Effects of Ezetimibe on Serum Polyunsaturated Fatty Acids in Patients With Coronary Artery Disease

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Summary

Residual risk of cardiovascular disease might stem, at least partially, from low serum concentrations of n-3 polyunsaturated fatty acid (PUFA). The purpose of this study was to evaluate the effects of ezetimibe on serum lipids and PUFAs in patients with coronary artery disease who were intolerant of new or high-dose statin therapy. The study population consisted of 13 patients who were intolerant of new statin therapy and 10 patients who were intolerant of high-dose statin therapy for the treatment of low-density lipoprotein (LDL) cholesterol. Patients who were intolerant of high-dose statin therapy continued taking a statin, but at a lower dose during the study period. Blood samples were collected before and 12 weeks after ezetimibe (10 mg). We measured serum lipids and PUFAs including dihomo-γ-linolenic acid, arachidonic acid (AA), eicosapentaenoic acid (EPA), and docosahexaenoic acid. Ezetimibe significantly decreased LDL cholesterol (138 ± 19 mg/dL to 97 ± 34 mg/dL, \( P < 0.01 \)), but did not significantly affect high-density lipoprotein cholesterol, triglyceride, or any of the PUFAs measured during the follow-up period. Consequently, it did not affect the ratio of EPA to AA (0.40 ± 0.17 to 0.43 ± 0.18, \( P = \text{ns} \)) or the ratio of n-3 PUFA to n-6 PUFA (1.10 ± 0.39 to 1.09 ± 0.36, \( P = \text{ns} \)) during the follow-up period. Ezetimibe in combination with a low-dose statin, or as monotherapy in statin-intolerant patients, decreased LDL cholesterol, but did not significantly affect serum PUFA concentrations in patients with coronary artery disease. (Int Heart J 2013; 54: 254-257)

Key words: Residual risk, Statin

Low-density lipoprotein (LDL) cholesterol-lowering therapy is an important aspect for the prevention of cardiovascular disease. Statins are most widely used because of not only their LDL cholesterol-lowering ability but also several pleiotropic effects. However, myopathy occurs in up to 10% of patients and is most commonly manifested by myalgias. Ezetimibe, a cholesterol absorption inhibitor, is recently being used not only as an alternative to a statin, but also as add-on therapy in these patients. Despite substantial progress in pharmacological treatment, residual risk of cardiovascular disease exists even in patients achieving LDL cholesterol goals. This residual risk might stem, at least partially, from low serum levels of n-3 polyunsaturated fatty acid (PUFA), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). There is increasing evidence that a low level of EPA plus DHA and a low ratio of EPA to arachidonic acid (AA) increase the risk of cardiovascular disease. In this study, we evaluated the effects of ezetimibe on serum lipids and PUFAs in patients with coronary artery disease who were intolerant of new or high-dose statin therapy.

Methods

Patients: The study population consisted of 13 patients who were intolerant of new statin therapy and 10 patients who were intolerant of high-dose statin therapy for the treatment of LDL cholesterol. Major causes were myalgias and muscle weakness, but a wide variety of complaints not related to the musculoskeletal system was included such as elevation of liver enzymes, diarrhea, constipation, headache and dizziness. Patients who were intolerant of high-dose statin therapy continued taking a statin, but at a lower dose during the study period. Coronary artery disease was defined as previous myocardial infarction, coronary intervention or confirmed angina pectoris. Patients with acute coronary syndrome or stroke within 3 months, an alanine aminotransferase level more than twice the upper limit of normal, malignant disease or secondary dyslipidemia were excluded from this study. All patients were recruited from the Department of Cardiovascular Medicine of Hiroshima University Hospital. Informed consent was obtained from all patients.

Study protocol: Blood samples were collected before and 12 weeks after LDL cholesterol-lowering therapy with ezetimibe (10 mg). When patients had been treated with a statin, the statin at the same dose was continued during the study period. All
blood samples were obtained in the postabsorptive state (9-15 hours after the last meal), separated by centrifugation at 2500 g for 10 min and immediately stored at -80°C until analysis. **Lipid analysis:** LDL cholesterol, high-density lipoprotein cholesterol, and triglycerides were measured using an autoanalyzer by routine methods at the central laboratory of our hospital. Fatty acid analysis has been described in detail elsewhere.\(^\text{19,20}\) Lipids were extracted from serum by chloroform/methanol according to a modified method described by Folch, et al.\(^\text{21}\) Tricosanoic acid was used as the internal standard. Methyllyation of fatty acids was carried out as described by Hoshi, et al.\(^\text{22}\) Fatty acid composition in the methylated sample was analyzed by gas chromatography. A fused polar silica capillary column was used. We measured PUFAs including dihomo-γ-linolenic acid (DGLA), AA, EPA and DHA. N-6 PUFA was defined as the sum of DGLA and AA, and n-3 PUFA was defined as the sum of EPA and DHA.

**Statistical analysis:** Continuous variables are expressed as the mean ± standard deviation. Categorical variables are expressed as the number and percentage. The paired Student t test was used for continuous variables. Differences were considered significant if the P value was < 0.05.

**RESULTS**

**Patient characteristics:** Patient characteristics are shown in Table I. There were 17 male and 6 female patients with a mean age of 70 years. Thirteen patients were intolerant of new or high-dose statin therapy. Ten patients had been treated with a statin, but were intolerant of its high-dose. Ten patients continued taking a statin at a lower dose during the study period, and the statin used was pravastatin in 2 patients (mean dose 7.5 mg/day), atorvastatin at a lower dose during the study period, and the statin used was pravastatin in 2 patients (mean dose 7.5 mg/day), atorvastatin in 5 patients (mean dose 12.0 mg/day), rosuvastatin in one patient (2.5 mg/day), and pitavastatin in 2 patients (mean dose 2.0 mg/day).

**Effects of ezetimibe on serum lipids and PUFAs:** The changes in serum lipids and PUFAs are shown in Table II. Ezetimibe significantly decreased LDL cholesterol after 12 weeks (138 ± 19 mg/dL to 97 ± 34 mg/dL, \(P < 0.01\)), and LDL cholesterol less than 100 mg/dL was achieved in 12 patients (52%). Ezetimibe did not significantly affect high-density lipoprotein cholesterol, triglycerides, DGLA, AA, EPA, DHA, n-6 PUFA, or n-3 PUFA during the follow-up period. Consequently, it did not affect the ratio of EPA to AA (0.40 ± 0.17 to 0.43 ± 0.18, \(P = \text{ns}\)) or the ratio of n-3 PUFA to n-6 PUFA (1.10 ± 0.39 to 1.09 ± 0.36, \(P = \text{ns}\)) during the follow-up period (Figure). No drug-related clinical and laboratory adverse events or discontinuations occurred during the study period.

**DISCUSSION**

**Present findings:** This study demonstrated that ezetimibe significantly decreased LDL cholesterol, but did not affect serum PUFAs concentrations in patients with coronary artery disease who were intolerant of new or high-dose statin therapy.

**Ezetimibe and statin:** Large clinical studies have shown that LDL cholesterol-lowering therapy with statins reduces cardiovascular events in patients with coronary artery disease.\(^\text{1}\)

**Table II. Serum Lipid and Polyunsaturated Fatty Acid Levels Before and After Ezetimibe**

<table>
<thead>
<tr>
<th></th>
<th>Before ezetimibe</th>
<th>After ezetimibe</th>
<th>(P)</th>
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<tbody>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>138 ± 19</td>
<td>97 ± 34</td>
<td>0.01</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>59 ± 18</td>
<td>59 ± 15</td>
<td>ns</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>119 ± 51</td>
<td>125 ± 68</td>
<td>ns</td>
</tr>
<tr>
<td>DGLA ((\mu)g/mL)</td>
<td>35 ± 12</td>
<td>36 ± 13</td>
<td>ns</td>
</tr>
<tr>
<td>AA ((\mu)g/mL)</td>
<td>181 ± 47</td>
<td>181 ± 46</td>
<td>ns</td>
</tr>
<tr>
<td>N-6 PUFA ((\mu)g/mL)</td>
<td>216 ± 55</td>
<td>216 ± 54</td>
<td>ns</td>
</tr>
<tr>
<td>EPA ((\mu)g/mL)</td>
<td>70 ± 31</td>
<td>75 ± 31</td>
<td>ns</td>
</tr>
<tr>
<td>DHA ((\mu)g/mL)</td>
<td>161 ± 65</td>
<td>154 ± 47</td>
<td>ns</td>
</tr>
<tr>
<td>N-3 PUFA ((\mu)g/mL)</td>
<td>231 ± 92</td>
<td>229 ± 73</td>
<td>ns</td>
</tr>
<tr>
<td>Ratio of EPA to AA</td>
<td>0.40 ± 0.17</td>
<td>0.43 ± 0.18</td>
<td>ns</td>
</tr>
<tr>
<td>Ratio of n-3 PUFA to n-6 PUFA</td>
<td>1.10 ± 0.39</td>
<td>1.09 ± 0.36</td>
<td>ns</td>
</tr>
</tbody>
</table>

LDL indicates low-density lipoprotein; HDL, high-density lipoprotein; PUFA, polysaturated fatty acid level; DGLA, dihomo-γ-linolenic acid; AA, arachidonic acid; EPA, eicosapentaenoic acid; and DHA, docosahexaenoic acid.

**Figure.** Effects of ezetimibe on the ratio of EPA to AA or the ratio of n-3 PUFA to n-6 PUFA. EPA indicates eicosapentaenoic acid; AA, arachidonic acid and; PUFA, polysaturated fatty acid.
However, some patients on statin monotherapy cannot achieve LDL cholesterol levels established by the guidelines. Recent studies have demonstrated that ezetimibe added to statins improves lipid profiles more than double-dose statin monotherapy in patients with hypercholesterolemia or coronary artery disease. Ezetimibe is also used as an alternative option in patients who are intolerant of statin therapy. However, residual risk of cardiovascular disease exists even in patients achieving LDL cholesterol goals. This residual risk might stem, at least partially, from low serum levels of n-3 PUFA. The key n-6 PUFA, AA, plays a considerable role in the inflammatory process and platelet activation in atherosclerosis in connection with free radical oxidation production, leukotriene, thromboxane and prostaglandins. Conversely, the key n-3 PUFA, EPA and DHA, have counter-effects on processes involved in atherosclerosis, exhibiting the opposite function to n-6 PUFA.

In the current study, we demonstrated that ezetimibe significantly decreased LDL cholesterol, but did not affect serum PUFA concentrations in patients with coronary artery disease who were intolerant of new or high-dose statin therapy. These results are supported by a previous preliminary study we conducted which showed no significant differences in serum lipids and PUFAs with an interval of 12 weeks in 30 patients with coronary artery disease (data not shown).

Niemann-Pick C1-like 1 (NPC1L1) is located on the apical surface of enterocytes as expected for a transport protein, and ezetimibe potently inhibits this process. Labonte, et al assessed the effects of ezetimibe and NPC1L1 on absorption of fatty acids using ezetimibe-treated and NPC1L1-null mice, and showed that ezetimibe or lack of NPC1L1 significantly reduced absorption of dietary saturated fatty acids, particularly stearate and palmitate, but only a small effect was observed for the unsaturated fatty acids oleate and linoleate. These experimental results for ezetimibe on unsaturated fatty acids are consistent with the results of our clinical study. We have recently reported that high-potency statin reduces serum n-3 PUFA concentrations in proportion to the decrease in LDL cholesterol. On the other hand, as shown in the current study, ezetimibe decreases LDL cholesterol, but does not significantly affect serum n-3 PUFA concentrations.

There is increasing evidence that maintaining n-3 PUFA as well as LDL cholesterol-lowering is important for the prevention of cardiovascular events. From this point of view, ezetimibe appears to be favorable in patients with coronary artery disease. It should be considered what kind of drugs or their combination are suitable for achieving LDL-cholesterol goals, avoiding side effects, and maintaining serum n-3 PUFA in each patient with coronary artery disease.

**Study limitations:** There are some limitations in this study. Firstly, it did not include a matched control group of patients receiving no LDL cholesterol-lowering therapy because lipid drugs have been established as essential in patients with coronary artery disease. Secondly, ezetimibe was added in only patients who were intolerant of new or high-dose statin therapy. Thirdly, we measured the concentrations of DGLA, AA, EPA and DHA, but did not evaluate their percentages of the total free fatty acid. Fourthly, lipids were measured only once at the beginning and once at the end of the study. The results have less precision than if measured in duplicate. Finally, the small sample size is a major limitation, and a large study should be performed to confirm our findings.

**Conclusions:** In conclusion, ezetimibe in combination with a low-dose statin, or as monotherapy in statin-intolerant patients, decreased LDL cholesterol, but did not significantly affect serum PUFA concentrations in patients with coronary artery disease.

**References**


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