Original Article

Ezetimibe Ameliorates Atherosclerotic and Inflammatory Markers, Atherogenic Lipid Profiles, Insulin Sensitivity, and Liver Dysfunction in Japanese Patients with Hypercholesterolemia

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Aim: Ezetimibe reduces serum low-density lipoprotein cholesterol (LDL-C) levels by inhibiting intestinal cholesterol absorption; however, the effects of ezetimibe, including its pleiotropic effects, have not been fully clarified. The aims of our study were to examine the efficacy of ezetimibe for hypercholesterolemia and its pleiotropic effects.

Methods: Outpatients with hyper LDL-C levels were treated with 10 mg ezetimibe once a day for 12 weeks. Serum lipid profiles, atherosclerotic and inflammatory markers, glucose, insulin, liver function, and cholesterol absorption and synthesis markers were measured before and after treatment.

Results: Seventy-five patients treated with ezetimibe monotherapy and 16 patients treated with combined therapy of ezetimibe with different statins completed this study. Following 12 weeks of ezetimibe monotherapy, serum LDL-C, triglyceride, remnant-like particles cholesterol, matrix metalloproteinase-9, insulin, homeostasis model assessment of insulin resistance, high-sensitivity C-reactive protein, the relative mobility of the peak of the LDL fraction, and cholesterol absorption markers were significantly decreased, and high-density lipoprotein cholesterol and lathosterol were significantly increased. In the combined therapy group, LDL-C and cholesterol absorption markers were significantly decreased after treatment. In patients with a high basal ALT level that were treated with monotherapy, ALT and the AST/ALT ratio were significantly decreased and increased, respectively, after treatment.

Conclusion: Ezetimibe ameliorated not only atherogenic lipid profiles but also atherosclerotic and inflammatory markers, insulin sensitivity, and liver dysfunction in Japanese hypercholesterolemia patients, suggesting that ezetimibe treatment is a beneficial and effective strategy for the treatment of hypercholesterolemia, especially patients with obesity, metabolic syndrome, and/or fatty liver.

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Key words; Ezetimibe, Hypercholesterolemia, Atherosclerosis, Insulin sensitivity, Fatty liver

Introduction

Hypercholesterolemia is a well-known major risk factor for cardiovascular disease not only in Western

countries but also in Japan. Increased concentrations of low-density lipoprotein cholesterol (LDL-C) have been shown to play a key role in the pathogenesis of atherosclerosis. Lowering LDL-C by 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors (statins) reduces the risk of myocardial infarction, stroke, and other cardiovascular events among individuals with established coronary disease, overt hyperlipidemia, and type 2 diabetes^{1,2}.

Ezetimibe selectively inhibits intestinal cholesterol absorption by inhibiting the transporter protein

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Niemann-Pick C1-like 1 and reduces serum LDL-C levels in both monotherapy and combination therapy with a statin³⁻¹¹). Ezetimibe was also reported to have pleiotropic effects including the amelioration of inflammation, insulin resistance and fatty liver^{3-7, 12-14}). Although long-term treatment with ezetimibe plus simvastatin reduced major atherosclerotic events in patients with chronic kidney disease by 17%¹⁵), neither the underlying mechanisms nor the anti-atherosclerotic effect of ezetimibe monotherapy are yet fully elucidated.

We conducted a prospective observational study to elucidate the clinical effects of ezetimibe, including changes in atherosclerotic markers such as matrix metalloproteinase-9 (MMP-9) and soluble vascular adhesion molecule-1 (sVCAM-1) that have not been previously studied, as well as soluble endothelial-selectin (sE-Selectin), soluble intracellular adhesion molecule-1 (sICAM-1), adiponectin, and total plasminogen activator inhibitor-1 (PAI-1) in Japanese patients with hypercholesterolemia.

Methods

Patients

Outpatients with hypercholesterolemia who had not achieved the serum LDL-C levels recommended in the guidelines of the Japan Atherosclerosis Society 2007, despite diet and exercise without anti-dyslipidemic agents (ezetimibe monotherapy) or with a statin (combined therapy) for at least 4 weeks, were enrolled. This study was approved by Miyazaki University Ethics Committee and all patients gave written informed consent.

All patients were examined at enrollment for coronary risk factors including age (≥ 45 years for men and ≥ 55 years for women), hypertension (systolic blood pressure (SBP) ≥ 140 mmHg and/or diastolic blood pressure (DBP) ≥ 90 mmHg), diabetes mellitus (including impaired glucose tolerance), current smoking, low high-density lipoprotein cholesterol (HDL-C) (< 40 mg/dL) and a family history of coronary artery diseases. Other data including the body mass index (BMI) and the use of anti-hypertensive, anti-diabetic and anti-platelet agents were also obtained.

Study Design

The enrolled patients were treated orally with 10 mg ezetimibe once a day for 12 weeks. Standard diet and exercise therapy for hypercholesterolemia were recommended during this study. Blood was sampled after an overnight fast and a physical examination was performed before and 12 weeks after ezetimibe admin-

istration. During these 12 weeks, anti-hyperlipidemic, anti-hypertensive and anti-diabetic agents other than ezetimibe were continued without dosage modification.

Laboratory Methods

The serum levels of LDL-C, triglyceride (TG), HDL-C, remnant like particles cholesterol (RLP-C), fasting plasma glucose (FPG), fasting immunoreactive insulin (IRI) and HbA_{1c} were measured using standard laboratory methods. Homeostasis model assessment insulin resistance (HOMA-IR) was calculated as $\text{FPG (mg/dL)} \times \text{fasting IRI } (\mu\text{U/mL}) / 405$ and used as a marker of insulin sensitivity. LDL particle size was evaluated using the relative mobility of the peak of the LDL fraction (LDL-R_m) in lipoprotein electrophoresis. In this method, an increase in the LDL-R_m ratio indicates a decrease in LDL particle size¹⁶). High-sensitivity C-reactive protein (hs-CRP), used as an inflammatory marker, sitosterol, campesterol and cholesterol, used as markers of cholesterol absorption from the small intestine, and lathosterol, used as a marker of cholesterol biosynthesis in liver, were measured by SRL Inc. (Tokyo, Japan). Serum levels of MMP-9, sE-selectin, sVCAM-1, sICAM-1, adiponectin, and PAI-1 in patients undergoing monotherapy were measured by GeneticLab Co., Ltd. (Hokkaido, Japan).

Statistical Analyses

Values are expressed as the means $\pm$ SEM. Variables that were not normally distributed and/or displayed homogeneity of variances were analyzed using the Mann-Whitney test for independent samples and the Wilcoxon test. Normally distributed variables were analyzed using an unpaired or paired *t* test. A *p* value < 0.05 was considered significant. Single regression analysis was used to assess the correlation between the LDL-C level and markers of cholesterol absorption and synthesis. Stepwise multiple linear regression analysis was used to determine the effects of age, sex, BMI, HOMA-IR, SBP, basal LDL-C, TG, lathosterol, and campesterol as independent variables on the percent decrease in LDL-C. Statistical analyses were performed using JMP 8.0.2 (SAS Institute. Cary, NC, USA).

Results

We enrolled 143 outpatients with hypercholesterolemia in the study; however, 31 patients were excluded because their baseline serum LDL-C levels achieved the recommended levels. Of the remaining 112 patients, ezetimibe monotherapy was initiated in 95 patients and combined therapy of ezetimibe with a

Table 1. Baseline characteristics of the patients

	All patients	Monotherapy	Combined therapy	<i>p</i> value
n (M/F)	91 (35/56)	75 (30/45)	16 (5/11)	0.58
Age	60.3 ± 1.2	60.7 ± 1.3	58.7 ± 3.4	0.52
BMI (kg/m ²)	24.0 ± 0.4	23.7 ± 0.4	25.5 ± 1.8	0.38
SBP (mmHg)	131.2 ± 1.9	132.0 ± 2.0	127.6 ± 5.0	0.39
DBP (mmHg)	77.5 ± 1.0	77.8 ± 1.1	76.1 ± 2.8	0.54
Number of coronary risk factors	2.1 ± 0.1	2.0 ± 0.1	2.3 ± 0.3	0.44
Aging	73 (80.2%)	62 (82.7%)	11 (68.8%)	0.26
Hypertension	51 (56.0%)	42 (56.0%)	9 (56.3%)	0.96
Diabetes	28 (30.8%)	19 (25.3%)	9 (56.3%)	0.03
Current smoking	14 (15.4%)	11 (14.7%)	3 (20.0%)	0.44
Low HDL-C	7 (7.7%)	7 (9.3%)	0 (0%)	0.35
Family history of coronary artery disease	14 (15.4%)	10 (13.3%)	4 (26.7%)	0.22

Values are expressed as the means ± S.E.M. or number of subjects. BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure.

statin was initiated in 17 patients. Seventy-five of the patients receiving monotherapy and 16 of the patients receiving combined therapy completed 12 weeks of treatment. In the combined therapy group, atorvastatin, rosuvastatin, pravastatin and pitavastatin was administered to 7, 4, 3, and 2 patients, respectively, before the addition of ezetimibe.

Table 1 shows the baseline characteristics of the patients. No significant differences were found in age, BMI, SBP, DBP and the number of coronary risk factors between the monotherapy and combined therapy groups, whereas the percentage of patients with diabetes was significantly higher in the combined therapy than in the monotherapy group.

Table 2 shows the laboratory findings before and 12 weeks after ezetimibe treatments. Serum levels of LDL-C, TG, LDL-C/HDL-C, RLP-C, IRI, LDL-Rm, campesterol, cholestanol, and sitosterol were significantly decreased, and HDL-C and lathosterol were significantly increased in all patients after 12 weeks of treatment. LDL-C, LDL-C/HDL-C, RLP-C, IRI, HOMA-IR, hs-CRP, LDL-Rm, campesterol, cholestanol, sitosterol and MMP-9 were significantly decreased, whereas HDL-C and lathosterol were significantly increased after 12 weeks of ezetimibe monotherapy. Adiponectin, total PAI-1, sE-Selectin, sVCAM-1, and sICAM-1 did not change after this treatment. LDL-C, LDL-C/HDL-C, campesterol, cholestanol and sitosterol were also significantly decreased, and lathosterol was significantly increased after 12 weeks' co-administration of ezetimibe and a statin. Serum LDL-C levels were decreased by $18.2 \pm 1.4\%$ and $24.3 \pm 3.1\%$ after monotherapy and combined therapy, respectively. In addition, 61.3% of the patients receiving monotherapy and 60% of the

patients receiving combined therapy achieved the recommended LDL-C level. Basal levels of campesterol, cholestanol and sitosterol were similar in the monotherapy and combined therapy groups ($p=0.95$, $p=0.83$, $p=0.74$, respectively), whereas lathosterol was significantly lower ($p=0.02$) in the combined therapy than in the monotherapy group (**Table 2**). Significant positive correlations were seen in the monotherapy group between the basal LDL-C level and campesterol ($r=0.32$, $p=0.002$), cholestanol ($r=0.39$, $p=0.0001$) or sitosterol ($r=0.31$, $p=0.003$), but not lathosterol ($r=0.09$, $p=0.41$).

Stepwise multiple linear regression analysis was performed in order to examine significant contributors to the prediction of percent decrease in LDL-C, resulting in the selection of only one variable, the basal LDL-C level, in the analysis of subjects in the monotherapy group (adjusted $R^2=0.12$, F value=10.3, $p=0.002$).

Serum ALT levels of patients with a high basal ALT level (≥ 32 U/L) who received monotherapy (high ALT group) were significantly decreased after 12 weeks of treatment, whereas, conversely, those of the remaining patients with a normal basal ALT level (normal ALT group) significantly increased (**Table 3**). The basal AST/ALT ratio, which is usually low in patients with fatty liver¹⁷⁾, was significantly lower in the high ALT group than in the normal ALT group. After 12 weeks of ezetimibe treatment, the AST/ALT ratio was significantly increased in the high ALT group, whereas, conversely, that in the normal ALT group significantly decreased (**Table 3**). These changes in ALT and the AST/ALT ratio were significantly different between the high and normal ALT groups (**Table 3**). In the high ALT group, fasting IRI and

Table 2. Laboratory findings before and after ezetimibe treatment

	All patients (n=91)			Monotherapy (n=75)			Combined therapy (n=16)		
	Baseline	12 weeks	p value	Baseline	12 weeks	p value	Baseline	12 weeks	p value
Body weight (kg)	58.3±1.2	58.3±1.2	1.00	58.1±1.2	58.2±1.2	0.76	58.9±3.9	58.8±5	0.27
BMI	24.0±0.4	23.9±0.5	0.72	23.7±0.4	23.7±0.4	0.98	25.5±1.8	25.6±2.3	0.29
LDL-C (mg/dL)	158.9±2.4	128.7±2.7	<0.0001	159.3±2.5	130.6±2.7	<0.0001	157.1±7.8	120.0±8.7	<0.0001
TG (mg/dL)	146.9±10.4	132.2±11.4	0.049	134.7±8.6	120.9±7.6	0.08	204.1±41.3*	184.2±53	0.37
HDL-C (mg/dL)	57.5±1.4	59.9±1.4	0.002	58.1±1.7	60.9±1.6	0.001	54.8±2.3	55.3±1.7	0.73
LDL-C/HDL-C	2.9±0.1	2.3±0.1	<0.0001	2.9±0.1	2.3±0.1	<0.0001	2.9±0.2	2.2±0.2	0.0002
RLP-C (mg/dL)	6.7±0.6	5.7±0.8	0.01	6.1±0.4	5.1±0.4	0.008	9.4±2.9*	8.6±4.0	0.56
FPG (mg/dL)	101.9±2.1	101.4±2.2	0.97	99.4±2.3	99.2±2.2	0.72	113.1±4.8*	111.3±6.7	0.69
IRI (μU/mL)	8.6±0.8	7.3±0.6	0.02	7.8±0.7	6.6±0.6	0.01	12.3±2.4*	10.4±2.9	0.41
HOMA-IR	2.2±0.2	1.9±0.2	0.06	1.9±0.2	1.6±0.2	0.048	2.9±0.7*	2.9±0.6	0.55
HbA _{1c} (%)	5.4±0.06	5.4±0.06	0.91	5.3±0.05	5.3±0.05	0.89	5.9±0.2	5.9±0.2	0.71
hs-CRP (ng/mL)	608.0±65.6	525.7±58.4	0.06	591.6±74.4	486.1±63.7	0.04	686.7±133.0	730.5±150.3	0.87
LDL-Rm	0.36±0.003	0.35±0.003	0.04	0.36±0.004	0.35±0.003	0.04	0.36±0.01	0.36±0.01	0.71
Campesterol (μg/mL)	4.3±0.3	2.4±0.2	<0.0001	4.4±0.3	2.5±0.2	<0.0001	3.9±0.4	2.2±0.3	<0.0001
Cholesterol (μg/mL)	2.7±0.1	2.5±0.1	0.002	2.7±0.1	2.5±0.1	0.03	2.8±0.3	2.4±0.3	0.001
Sitosterol (μg/mL)	3.0±0.2	2.1±0.1	<0.0001	3.0±0.2	2.2±0.1	<0.0001	2.7±0.2	1.8±0.1	<0.0001
Lathosterol (μg/mL)	2.2±0.1	3.4±0.2	<0.0001	2.3±0.1	3.5±0.2	<0.0001	1.9±0.3*	2.7±0.4	0.0006
AST (U/L)	23.7±0.9	25.0±0.9	0.18	23.1±0.8	24.8±0.9	0.08	26.8±3.7	25.7±2.5	0.64
ALT (U/L)	22.7±1.4	25.1±1.4	0.07	21.3±1.3	23.5±1.2	0.12	29.5±4.9	32.6±4.8	0.30
γ-GTP (U/L)	44.4±4.4	47.0±6.3	0.44	42.7±4.7	53.0±10.4	0.26	52.1±11.7	57.1±15.4	0.36
Adiponectin (μg/mL)				15.2±1.4	15.9±1.4	0.10			
Total PAI-I (ng/mL)				75.7±4.6	77.9±5.4	0.90			
MMP-9 (ng/mL)				197.7±11.3	174.1±13.0	0.03			
sE-Selectin (ng/mL)				35.6±1.9	37.7±1.7	0.99			
sVCAM-1 (ng/mL)				778.1±32.0	818.8±38.3	0.97			
sICAM-1 (ng/mL)				125.8±8.1	126.7±8.3	0.75			

Values are expressed as the means ± S.E.M. PAI-1: plasminogen activator inhibitor-1, MMP-9: Matrix metalloproteinase-9, sE-Selectin: soluble endothelial-selectin, sVCAM-1: soluble vascular cell adhesion molecule-1, sICAM-1: soluble intercellular adhesion molecule-1, **p* < 0.05 vs baseline in the monotherapy group.

HOMA-IR at baseline were significantly higher than in the normal ALT group, and were significantly decreased to levels similar to those of the normal ALT group after treatment (**Table 3**). The reductions in fasting IRI and HOMA-IR in the high ALT group tended to be greater (*p*=0.06 and 0.08, respectively) than those in the normal ALT group. Diabetes, obesity, low HDL-C and high TG levels, as well as the basal levels and changes in BMI, LDL-C, HDL-C, TG, RLP-C, and FPG were not different between the high and normal ALT groups (data not shown).

No marked side effects or harmful disorders were noted in either group during the 12 weeks of treatment.

Discussion

Twelve weeks of ezetimibe treatment ameliorated

not only atherogenic lipid profiles but also atherosclerotic and inflammatory markers, insulin sensitivity and liver dysfunction in Japanese hypercholesterolemia patients. Ezetimibe reduced serum LDL-C levels regardless of age, sex, BMI, insulin sensitivity and basal cholesterol absorption and synthesis.

This study showed for the first time that ezetimibe significantly reduced serum MMP-9 levels. In humans, MMP-9 is a well-recognized marker of plaque vulnerability¹⁸⁾ and of atherosclerosis burden¹⁹⁾, and is regarded as the matrix metalloproteinase that best predicts rapid coronary artery narrowing, the incidence of ischemic heart disease, and worse outcome in patients with stroke and cardiovascular death²⁰⁾. When patients with an abdominal aortic aneurysm were pretreated with 40 mg simvastatin plus ezetimibe or with a placebo, the concentration of

Table 3. Liver function and insulin sensitivity before and after ezetimibe monotherapy

	High ALT group (<i>n</i> = 10)			Normal ALT group (<i>n</i> = 65)		
	Baseline	12 weeks	<i>p</i> value	Baseline	12 weeks	<i>p</i> value
ALT (U/L)	42.5 ± 2.3	30.0 ± 3.3 **	0.02	18.0 ± 0.9 ††	22.5 ± 1.3 §	0.0001
AST/ALT	0.78 ± 0.1	0.98 ± 0.1 *	0.03	1.26 ± 0.04 ††	1.17 ± 0.04	0.01
IRI (μU/mL)	11.8 ± 2.0	7.9 ± 1.6	0.004	7.4 ± 0.8 †	6.3 ± 0.6	0.03
HOMA-IR	3.0 ± 0.6	1.9 ± 0.5	0.007	1.9 ± 0.2 †	1.6 ± 0.2	0.06
BMI	24.7 ± 1.1	24.5 ± 0.7	0.70	23.5 ± 0.4	23.6 ± 0.4	0.78
LDL-C (mg/dL)	164.1 ± 7.6	129.1 ± 4.4	0.002	158.5 ± 2.6	130.8 ± 3.0	< 0.0001

Data are the means ± S.E.M. **p* < 0.005, ***p* < 0.0005, change of value during 12 weeks in the high ALT group vs normal ALT group. †*p* < 0.05, ††*p* < 0.0001, normal ALT group vs baseline value of high ALT group. §*p* < 0.05, normal ALT group vs 12 weeks value of high ALT group.

MMP-9 in the extirpated aortic wall was significantly lower in the ezetimibe group than in the placebo group²¹. Based on our data, ezetimibe may stabilize vulnerable plaques and prevent plaque rupture. We confirmed the previously reported reduction in serum RLP-C, hs-CRP, and LDL particle size by ezetimibe treatment^{3,7, 21}. LDL-C, remnant lipoproteins, and small dense LDL are major risk factors for arteriosclerosis, and inflammation is an important process of arteriosclerosis. The reduction in serum levels of MMP-9, hs-CRP, LDL-C, LDL-C/HDL-C, RLP-C, and LDL-Rm observed in this study suggests that ezetimibe has an anti-arteriosclerotic effect; however, long-term prospective studies to examine arteriosclerotic images and events are needed to confirm this point.

In this study, ezetimibe monotherapy and combined therapy with a statin reduced LDL-C levels by 18.2 ± 1.4% and 24.3 ± 3.1%, respectively. These results are similar to those of previous reports³⁻⁹. In the combined therapy group, various statins were administered before ezetimibe treatment. Although each statin has specific characteristics, including the strength of LDL-C reduction, HDL-C increase and oxidative stress reduction, we could not compare the effects of different statins because the number of patients was too small. Although significant differences in HDL-C, IRI, HOMA-IR, hs-CRP, and LDL-Rm were not observed between the combined therapy group and the monotherapy group in this study, the mechanisms underlying the different effects of the therapies may become noticeable if the number of combined therapy patients is increased. The basal values of TG, RLP-C, FPG, IRI and HOMA-IR as well as the changes in HDL-C, RLP-C, IRI, HOMA-IR, LDL-Rm and hs-CRP after ezetimibe treatment were different between the monotherapy and combined therapy groups (Table 2). Although the percentage of

patients with obesity (data not shown) and basal BMI were not significantly different between the monotherapy and combined therapy groups, the high percentage of diabetes in the combined therapy group (Table 1) and the small number of patients analyzed may be reasons for these discrepancies.

We also confirmed a reduction in cholesterol absorption markers and an increase in a cholesterol synthesis marker following both monotherapy and combined therapy^{3, 10, 22}. Although ezetimibe was expected to strongly reduce LDL-C and remnant lipoprotein levels in patients with high cholesterol absorption, there was no correlation between the percentage decrease in LDL-C, RLP-C, or TG, and the level of basal cholesterol absorption markers in this study (data not shown). Since we used campesterol, cholestanol and sitosterol as surrogate markers for cholesterol absorption, these markers may not reflect cholesterol absorption *in vivo*. Identification of novel markers and methods for analysis of cholesterol metabolism after food intake is needed to clarify the effective usage of ezetimibe *in vivo*.

Ezetimibe was reported to improve the serum ALT level, hepatic steatosis and insulin resistance in both rodents and humans^{3, 7, 22-27}. In the present study, we confirmed that ezetimibe improves insulin resistance by reducing fasting IRI and HOMA-IR. The serum ALT level and the AST/ALT ratio, which are usually low in patients with fatty liver¹⁷, were significantly decreased and increased, respectively after ezetimibe monotherapy in patients with high basal ALT levels. Although we did not confirm fatty liver using ultrasonography or computed tomography, these results suggest that ezetimibe improves fatty liver. In humans, ezetimibe treatment significantly improved not only metabolic parameters, including the visceral fat area, IRI, HOMA-IR, hs-CRP, TG, LDL-C, oxidative-LDL, the net electronegative charge

modified-LDL, and profiles of lipoprotein particle size and fatty acid components, but also histological findings of hepatic triglyceride content, steatosis grade, necroinflammatory grade, ballooning score, and NAFLD activity score in patients with obesity and/or NAFLD^{7, 22-25}). Ezetimibe treatment or knockdown of NPC1L1 in hepatocytes reduced hepatic insulin resistance through a reduction in reactive oxygen species and endoplasmic reticulum stress, activation of insulin-induced Akt, and inhibition of SREBP-1 expression in the liver^{12, 14}). Improvement of postprandial hyperlipidemia induced by ezetimibe is also thought to reduce insulin resistance²⁸). A postprandial increase in the TG level induces an increase in free fatty acid (FFA), which is known to induce insulin resistance by inhibiting the binding of insulin to the insulin receptor. Recently, ezetimibe was reported to inhibit the absorption of FFA by downregulation of fatty acid transfer protein-4^{29, 30}). Ezetimibe is also thought to inhibit postprandial chylomicron secretion³¹), and this effect secondarily causes a reduction in TG transport to the liver as well as reduced serum FFA levels. Since we could not find background characteristics specific to the high ALT group, additional studies using a larger number of patients are needed to determine such characteristics. Nonetheless, previous data and our results suggest that ezetimibe improves insulin resistance, especially in the liver.

The present study has several limitations. First, this was an observational study without a control group; therefore, the reported lowering of lipid levels as well as other markers may be overestimated. Second, the number of patients and the duration of this study may have been insufficient to evaluate the true effects of ezetimibe. Additional studies with larger sample sizes and a randomized controlled trial are needed to further assess the role of ezetimibe in the management of atherogenic lipid profiles, atherosclerosis, insulin sensitivity, and inflammation accompanying hypercholesterolemia.

In conclusion, ezetimibe ameliorated not only atherogenic lipid profiles but also atherosclerotic and inflammatory markers, insulin sensitivity, and liver dysfunction in Japanese hypercholesterolemia patients. Our findings indicated that ezetimibe might be a beneficial and effective strategy for the treatment of hypercholesterolemia, especially for patients with obesity, metabolic syndrome, and/or fatty liver.

Conflict of Interest

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