Short communication

Relationships among the serum omega fatty acid levels, serum C-reactive protein levels and arterial stiffness/wave reflection in Japanese men

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ARTICLE INFO

Article history:
Received 11 February 2011
Received in revised form 29 March 2011
Accepted 4 April 2011
Available online xxx

Keywords:
Augmentation index
Central systolic pressure
Arterial stiffness
Omega-fatty acids
Inflammation

ABSTRACT

Objective: We examined the relationship among the serum omega-3 and omega-6 fatty acid (O3FA and O6FA) levels, serum C-reactive protein (CRP) levels, and arterial stiffness/wave reflection (AS/WR) in healthy Japanese men.

Methods: In 2206 Japanese healthy men, parameters related to the AS/WR (i.e., brachial–ankle pulse wave velocity and radial arterial pulse wave analysis) were measured.

Results: No significant inverse relationships were observed between the serum O3FA levels and the AS/WR-related parameters. Adjusted values of the AS/WR-related parameters and serum CRP levels were higher in the subjects with serum O6FA levels in the highest tertile than in those with serum O6FA levels in the lowest tertile.

Conclusions: In healthy Japanese men with known high dietary intakes of O3FAs, the serum O3FA levels may not reflect the pathophysiological abnormalities related to AS/WR. Increased serum O6FA levels appeared to be independently associated with the unfavorable conditions related to AS/WR and inflammation.

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1. Introduction

Omega-3 fatty acids (O3FAs) and omega-6 fatty acids (O6FAs) are essential fatty acids [1,2]. The pathophysiological abnormalities related to arterial stiffness/wave reflection have been much focused on as important, independent determinants of the cardiovascular risk [3]. Recently, Anderson et al. reported that both the serum O3FA and O6FA levels were inversely related to the pulse wave velocity, a marker of stiffness of the large arteries, in the British people, a population known for its low dietary intakes of O3FAs [4]. However, the relationships of the serum O3FA and O6FA levels with arterial stiffness/wave reflection still remain to be confirmed in populations with high dietary intakes of O3FAs. Furthermore, several studies have demonstrated the anti-inflammatory effects of O3FAs [2], therefore, it is possible that inflammation is involved in these relationships.

The aim of the present cross-sectional study, conducted in middle-aged healthy Japanese men (i.e., not receiving medications for cardiovascular diseases or their risk factors), a population known for its high dietary intakes of O3FAs, was to examine the relationships among the serum O3FA and O6FA levels, arterial stiffness/wave reflection, and inflammation.

2. Methods

2.1. Study cohort

Annual health checkups, including evaluation of the cardiovascular risk factors and measurements of the brachial–ankle pulse wave velocity (brachial–ankle PWV) and radial augmentation index (rAI), measurements of the serum O6FA, O3FA and C-reactive protein (CRP) levels, were conducted in the 3243 employees of a single large construction company. Verbal informed consent was obtained from all of the participants prior to the measurements. The study was conducted with the approval of the Ethical Guidelines Committee of Tokyo Medical University. Among the subjects, those who fulfilled the following criteria were excluded from the study: (1) ankle/brachial systolic blood pressure index of less than 0.95 (n = 22); (2) presence of atrial fibrillation (n = 13); (3) plasma levels of CRP ≥ 10 mg/L (n = 34); (4) standard deviation of the rAI, calculated from ten radial pressure waveform records, of greater than 6% (n = 78); (5) compression pressure for applana tion tonometry of the radial artery exceeded the first peak of the radial systolic pressure (SBP1) (n = 49); (6) receiving medications for heart disease, stroke, or risk factors for cardiovascular diseases.
(n = 382); (7) women (n = 465). Finally, the data of 2206 men were analyzed.

2.2. Measurements

2.2.1. Parameters related to arterial stiffness/wave reflection

The left radial arterial waveform was recorded by arterial applanation tonometry (HEM-9001AI; Omron Healthcare Co., Ltd.) in accordance with a previously described methodology [5]. Then, the first and second peaks of the peripheral systolic pressure (SBP1 and SBP2) and radial diastolic pressure (DBP) were automatically detected, and the rAI was calculated as follows: (SBP2 − DBP)/(SBP1 − DBP) × 100 (%). The brachial–ankle PWV was measured using a volume-plethysmographic apparatus (Form/ABI, Colin Co. Ltd., Komaki, Japan) in accordance with a previously described methodology [6].

2.2.2. Laboratory measurements

The serum CRP level was determined by the latex-aggregation method (Eiken Co., Tokyo). The fatty acid composition in the methylated samples was analyzed by gas chromatography (HP5890A, Agilent Technologies Inc., Santa Clara, CA, USA) equipped with a capillary column (TC-WAX, GL Sciences, Tokyo, Japan) [7]. In this analysis, we measured the serum O3FA profile [serum eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) levels, and the serum EPA/AA ratio] and serum O6FA levels [arachidonic acid (AA) and dihomo-gamma-linolenic acid (DGLA) levels]. All the blood samples were obtained in the morning after the patients had fasted overnight.

2.3. Statistical analysis

Data were expressed as means ± SD, and figures are shown with error bars. Since the serum levels of CRP were skewed rightward, the values were log-transformed for the analyses. The significances of the relationships were assessed by univariate and/or multivariate linear regression analyses. The covariates used for the adjustments were; for SBP2 = Model 1, which included the age, height, waist circumference, smoking status, alcohol intake status, serum levels of low-density lipoprotein cholesterol, triglycerides and high-density lipoprotein cholesterol, creatinine and fasting blood glucose, plus the heart rate; for the rAI, baPWV and log-transformed serum CRP levels = Model 2 plus the heart rate and mean blood pressure obtained at each occasion of measurement.

For assessment of the differences in the status of each variable among the groups, a general linear model (GLM) multivariate analysis of variance with post hoc multiple comparison was applied with the same adjustments. A GLM with interaction terms was also applied, with the same adjustments, to assess the significance of the interaction between the variables. All of the analyses were conducted using the IBM/SPSS software for Windows, version 17.0J (IBM/SPSS Inc., Chicago, IL); p values of <0.05 were considered to denote statistical significance.

3. Results

Table 1 shows the clinical characteristics of the study subjects. The multivariate linear regression analysis with adjustments demonstrated no significant relationships of the serum O3FA profiles with the parameters related to arterial stiffness/wave reflection (rAI, SBP2 and baPWV) or to the log-transformed serum CRP levels (data not shown).

After the adjustments (see Section 2.3), multivariate linear regression analysis demonstrated that not only the serum AA levels, but also the serum DGLA levels showed significant positive relationships with some parameters related to arterial stiffness/wave reflection and the log-transformed serum CRP levels (Supplemental table). As shown in Table 1, the serum levels of EPA and DHA varied widely based on the SD values. However, no heterogeneity of the significances of the relationships of the serum O6FA levels with the parameters related to arterial stiffness/wave reflection were observed between subjects with high and low O3FA levels.

Then, the serum levels of AA and DGLA in the men were divided into tertile ranges. After the same adjustments, the adjusted values of rAI and SBP2 were higher in the subjects with serum AA levels in the highest tertile than in those with serum AA levels in the lowest tertile, and the adjusted values of SBP2, brachial–ankle PWV and serum CRP levels were higher in the subjects with serum DGLA levels in the highest tertile than in those with serum DGLA levels in the lowest tertile (Fig. 1).

GLM analyses conducted with the same adjustments demonstrated no significant interactions of either the effect of the serum AA levels or the effects of the serum DGLA levels with that of the log-transformed serum CRP levels on the parameters related to arterial stiffness/wave reflection.

4. Discussion

Serum O3FA levels have been shown to be inversely associated with parameters related to arterial stiffness/wave reflection in a population with low dietary intakes of O3FAs [4]. However, the present study demonstrated no significant relationships of the serum O3FA profiles with the parameters related to arterial stiffness/wave reflection or with the log-transformed serum CRP levels in middle-aged Japanese healthy subjects.

### Table 1

Clinical characteristics of the study subjects.

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>44 ± 9</td>
</tr>
<tr>
<td>BMI</td>
<td>23.9 ± 3.0</td>
</tr>
<tr>
<td>WC (cm)</td>
<td>84.2 ± 8.1</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>692 (31)</td>
</tr>
<tr>
<td>ALC (non/mimo/heav) (%)</td>
<td>283/1364/559 (12.8/61.8/25.4)</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>123 ± 14</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>76 ± 11</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.2 ± 0.8</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.6 ± 0.4</td>
</tr>
<tr>
<td>TG (mmol/L)</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>FPG (mmol/L)</td>
<td>4.9 ± 0.6</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0.8 ± 1.2</td>
</tr>
<tr>
<td>rAI (%)</td>
<td>71.2 ± 13.1</td>
</tr>
<tr>
<td>SBP2 (mmHg)</td>
<td>111 ± 16</td>
</tr>
<tr>
<td>SBP1 (mmHg)</td>
<td>125 ± 14</td>
</tr>
<tr>
<td>baPWV (cm/sec)</td>
<td>1293 ± 186</td>
</tr>
<tr>
<td>EPA (µg/ml)</td>
<td>52.4 ± 32.8</td>
</tr>
<tr>
<td>DHA (µg/ml)</td>
<td>121.5 ± 45.5</td>
</tr>
<tr>
<td>AA (µg/ml)</td>
<td>172.4 ± 41.9</td>
</tr>
<tr>
<td>DGLA (µg/ml)</td>
<td>33.2 ± 10.9</td>
</tr>
<tr>
<td>EPA/AA</td>
<td>0.31 ± 0.20</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMI = body mass index; WC = waist circumference; ALC (non/mimo/heav) = alcohol intake status, non = non-drinker, mimo = mild-to-moderate alcohol intake (1–29 g/day), heav = heavy alcohol intake (over 30 g/day); SBP = systolic blood pressure measured at the time of the annual health checkup; DBP = diastolic blood pressure measured at the time of the annual health checkup; TC = serum total cholesterol level; HDL = serum high-density lipoprotein cholesterol level; TG = serum triglyceride level; FPG = fasting plasma glucose level; CRP = serum C-reactive protein level; rAI = radial augmentation index; SBP2 = second peak of the radial pressure waveform; SBP1 = first peak of the radial pressure waveform; baPWV = brachial–ankle pulse wave velocity; EPA = serum eicosapentaenoic acid level; DHA = serum docosahexaenoic acid level; AA = serum arachidonic acid level; DGLA = serum dihomo-gamma-linolenic acid level; EPA/AA = serum eicosapentaenoic acid/serum arachidonic acid ratio.

In subjects known to have high dietary intakes of O3FAs, such as Japanese and Koreans, several studies have suggested the existence of an inverse correlation between the serum O6FA levels and the risk of development of unfavorable cardiovascular conditions [8–10]. Vasoactive substances derived from AA or DGLA exert pro-inflammatory effects, elevate the blood pressure, and/or promote atherosclerosis [11,12]. In the present study, the adjusted values of the SBP2, rAI, brachial–ankle PWV and serum CRP levels were higher in the subjects with serum O6FA levels in the highest tertile than in those with serum O6FA levels in the lowest tertile. Thus, increased serum O6FA levels may be directly associated with increased arterial stiffness/augmented wave reflection and/or inflammation.

The serum AA or DGLA levels and log-transformed serum CRP levels were related to the SBP2, rAI and brachial–ankle PWV without interaction, therefore, the present study could not confirm the involvement of inflammation in the relationship between the serum O6FA levels and increased arterial stiffness/augmented wave reflection.

The present study had some limitations, as follows: (1) The relationship between the serum O6FA and O3FA compositions and the arterial stiffness were not examined. In addition, the fatty acids in phospholipids, which are stable and related to long-term dietary intakes [13], were not measured in the present study. Recently, Pase et al. reported that O3FA supplementation attenuated arterial stiffening [14], and our previous study demonstrated that O3FA supplementation had a beneficial effect on the arterial stiffness, even in Japanese subjects [15]. Thus, the precise relationships especially among the dietary intakes of O3FAs, serum O3FA levels and the central hemodynamics in subjects known for their high dietary intakes of O3FAs remain to be examined in a future study. (3) Parameters related to arterial stiffness/wave reflection were assessed by simple methods [5,6] and not by the standard methods [2].

5. Conclusion

In middle-aged healthy Japanese urban men, a population known for its high dietary intakes of O3FAs, the serum O3FA profiles may not reflect the unfavorable conditions related to arterial stiffness/wave reflection or inflammation. On the contrary, increased serum O6FA levels appeared to be associated with these abnormalities, although inflammation did not appear to be involved in the relationships between the serum O6FA levels and the cardiovascular unfavorable conditions.

Conflict of interests

This study was supported in part by a fund from OMRON Health Care Company (Kyoto, Japan).

Appendix A. Supplementary data


References


