Significance of Imbalance in the Ratio of Serum n-3 to n-6 Polyunsaturated Fatty Acids in Patients With Acute Coronary Syndrome

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This study aimed to assess the balance of serum n-3 to n-6 polyunsaturated fatty acids (PUFAs) in patients with acute coronary syndrome (ACS). We enrolled 1,119 patients who were treated and in whom serum PUFA level was evaluated in 5 divisions of cardiology in a metropolitan area in Japan. Serum levels of PUFAs, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA), were compared between patients with and without ACS. We also evaluated the balance of serum n-3 to n-6 PUFAs, including EPA/AA and DHA/AA ratios. EPA/AA values were 0.46 ± 0.32 and 0.50 ± 0.32 in the ACS and non-ACS groups, respectively. DHA/AA values were 0.95 ± 0.37 and 0.96 ± 0.41 in the ACS and non-ACS groups, respectively. Next, we divided the patients into 3 groups based on the tertiles of EPA/AA or tertiles of DHA/AA to determine the independent risk factors for ACS. According to multivariate logistic regression analysis, the group with the lowest EPA/AA (<0.33) had a greater probability of ACS (odds ratio 3.14, 95% confidence interval 1.16 to 8.49), but this was not true for DHA/AA. In conclusion, an imbalance in the ratio of serum EPA to AA, but not in the ratio of DHA to AA, was significantly associated with ACS.

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Lipid control with statins reduces the risk of acute coronary syndrome (ACS) through the regression or stabilization of coronary artery plaques. However, patients treated with statins may still develop ACS. Sachdeva et al analyzed a large cohort of patients hospitalized with coronary artery disease (CAD) and found that >1/2 were readmitted, although they had low-density lipoprotein cholesterol levels <100 mg/dl. Therefore, we need to focus on the residual risks in patients on statin therapy to further reduce cardiovascular events. Several observational studies reported that n-3 polyunsaturated fatty acids (PUFAs), especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), contributed to reduction in the risk of CAD in healthy subjects. It is well known that PUFAs play important roles in the initiation and progression of CAD. In the Japan EPA Lipid Intervention Study, which reported the beneficial effect of pure EPA administration for reducing coronary events, a high EPA/arachidonic acid (AA) ratio was associated with a low incidence of coronary events. Based on these previous studies, n-3 PUFAs and the balance of n-3 to n-6 PUFAs may play important roles in residual cardiovascular risk reduction. However, it is still unclear which n-3 PUFA and the balance of which n-3 PUFA to n-6 PUFAs play an important role in the development of ACS. This study aimed to assess serum levels of PUFAs and the balance of n-3 to n-6 PUFAs, including EPA, DHA, AA, and dihomo-γ-linolenic acid in patients with ACS.

Methods

This was a multicenter observational study performed at 5 centers (4 university hospitals and 1 community hospital) located in Tokyo. We enrolled 1,119 patients who were treated in the divisions of cardiology at these 5 centers from January 2004 to May 2011. All these patients had evaluation of serum PUFAs. This cohort consisted of 1,037 patients without ACS and 72 patients with ACS. Acute myocardial infarction was defined as a transient increase of the MB fraction of creatine kinase or troponin T level in patients with ischemic symptoms and/or typical electrocardiographic findings (ST elevation). Unstable angina was defined as angina at rest, accelerated exertional angina combined with typical electrocardiographic changes (ST depression), or an increase in the intensity of anti-ischemic therapy. Patients were excluded if they were
Table 1
Comparison of clinical data among eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio tertiles (n = 1,119)

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Measurements</th>
<th>EPA/AA ≤0.33 (n = 366)</th>
<th>0.33 &lt; EPA/AA ≤ 0.55 (n = 386)</th>
<th>0.55 &lt; EPA/AA (n = 367)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>1,119</td>
<td>59.3 ± 13.6</td>
<td>65.4 ± 11.1</td>
<td>67.1 ± 8.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Men</td>
<td>1,119</td>
<td>69.1</td>
<td>69.7</td>
<td>77.9</td>
<td>0.011*</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>1,059</td>
<td>24.5 ± 4.3</td>
<td>24.3 ± 3.3</td>
<td>24.2 ± 3.1</td>
<td>0.514</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1,119</td>
<td>52.5</td>
<td>53.1</td>
<td>58.3</td>
<td>0.217</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1,119</td>
<td>29.0</td>
<td>35.0</td>
<td>37.9</td>
<td>0.034*</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>1,119</td>
<td>64.8</td>
<td>66.3</td>
<td>65.1</td>
<td>0.894</td>
</tr>
<tr>
<td>Family history of ischemic heart disease</td>
<td>1,119</td>
<td>16.1</td>
<td>16.1</td>
<td>13.6</td>
<td>0.56</td>
</tr>
<tr>
<td>Smoking</td>
<td>1,119</td>
<td>38.0</td>
<td>39.6</td>
<td>38.1</td>
<td>0.875</td>
</tr>
<tr>
<td>Number of risk factors</td>
<td>1,119</td>
<td>2.9 ± 1.4</td>
<td>3.2 ± 1.4</td>
<td>3.3 ± 1.4</td>
<td>0.034*</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>893</td>
<td>198.0 ± 36.6</td>
<td>196.5 ± 38.2</td>
<td>194.4 ± 33.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Triglyceride (mg/dl)</td>
<td>913</td>
<td>153.7 ± 90.1</td>
<td>153.7 ± 130.0</td>
<td>137.2 ± 74.8</td>
<td>0.07</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol (mg/dl)</td>
<td>924</td>
<td>115.6 ± 31.6</td>
<td>114.0 ± 31.4</td>
<td>112.0 ± 29.1</td>
<td>0.343</td>
</tr>
<tr>
<td>High-density lipoprotein cholesterol (mg/dl)</td>
<td>917</td>
<td>53.8 ± 17.6</td>
<td>53.5 ± 18.3</td>
<td>54.8 ± 17.9</td>
<td>0.607</td>
</tr>
<tr>
<td>Low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio</td>
<td>917</td>
<td>2.4 ± 1.0</td>
<td>2.4 ± 1.0</td>
<td>2.3 ± 0.9</td>
<td>0.218</td>
</tr>
</tbody>
</table>

Data are represented as mean ± SD or %.

* p <0.05. p Values are from analysis of variance for continuous data and from Mantel-Haenszel “analysis of variance” test of 2 degrees of freedom for presence-absence data.

receiving hemodialysis or taking pure EPA. Patients with ongoing congestive heart failure, severe liver dysfunction, or other systemic diseases, including malignancy and collagen disease, were also excluded. Patients with a medical history of percutaneous coronary intervention, coronary artery bypass grafting, and old myocardial infarction were also excluded. We also evaluated the use of the following medications: statins, antiplatelet agents, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, calcium channel blockers, β blockers, and hypoglycemic agents. This study was approved by the institutional ethics committee of each hospital, and all subjects gave informed consent.

Fasting blood samples were obtained in the morning, and serum levels of EPA, DHA, AA, and dihomo-γ-linolenic acid were measured at an external laboratory (SRL Inc., Tokyo, Japan). We also evaluated the following laboratory parameters: total cholesterol, fasting triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol/high-density lipoprotein cholesterol ratio, fasting plasma glucose, hemoglobin A1c, uric acid, serum creatinine (Cr), and estimated glomerular filtration rate. The estimated glomerular filtration rate was calculated based on the Japanese equation that uses serum Cr level, age, and gender as follows: estimated glomerular filtration rate (ml/min/1.73 m²) = 194 × Cr⁻¹.094 × age⁻⁰.287 (female × 0.739). The risk of ACS in patients in the different tertiles of EPA/AA and DHA/AA was compared using crude odds ratios (ORs) and their 95% confidence intervals. To adjust ORs for patients’ clinical characteristics, we used a multivariate logistic regression model that included age, gender, body mass index, hypertension, diabetes mellitus, dyslipidemia, smoking, family history of CAD, serum Cr level, and the use of statins, antiplatelet agents, renin-angiotensin system inhibitors, calcium channel blockers, β blockers, or hypoglycemic agents. Patients with missing information for each variable were excluded in the multivariate analysis. The α level for
all statistical tests was set at 0.05; thus, all confidence intervals were presented at the 95% level. All analyses were carried out with SAS, version 9.2 (SAS Institute, Cary, North Carolina).

### Results

In all 1,119 subjects, the mean ± SD serum levels of EPA, AA, DHA, and dihomo-γ-linolenic acid were 76.4 ± 47.8,
The present study showed that a low EPA/AA ratio but not DHA/AA ratio had a significant relation with occurrence of ACS in a multicenter observational study.

It has been reported that n-3 PUFA{s} have multiple actions to prevent CAD, including an anti-inflammatory effect, reduction of platelet aggregation, stabilization of atherosclerotic plaques, and an effect on red cell deformability. Although EPA and DHA are both n-3 PUFA{s}, it is still unclear which fatty acid has a greater effect on cardiovascular risk reduction. Domei et al measured the serum concentrations of various fatty acids and evaluated their relation with major adverse cardiac events that occurred in 284 patients who underwent elective percutaneous coronary intervention. They reported that the patients with a higher EPA/AA ratio (>.40), but not DHA/AA, had significantly fewer major adverse cardiac events than subjects with a low EPA/AA ratio. The results of the present study are consistent with their results; however, the present study included a large control group without ACS and was conducted at multiple centers.

Nozue et al recently reported the relation between the percent change in plaque volume and the changes in the EPA/AA ratio, DHA/AA ratio, and (EPA + DHA)/AA using virtual histology intravascular ultrasound in statin-treated patients with CAD. Negative correlations were observed between the percent change in plaque volume and change in not only EPA/AA but also DHA/AA and (EPA + DHA)/AA. A recent study reported the association between plaque progression and/or regression and coronary events. Further large-scale prospective studies are needed to investigate the associations among the EPA-DHA-AA balance, plaque volume, and/or morphology, and cardiovascular events.

Discussion

We surmise that one of the reasons responsible for the difference between EPA and DHA is a difference in the uptake of EPA and DHA into plaques. The result of an intervention study in patients before carotid endarterectomy showed that the phospholipid EPA value in carotid plaques in patients who received oral EPA and DHA significantly increased to twice the value of the control patients, whereas there was no significant change in DHA level compared with that of the control group. It was also reported that the relation between serum and erythrocyte membrane levels is stronger for EPA than DHA. EPA and DHA may have differences in integration characteristics into cells or organs as those reports indicate, and this mechanism needs to be investigated in future studies.

There are several limitations of the present study. This was a multicenter study with >1,100 patients, but all the centers were located in the metropolitan Tokyo area. Therefore, the study results are not necessarily applicable to patients living in rural areas. Furthermore, we were unable to determine if a low EPA/AA value was the cause of ACS because of the cross-sectional design of our study. ACS prevalence was relatively low in the present study because patients with a history of percutaneous coronary intervention, coronary artery bypass grafting, and old myocardial infarction were excluded. Therefore, a large-scale, multicenter, prospective study is necessary to confirm the result of this study. In addition, no data were obtained on inflammatory markers such as highsensitivity C-reactive protein that is assumed to have a strong association with ACS.

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Disclosures


