to confirm these effects in the present study. To clarify the anti-atherogenic effects of ezetimibe in subjects with cardiovascular risk factors, further evidence from mega-trials, such as IMPROVE-IT and EWTOPIA, will be essential.

**Study Limitations**

The present study has several limitations. Because the number of subjects was relatively small and the duration of ezetimibe treatment was only 4 weeks, this study might be underpowered for assessing the effects of ezetimibe on postprandial hyperlipidaemia and hyperglycaemia. Furthermore, because the duration of ezetimibe treatment was only 4 weeks, the results of this study may differ from the long-term effects of ezetimibe treatment. Large-scale studies should be performed to confirm the findings obtained in the present study.

**Conclusions**

Ezetimibe reversed postprandial lipid dysregulation but did not affect glucose metabolism in a double-blind randomized crossover trial.

**Acknowledgments**

We are grateful for the unrestricted support from the Schering-Plough Research Institute (MSD) and Bayer for this clinical study. This work was supported by the Yokohama City University Center of Excellence Program of MEXT and a grant for the Strategic Research Project of Yokohama City University (to Y.T.).

**Conflict of Interest**

None.

**References**

11) Funada J, Sekiya M, Otani T, Watanabe K, Sato M,
Akutsu H: The close relationship between postprandial remnant metabolism and insulin resistance. Atherosclerosis, 2004; 172: 151-154


21) Nozue T, Michishita I, Mizuguchi I: Effects of ezetimibe on remnant-like particle cholesterol, lipoprotein (a), and oxidized low-density lipoprotein in patients with dyslipidaemia. J Atheroscler Thromb, 2010; 17: 37-44


Effects of Ezetimibe on Hyperlipidaemia and Hyperglycaemia 1101