Serum eicosapentaenoic acid to arachidonic acid ratio is associated with cardio-healthy exceptional longevity

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Letter to the Editor

Serum eicosapentaenoic acid to arachidonic acid ratio is associated with cardio-healthy exceptional longevity

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1. Introduction

Long-chain ω-3 polyunsaturated fatty acids (PUFAs) eicosapentaenoic acid (EPA; 20:5(n-3)) and docosahexaenoic acid (DHA; 22:6(n-3)) are associated with coronary heart disease (CHD) [1]. Specifically, high serum levels of EPA and DHA as well as reduced concentrations of the ω-6 PUFAs arachidonic acid (AA; 20:4(n-6)) are associated with lower CHD risk [2] and a higher EPA/AA ratio portends a decreased risk of acute myocardial infarction (AMI) and sudden cardiac death [3]. The biological effects of ω-3 PUFAs on the cardiovascular system involve, among numerous pathways, transformation to bioactive metabolites, alteration of physical and chemical properties of cellular membranes, modulation of membrane channels and proteins, regulation of gene expression, or changes in eicosanoid profiles [1].

Owing to the limited ability of humans to synthesize EPA, the Dietary Guidelines for Americans recommend obtaining them from marine oils or supplements [4]. However, some controversy exists with recent evidence not supporting a strong cardiovascular benefit of omega-3 PUFA consumption [5]. The potential preventive effect of ω-3 PUFAs also varies depending on the dosages employed and the characteristics of selected patients [6].

In general, three major points during the course of human aging can be identified: 60 years old (the average age of onset of major age-associated diseases), 80 years old (average life expectancy in the Western world), and 100 years old (exceptional longevity [EL]). People who reach EL may be further divided into three subgroups: 1) ‘survivors’ — those who survive to become centenarians in spite of the onset of major age-associated diseases, including CHD, at an age comparable to the general population, i.e. at the age of 60 years (thus characterized by a long lifespan but a short healthy lifespan); 2) ‘delayers’ — those who develop age-related diseases much later than the control population, i.e. at the age of 80 years instead of 60 years (therefore having a long healthy lifespan), and 3) ‘dodgers’ or healthy centenarians — those who fail to develop age-related illnesses naturally throughout their lifespan [7]. The question as to whether PUFAs may be associated with EL — especially in CHD-free centenarian ‘dodgers’ — remains open. With the intent of gaining insights into the CHD and longevity-predictive value of blood PUFAs, we compared under a case–control design the EPA/AA ratio among CHD-free centenarian ‘dodgers’ and younger adults with or without CHD.

2. Methods

The study complied with the tenets of the Declaration of Helsinki and was approved by the local ethics committee. Written informed consent was obtained from all participants. The following three groups of subjects were analyzed: CHD-free centenarian ‘dodgers’, patients who experienced AMI at less than 40 years of age, and apparently healthy young controls (Table 1). The participants’ ages were defined by the dates of birth as stated on identity cards. All subjects were Caucasian whites ascertained to be of Italian descent (Northern Italy, mainly from Lombardy and Piedmont). The sample has been previously described [8].

The centenarian ‘dodgers’ were ascertained mainly via general practitioners in the community. The history of past and current diseases was accurately collected, checking the centenarians’ medical documentation and their current drug therapy. Accordingly, all of them were ‘dodgers’
Table 1
Main demographic and clinical characteristics of the three study groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Centenarian ‘dodgers’</th>
<th>Healthy controls</th>
<th>AMI controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample size</td>
<td>79</td>
<td>180</td>
<td>178</td>
</tr>
<tr>
<td>Number of males/females</td>
<td>39/40</td>
<td>103/77</td>
<td>101/77</td>
</tr>
<tr>
<td>Age range (years)</td>
<td>100–104</td>
<td>28–39</td>
<td>27–39</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0%</td>
<td>0%</td>
<td>36%</td>
</tr>
<tr>
<td>Obesity</td>
<td>0%</td>
<td>0%</td>
<td>21%</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0%</td>
<td>25%</td>
<td>69%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0%</td>
<td>0%</td>
<td>54%</td>
</tr>
<tr>
<td>Hypertriglyceridemia</td>
<td>0%</td>
<td>0%</td>
<td>22%</td>
</tr>
</tbody>
</table>

Abbreviation: AMI, acute myocardial infarction.

Table 2
ω-6 and ω-3 PUFA levels in the 3 study groups.

<table>
<thead>
<tr>
<th>PUFA</th>
<th>Centenarian ‘dodgers’</th>
<th>Healthy controls</th>
<th>AMI controls</th>
<th>P-value for group effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA (μg/mL)</td>
<td>134.5 ± 32.7</td>
<td>140.5 ± 29.9</td>
<td>148.7 ± 27.1</td>
<td>0.007</td>
</tr>
<tr>
<td>DHA (μg/mL)</td>
<td>175.8 ± 55.6</td>
<td>177.1 ± 52.1</td>
<td>172.5 ± 50.1</td>
<td>0.320</td>
</tr>
<tr>
<td>EPA (μg/mL)</td>
<td>91.4 ± 44.8</td>
<td>81.3 ± 39.7</td>
<td>70.5 ± 33.3</td>
<td>-0.001</td>
</tr>
<tr>
<td>EPA/AA</td>
<td>0.68 ± 0.3</td>
<td>0.58 ± 0.4</td>
<td>0.47 ± 0.4</td>
<td>-0.001</td>
</tr>
</tbody>
</table>

Data are means ± standard deviations. Abbreviations: AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; PUFA, ω-3 polyunsaturated fatty acids. Significant P-values for the main group effect are in bold.

3. Results

AMI patients had significantly higher AA levels compared with centenarian ‘dodgers’ (P < 0.001) but not with healthy controls (P = 0.09) and no significant differences were found for DHA (Table 2). We found significant differences for all between-group comparisons of EPA or EPA/AA (all P < 0.001), with AMI patients and centenarian ‘dodgers’ showing the lowest and highest values, respectively. In multivariable analysis, the OR of having an EPA/AA ratio < 0.38 was 3.22 (95% CI: 2.78, 4.13) for AMI patients and 0.51 (95% CI: 0.23, 0.68) for centenarian ‘dodgers’ (all P < 0.001).

4. Discussion

The results of our study indicate that the EPA/AA ratio was lowest in AMI patients and highest in CHD-free centenarian ‘dodgers’, whereas the opposite blood profile was found for serum AA levels. The findings obtained in our young AMI patients are in agreement with accumulating evidence that ω-3 PUFA levels are associated with a reduced burden of CHD [2,3,9]. Further, moderate (1–2 servings/week) fish consumption, especially of species rich in EPA and DHA reduces the risk of CHD-related mortality by 36%/10).

This is the first report demonstrating a significant association between EPA/AA ratio and CHD-free centenarian ‘dodgers’. These findings might be related to centenarian-specific metabolic features that may protect against CHD and other common age-related disorders. Alternatively, higher fish consumption among people who reach healthy EL may explain the observed differences. Regardless of the potential mechanisms, the positive association of serum EPA/AA ratio and disease-free EL suggests a potential protective effect of EPA/AA ratio against major age-related diseases. Because the world population is continuously aging and centenarians are the most successfully aged individuals, who have avoided or at least postponed major diseases, future long-term follow-up studies in ethnically distinct groups are needed to determine if dietary strategies aiming at improving the blood PUFA profile in the oldest old may have a positive impact on CHD-related or all-cause mortality at the end of the human lifespan.

List of abbreviations

AA Arachidonic acid
AMI Acute myocardial infarction
CHD Coronary heart disease
CI Confidence interval
DHA Docosahexaenoic acid
EL Exceptional longevity
EPA Eicosapentaenoic acid
OR Odds ratio
PUFAs Polyunsaturated fatty acids

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

References