Ezetimibe Monotherapy Ameliorates Vascular Function in Patients with Hypercholesterolemia Through Decreasing Oxidative Stress

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Aim: Ezetimibe, an inhibitor of cholesterol intestinal absorption, is a lipid lowering agent. However, anti-atherogenic effects of ezetimibe have not been fully elucidated. Therefore, the objective in this study was to clarify the vascular protective effects of ezetimibe in patients with hypercholesterolemia.

Methods: Ezetimibe was administered to 20 patients with hypercholesterolemia (group E), and 20 age- and sex-matched patients with hypercholesterolemia were followed as controls (group C). Difference in metabolic profiles and cardiovascular surrogate markers before ezetimibe treatment and after 12 weeks of ezetimibe treatment were statistically evaluated.

Results: Ezetimibe treatment significantly reduced serum levels of low-density lipoprotein cholesterol (LDL-C) and malondialdehyde-modified low-density lipoprotein (MDA-LDL). In addition, the values of body mass index, body weight, waist circumference, plasma HbA1c and urinary albumin were significantly decreased in group E compared to those in group C. On the other hand, high-density lipoprotein cholesterol (HDL-C) and adiponectin levels were significantly increased in group E compared to those in group C. The values of brachial-ankle pulse wave velocity (ba-PWV), mean arterial blood pressure (m-ABP), and % of flow-mediated dilation (FMD) were significantly improved in group E. Furthermore, ultrasonic studies demonstrated amelioration of the vascular stiffness of common carotid arteries in group E but not in group C. These vascular protective effects of ezetimibe were statistically correlated with the decreased values of MDA-LDL and MDA-LDL-to-LDL-C ratio but not with those of LDL-C.

Conclusion: Ezetimibe has a lipid lowering-independent vascular protective effect in patients with hypercholesterolemia through decreasing oxidative stress.


Key words; Ezetimibe, Vascular function, Oxidative stress

Introduction

Low-density lipoprotein-cholesterol (LDL-C) is the strongest risk factor in patients with cardiovascular disease by progression of atherosclerosis, and the number of patients with hypercholesterolemia in Japan has been increasing due to changes in the diet. Guidelines
published by the American Heart Association, European Society of Cardiology and Japanese Atherosclerosis Society indicate the necessity for serum lipid control in patients with hypercholesterolemia to prevent the development of atherosclerosis diseases.

Statins, HMG-CoA reductase inhibitors, have been administered to many patients with hypercholesterolemia worldwide, and clinical evidence has shown that statins ameliorate dyslipidemia and have vascular protective effects\(^1\). On the other hand, there is a the risk of serious adverse effects with high-dose statins\(^2\) and only 67% of patients are treated successfully with high doses of statins because of their side effects\(^3\).

Ezetimibe is a novel agent that inhibits the intestinal absorption of cholesterol by blocking the function of Niemann-Pick C1-like 1 protein for cholesterol transport\(^4,5\). Some reports have provided clinical evidence of improved hypercholesterolemia by ezetimibe or by combination treatment with a statin and ezetimibe\(^6\); however, the anti-atherogenic effects of ezetimibe have not been fully elucidated.

**Aim**

The aim of this study was to clarify the vascular protective effects of ezetimibe in patients with hypercholesterolemia. In addition, we attempted to clarify the association between the reduction in the serum LDL-C or MDA-LDL and vascular functions after ezetimibe treatment.

**Methods**

**Subjects**

We studied 20 patients with hypercholesterolemia not receiving statin treatment whose serum lipid profiles did not reach the management goals promulgated by the guidelines for the prevention of atherosclerotic cardiovascular diseases of the Japanese Atherosclerosis Society 2007\(^7\) (ezetimibe group). The controls were 20 age- and sex-matched patients with hypercholesterolemia without statin treatment (control group).

The subjects, who were outpatients with lifestyle-related diseases, were recruited consecutively from Tokushima University Hospital, Tokushima, Japan between January 2009 and November 2009. The patient profiles are shown in **Table 1**; the two groups did not significantly differ with respect to patient characteristics, except for weight.

Exclusion criteria included severe left ventricular dysfunction (ejection fraction evaluated by echocardiography <40%), apparent renal disease (serum creatinine >2.0 mg/dL, urinary albumin excretion >300 mg/g-creatinine), clinical conditions that could lead to increased inflammatory cytokine levels (i.e. rheumatoid arthritis and sepsis), and liver disease as defined by hepatic enzymes >2 times the upper normal limit. Also excluded were patients who were newly medicated or whose medications for hypertension, dyslipidemia, and insulin resistance had been changed less than one year before the start of this study.

Written informed consent was obtained from all subjects before enrollment in this study in accordance with protocols approved by the Tokushima University Hospital Ethics Committee (UMIN-CTR registration number: UMIN000003008).

**Treatment**

Patients in the ezetimibe group received 10 mg ezetimibe perorally daily in the morning and continued their previous treatments, including appropriate diet and exercise therapy. Patients who chose lifestyle modifications without a lipid-lowering agent were registered in the control group, and diet and exercise therapy continued after enrollment in this study.

Blood and urine samples and vascular function analysis data were collected before and 3 months after the start of treatment. During the study period, the patients’ medication regimens were unchanged except for receiving ezetimibe, diet, and exercise therapy. None of the patients treated with ezetimibe had severe adverse effects, although one patient had mild diarrhea.

**Biochemical Analysis**

After an overnight fast, blood samples were collected before noon from the antecubital vein. Lipid parameters, including high-density lipoprotein cholesterol (HDL-C), triglyceride (TG) and LDL-C, were assayed by enzymatic methods. Plasma HbA1c was measured by high-performance liquid chromatography. Serum malondialdehyde-modified LDL (MDA-LDL) and serum adiponectin levels were measured by enzyme-linked immunosorbent assay (ELISA) at a commercially laboratory (SRL Inc., Tokyo, Japan). High-sensitivity C-reactive protein (hs-CRP) levels were measured at a commercially laboratory (Bio Medical Laboratories, Tokyo, Japan) by nephelometry, a latex particle-enhanced immunoassay (N Latex CRP II).

Spot urine samples were collected and creatinine and urinary albumin were analyzed; the urinary albumin excretion rate was calculated and expressed as the mg/g-creatinine rate.

**Vascular Functional Analysis**

Blood pressure (BP), maximum carotid intima-
media thickness (IMT), resistive index (RI) of common carotid arteries, brachial-ankle pulse wave velocity (ba-PWV) and flow-mediated dilatation (FMD) were used as surrogate makers of arterial function. These physical studies were conducted in a quiet temperature-controlled room.

The ba-PWV was automatically measured as a marker of arterial stiffness, including stiffness of both elastic and muscular arteries (Form/ABI; Colin Co. Ltd., Komaki, Japan).

Endothelial function was assessed in the brachial artery using the FMD technique (UNEX Corporation, Nagoya, Japan) as previously described.

High-resolution B mode, color Doppler, and pulse Doppler ultrasonography of both carotid arteries was performed with an ultrasound machine equipped with a 4-11 MHz linear array transducer. Patients were examined in the supine position with the head tilted backwards. The maximum IMT was measured at the near and far walls of the common carotid artery, the bifurcation, and the internal carotid arteries. In the middle of the common carotid arteries (CCAs), angle-corrected blood flow velocity was measured with the pulsed Doppler sample volume expanded to encompass the entire vessel diameter. Visual control of the maximum luminal width and acoustic control of an optimum Doppler frequency shift ascertained that the sample volume was centered on the vessel axis. The angle of incidence was kept as low as possible, less than 60°. Measurements performed on the left and right CCAs were peak systolic maximal blood flow velocity (Vps), end diastolic maximal blood flow velocity (Ved), and time-averaged maximum blood flow velocity (TAV). From these data, the RI was cal-

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>All cases (n=40)</th>
<th>Control (n=20)</th>
<th>Ezetimibe (n=20)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td>64.0 ± 14.1</td>
<td>66.2 ± 9.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>17 (85)</td>
<td>16 (80)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Hypertension, n (%)</strong></td>
<td>11 (55)</td>
<td>13 (65)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>DM/IGT, n (%)</strong></td>
<td>8 (40)</td>
<td>7 (35)</td>
<td>n.s.</td>
</tr>
<tr>
<td><em><em>Dyslipidemia</em>, n (%)</em>*</td>
<td>20 (100)</td>
<td>20 (100)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Smoking history, n (%)</strong></td>
<td>12 (60)</td>
<td>10 (50)</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Body weight, kg</strong></td>
<td>62.7 ± 9.4</td>
<td>66.3 ± 10.8</td>
<td>0.016</td>
</tr>
<tr>
<td><strong>Body mass index, kg/m²</strong></td>
<td>23.7 ± 3.3</td>
<td>24.8 ± 2.8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Waist circumference, cm</strong></td>
<td>85.4 ± 7.4</td>
<td>88.8 ± 7.8</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Systolic BP, mmHg</strong></td>
<td>129.4 ± 17.8</td>
<td>130.6 ± 12.5</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Mean BP, mmHg</strong></td>
<td>97.8 ± 13.2</td>
<td>101.3 ± 11.3</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Diastolic BP, mmHg</strong></td>
<td>73.7 ± 6.9</td>
<td>78.0 ± 11.7</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>LDL-cholesterol, mg/dL</strong></td>
<td>122.7 ± 23.5</td>
<td>130.6 ± 24.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Triglycerides, mg/dL</strong></td>
<td>138.6 ± 47.8</td>
<td>165.6 ± 96.0</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>HDL-cholesterol, mg/dL</strong></td>
<td>54.1 ± 14.3</td>
<td>51.6 ± 12.9</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>LDL/HDL ratio</strong></td>
<td>2.39 ± 0.62</td>
<td>2.69 ± 0.92</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>MDA-LDL, U/L</strong></td>
<td>128.9 ± 29.4</td>
<td>156.1 ± 54.6</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td>5.52 ± 0.71</td>
<td>5.70 ± 0.81</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>U-albumin, mg/g creatinine</strong></td>
<td>27.9 ± 39.8</td>
<td>30.9 ± 31.3</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>eGFR, mL/min/1.73 m²</strong></td>
<td>66.2 ± 21.5</td>
<td>67.6 ± 21.2</td>
<td>n.s.</td>
</tr>
<tr>
<td><strong>Serum creatinine</strong></td>
<td>0.90 ± 0.25</td>
<td>0.92 ± 0.30</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

Current medication, n (%)

| Statins | 0 (0) | 0 (0) | n.s. |
| β-blockers | 4 (20) | 5 (25) | n.s. |
| ACEI/ARB | 8 (40) | 10 (50) | n.s. |
| Calcium channel blockers | 8 (40) | 7 (35) | n.s. |

DM, diabetes mellitus; IGT, impaired glucose tolerance; BP, blood pressure; MDA-LDL, malondialdehyde-modified LDL cholesterol; EPA, eicosapentaenoic acid; AA, arachidonic acid; Hb, hemoglobin; U-albumin, urinary albumin excretion; eGFR, estimated glomerular filtration rate; U-8-OHdG, urinary excretion of 8-hydroxy-2'-deoxyguanosine; ACEI, ACE inhibitors; ARB, angiotensin II receptor blockers

* Dyslipidemia Criteria; LDL-C > 140, HDL-C < 40, TG > 150
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Calculated as [(Vps-Ved)/Vps].

Statistical Analysis

Lipid profiles and other biomarkers were compared before and after ezetimibe treatment using the paired t-test. All data are expressed as the means ± S.D.

Single regression analysis was used to assess the correlations between decreased LDL-C and MDA-LDL and other indices. These analyses were performed on a Microsoft Windows computer running SPSS software (IBM Corporation, NY, USA) and Graph PAD 5 software (GraphPad Software, Inc., CA, USA). Differences were considered significant at p < 0.05.

Results

Ezetimibe Treatment Results in Decreased Weight, Waist Circumference and Body Mass Index (BMI)

Ezetimibe treatment significantly reduced weight (from 68.3 ± 10.8 to 66.6 ± 11.8 kg, p < 0.05), body mass index (BMI) (from 24.7 ± 2.8 to 24.0 ± 3.0 kg/m², p < 0.05), and waist circumference (from 88.8 ± 7.8 to 87.8 ± 8.1 cm, p < 0.05) (Fig. 1).

On the other hand, there were no changes in weight, waist circumference and BMI in the control group during the study period.

Ezetimibe Treatment Ameliorates Serum Lipid Profiles

Ezetimibe treatment significantly reduced LDL-C (from 130.6 ± 24.9 to 103.8 ± 23.5 mg/dL; −20.5%, p < 0.001) and MDA-LDL (from 156.1 ± 54.6 to 104.2 ± 37.4 U/L; −33.3%, p < 0.001) and increased HDL-C (from 51.6 ± 12.9 to 57.5 ± 16.6 mg/dL; +11.5%, p < 0.005), whereas triglycerides were not affected by ezetimibe administration (pre- and post-treatment: 165 ± 78.8 and 163.8 ± 97.7 mg/dL, respectively) (Fig. 2).

In the control group, we observed no significant differences in measurements before and after the start of the study (LDL-C: 122.7 ± 23.5 mg/dL before and 121.9 ± 30.7 mg/dL after, MDA-LDL 128.9 ± 29.4 U/L before and 133.2 ± 36.4 U/L after, triglycerides 133.6 ± 47.8 mg/dL before and 138.1 ± 54.3 mg/dL after, HDL-C 54.1 ± 14.3 mg/dL before and 56.9 ± 15.9 mg/dL after).
In addition, the MDA-LDL: LDL ratio was calculated. This ratio was significantly reduced in the ezetimibe group (from 1.19 ± 0.31 to 1.01 ± 0.31 mg/dL; -13.6%, p < 0.001), though the ratio in the control group was not changed (1.07 ± 0.23 before and 1.10 ± 0.23).

**Ezetimibe Treatment Improved HbA1c, Adiponectin, Urinary Albumin Excretion and Oxidative Stress**

Ezetimibe treatment significantly decreased hemoglobin A1c (HbA1c) (from 5.70 ± 0.81 to 5.51 ± 0.67%; -3.3%, p < 0.05) and significantly increased serum adiponectin (from 9.30 ± 5.21 to 11.29 ± 5.69 mg/mL; +11.3%, p < 0.05). It also attenuated urinary albumin excretion (from 31.85 ± 35.72 to 19.73 ± 28.70 mg/g creatinine; -36.0%, p < 0.05) without significant changing the estimated glomerular filtration rate (from 67.62 ± 21.23 to 77.10 ± 71.5 mL/minute/1.73 m²) (Fig. 3).

On the other hand, no differences in these parameters before and after the start of the study were found in the control group. (HbA1c: 5.52 ± 0.71% before and 5.59 ± 0.75% after, adiponectin: 10.19 ± 3.78 mg/mL before and 11.28 ± 4.64 mg/mL after, uri-
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Ezetimibe Treatment Reduced Blood Pressure and ba-PWV and Ameliorates FMD

Ezetimibe treatment significantly decreased mean arterial blood pressure (BP) (from 101.30 ± 11.26 to 93.17 ± 11.06 mmHg; -8.0%, p < 0.005), systolic BP (from 130.57 ± 12.45 to 120.48 ± 12.96 mmHg; -7.7%, p < 0.005) and diastolic BP (from 78.04 ± 11.77 to 71.83 ± 9.43 mmHg; -8.0%, p < 0.005). No differences in measurements of BPs before and after the start of the study were found in the control group (mean BP: 97.78 ± 13.24 mmHg before and 99.78 ± 14.21 mmHg after, systolic BP: 129.39 ± 17.83 mmHg before and 132.44 ± 21.64 mmHg after, diastolic BP: 73.65 ± 6.93 mmHg before and 74.11 ± 9.45 mmHg after) (Fig. 4A).

Ezetimibe treatment also significantly reduced urinary albumin excretion: 27.86 ± 34.67 mg/g·creatinine before and 30.42 ± 51.67 mg/g·creatinine after, estimated glomerular filtration rate: 66.21 ± 21.48 mL/minute/1.73 m² before and 65.10 ± 18.37 mL/minute/1.73 m² after).

Ezetimibe treatment also significantly reduced ba-PWV (from 1654.57 ± 349.71 to 1451.91 ± 302.23 cm/sec.; -12.3%, p < 0.0001) and improved FMD (from 3.96 ± 1.81 to 4.75 ± 1.90%; +20.1%, p < 0.01), although the controls showed no differences in measurements of those parameters before and after the start of the study (ba-PWV: 1613.13 ± 441.28 cm/sec. before and 1727.83 ± 544.07 cm/sec. after, FMD: 3.85 ± 2.14% before and 3.71 ± 2.15% after) (Fig. 4B, C).

Ezetimibe Treatment Improves Vascular Resistance of the Common Carotid Artery

Ezetimibe treatment had no effect on max-IMT during the study period (from 2.03 ± 0.83 to 1.99 ± 0.81 mm; -1.98%, not significant); however, ezetimibe significantly improved RI (0.76 ± 0.08 to 0.73 ± 0.07; -4.9%, p < 0.05), which is a surrogate marker of carotid arterial resistance evaluated by Doppler ultrasonography; however, the controls showed no differences in this measurement before and after the start of the study (RI value: 0.75 ± 0.07 before and 0.75 ± 0.08 after) (Fig. 4D).
Discussion

Serum cholesterol is regulated by the combination of synthesis in the liver and absorption from the intestine. Most patients with dyslipidemia have received statin therapy, which reduces cholesterol synthesis in the liver\(^{10, 11}\). On the other hand, ezetimibe is a novel agent that potently inhibits intestinal absorption of cholesterol from dietary and biliary sources by blocking the function of Niemann-Pick C1-like 1 protein\(^{12-14}\). While statins are known to have several serious side effects, including muscular pain and rhabdomyolysis, ezetimibe seems to have fewer clinical adverse effects. Although the clinical use of ezetimibe is increasing in the world, the effects of ezetimibe monotherapy on vascular functions, including endothelial function in patients with dyslipidemia, have not been elucidated yet.

The present study showed that ezetimibe improved vascular functions, including blood pressure, ba-PWV, FMD, and RI of CCAs along with amelioration of dyslipidemia, levels of MDA-LDL, HbA1c, adiponectin and urinary excretion of albumin. Yagi et al. have already reported that ezetimibe ameliorates insulin resistance, the degree of inflammation and oxidative stress\(^6\). In addition, Nakagami et al. reported that ezetimibe treatment prevented the progression of atherosclerosis by suppressing oxidative stress in mice lacking apolipoprotein E\(^{15}\).

Since it has been reported that oxidative stress was involved in hypertension or renal dysfunction in conditions with an activated renin-angiotensin system\(^{16, 17}\), attenuation of oxidative stress by pharmacological manipulation is thought to be a valid therapeutic approach for preventing cardiovascular diseases. Therefore, the potential mechanisms of improved blood pressure, FMD, ba-PWV and vascular resistance of CCAs by ezetimibe monotherapy were associated with decreased levels of oxidative stress biomarkers, including MDA-LDL. Fukuda et al. demonstrated that ezetimibe reduced vascular superoxide levels in type 2 diabetic db/db mice with attenuation of NADPH oxidase subunit gp91\(^{phox}\) and Nox4 expression and with preservation of Cu/Zn-superoxide dismutase (SOD) and extracellular SOD content\(^{18}\). These results may partly explain the mechanism of the
antioxidant action of ezetimibe treatment. In addition, although the reductions of LDL-C by ezetimibe treatment were not associated with the amelioration of vascular functions, the reductions of MDA-LDL were significantly correlated with the amelioration of m-ABP, ba-PWV, FMD and carotid vascular resistance (Fig. 5A, C, E). Moreover, reduction of the MDA-LDL: LDL-C ratio was more closely correlated with the amelioration of m-ABP, ba-PWV, FMD and carotid vascular resistance than was reduced MDA-LDL (Fig. 5B, D, F). These results suggested that the efficiency of ezetimibe-induced antioxidant action on LDL-C reduction is one of the most pivotal factors for improving vascular function in patients with dyslipidemia.

In the present study, we demonstrated that ezeti-
mibe treatment reduced weight, BMI and abdominal circumference. Chan et al. showed that ezetimibe induced weight loss along with reducing intrahepatic triglyceride content, plasma markers of inflammation including high-sensitive CRP and interleukin 6, and apoB-100 metabolism in obese subjects. Since the combination of central obesity and insulin resistance is thought to be associated with dysregulation of apoB-100 metabolism, ezetimibe treatment-induced weight reduction may be partly accounted for by normalization of apoB-100 metabolism.

Evidence of improved vascular functions by statin treatment has been provided by numerous experimental and clinical studies. In cholesterol-fed rabbits, pitavastatin showed anti-atherogenic effects, resulting in reduced aortic stiffness. In a clinical study, treatment with simvastatin, fluvasstatin or atorvastatin resulted in improved peripheral PWV in patients with dyslipidemia. Previous studies have also shown a BP-lowering effect of statins in hyperlipidemic hypertensive patients who were not taking any antihypertensive drugs and in patients who had already received antihypertensive therapy. In contrast, non-statin lipid-lowering agents, such as clofibrate and probucol, failed to improve these parameters. Although the present study showed that ezetimibe monotherapy has favorable clinical effects on vascular functions independent of its LDL-C-lowering effect, long-term follow-up of patients with dyslipidemia who have received ezetimibe treatment is necessary to clarify the effects of ezetimibe on vascular functions. When several large-scale clinical trials of ezetimibe confirm its potential for vascular protection via not only LDL-C-lowering but also pleiotropic effects, ezetimibe should be chosen not only as the second-choice treatment for patients with resistance to statin treatment or as additional treatment to a statin, but also as the first-choice treatment for patients with hyperlipidemia and/or coronary artery diseases.

Conclusion
Ezetimibe ameliorates vascular functions in patients with hypercholesterolemia by decreasing oxidative stress but not LDL-C reduction. Although the mechanism by which oxidative stress is reduced has not yet been elucidated, ezetimibe should be considered to have pleiotropic effects on vascular protection against cardiovascular diseases.

Limitations
Since the subjects decided whether or not to take ezetimibe, this was not a randomized study; however, there were no differences in the characteristics of subjects, except weight, at the start of this study.

Acknowledgement
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