Heart and Vessels (2019) 34:189–196
https://doi.org/10.1007/s00380-018-1226-1

SHORT COMMUNICATION

A longitudinal study of the association of the eicosapentaenoic acid/arachidonic acid ratio derived from fish consumption with the serum lipid levels: a pilot study

Shigemasa Tani[1,2,3] · **Rei Matsuo**[2,3] · **Naoya Matsumoto**[2,3]

Received: 27 March 2018 / Accepted: 6 July 2018 / Published online: 16 July 2018

Abstract

It has been demonstrated that regular fish consumption is associated with a reduced mortality from atherosclerotic cardiovascular disease (ASCVD). However, data are scarce regarding the correlation between the changes in the serum eicosapentaenoic acid/arachidonic acid (EPA/AA) ratio associated with regular fish consumption and the changes in the serum lipid profile variables. This study was designed as a hospital-based longitudinal study to investigate the relationship between the changes in the serum EPA/AA ratio and changes of the serum lipid levels in patients with one or more risk factors for ASCVD. In 475 patients followed-up for at least 1 year, univariable and multivariable regression analyses conducted after adjustments for the risk factors of ASCVD revealed that the absolute change of the EPA/AA ratio (ΔEPA/AA ratio) was independently and significantly associated with the changes of the serum levels of low-density lipoprotein cholesterol (LDL-C) ($\beta = -0.129$, $p = 0.005$), triglyceride (TG) ($\beta = -0.108$, $p = 0.019$), non-high-density lipoprotein cholesterol (non-HDL-C) ($\beta = -0.149$, $p = 0.001$), and TG/HDL-C ratio, a marker of the LDL particle size ($\beta = -0.104$, $p = 0.02$), while not being correlated with any other lipid parameters. On the other hand, while the Δ docosahexaenoic acid (DHA)/AA ratio was inversely correlated with the changes of the serum HDL-C level and positively correlated with the changes of the TG/HDL-C ratio, possibly serving to promote development of atherosclerosis. The results suggest that an increase of the EPA/AA ratio might be associated with decrease of the serum levels of LDL-C, TG and non-HDL-C levels, as well as with an increase of the TG/HDL-C ratio, which represents increased LDL particle size, all of which play a role in the development of ASCVD. A high EPA/AA ratio, but not DHA/AA ratio, derived from fish consumption might reduce the risk of ASCVD through reducing the risk of development of atherosclerosis.
Clinical Trial Registration Information: UMIN (http://www.umin.ac.jp/), Study ID: UMIN000010603.

Keywords Atherosclerotic cardiovascular disease (ASCVD) · Arachidonic acid · Eicosapentaenoic acid · Coronary artery disease (CAD) · EPA/AA ratio · n-3 polyunsaturated fatty acid (n-3 PUFA)

Introduction

Japan ranks very high among the nations in the world in terms of dietary fish consumption of the population [1]. Regular fish consumption has been correlated with a reduced mortality from coronary artery disease (CAD), and it has been suggested that the cardioprotective effects associated with elevated levels of n-3 polyunsaturated fatty acids (n-3 PUFAs) associated with fish consumption might have a bearing on the suppression of CAD morbidity in the Japanese population [2–5]. The Japan EPA Lipid Intervention Study (JELIS) reported a 19% reduction of the risk for CAD after long-term use of pure eicosapentaenoic acid (EPA) in Japanese hypercholesterolemic patients [6]. This result suggests

✉ Shigemasa Tani
tani.shigemasa@nihon-u.ac.jp

1 Department of Health Planning Center, Nihon University Hospital, 1-6 Kanda-Surugadai, Chiyoda-ku, Tokyo 101-8309, Japan

2 Department of Cardiology, Nihon University Hospital, Tokyo, Japan

3 Division of Cardiology, Department of Medicine, Nihon University School of Medicine, Tokyo, Japan

that interventions targeting the serum EPA/arachidonic acid (AA) ratio could be useful for the prevention of CAD [7].

It has been suggested that measurement of the EPA/AA ratio may possibly serve various cardioprotective effects, such as anti-inflammatory effect, vascular endothelium function-improving effect, and inhibition of platelet aggregation [8, 9]. However, there are few reports of observational studies conducted to investigate the mechanisms underlying the suppression of ASCVD by elevation of the serum EPA/AA ratio, particularly the effect of fish intake-dependent changes of the EPA/AA ratio on the serum lipid profile. We therefore ventured the hypothesis that the improved serum lipid profile mainly involved in suppressing the risk of ASCVD in regular fish eaters might be related to increase of the EPA/AA ratio associated with such a diet.

The purpose of this study was to examine the relationship of the changes of the serum EPA/AA ratio with the changes in the serum lipid profile through a longitudinal study approach.

Method

Study design and populations

This study was designed as a hospital-based longitudinal study to investigate the relationship between the changes in the serum EPA/AA ratio and changes in the serum levels of each important lipid parameter in subjects who were available for additional measurements 1 year after their participation in our previous study. The study population for this study were those subjects from our previous cross-sectional study [UMIN (http://www.umin.ac.jp/); Study ID: UMIN000010603], who underwent follow-up hematologic and blood biochemical tests at this institution at least 1 year after their participation in the previous study [10, 11].

The criterion for patient registration was the presence of one or more risk factors for atherosclerosis. The diagnostic criteria for coronary risk factors were as follows: a diagnosis of hypertension was made when the systolic pressure was ≥ 140 mmHg, the diastolic pressure was ≥ 90 mmHg, or the patient was taking anti-hypertensive medication. Diabetes mellitus (DM) was defined as a fasting plasma glucose concentration ≥ 126 mg/dL and an HbA1c ≥ 6.5% or current treatment with anti-diabetic agents. A diagnosis of dyslipidemia was made when the LDL cholesterol (LDL-C) level was ≥ 140 mg/dL, triglyceride (TG) level was ≥ 150 mg/dL, the high-density lipoprotein cholesterol (HDL-C) level was ≤ 40 mg/dL, or if the patient was already taking lipid-lowering medication. A diagnosis of hyperuricemia was made when the serum uric acid level was ≥ 7.0 mg/dL or the patient was taking medications. The severity of chronic kidney disease (CKD) was determined based on the estimated glomerular filtration rate (eGFR) using the abbreviated modification of diet in renal disease (MDRD) study equation, modified by a Japanese coefficient [12]; CKD was defined as eGFR < 60 mL/min/1.73 m^2. Obesity was defined as a body mass index (BMI) ≥ 25 kg/m^2.

Patients were not enrolled if they met any of the following exclusion criteria: hepatic dysfunction (alanine aminotransferase and aspartate aminotransferase ≥ 2 times the upper limit of the normal values), known malignant disease, refusal to provide consent for participation in the study, current treatment with n-3 PUFAs, or the diagnosis of acute coronary syndrome within 3 months prior to the study. The Nihon University Surugadai Hospital Ethics Committee approved the design and purpose of the study.

Measurement of laboratory parameters

Fasting blood samples were collected early in the morning after a 12-h fast. The serum fatty acid levels were measured using capillary gas chromatography (SRL Co., Ltd., Tokyo, Japan). The serum total cholesterol (TC), HDL-C, and TG levels were measured using standard methods. LDL-C levels were estimated using the Friedewald formula [13]. The RLP-C level was measured using an immunoadsorption assay (SRL). The serum apo and Lp (a) levels were determined using turbidimetric latex agglutination assays (Daiichi Pure Chemicals Co., Ltd., Tokyo, Japan). The malondialdehyde-modified LDL (MDA-LDL) level was measured using an enzyme-linked immunosorbent assay (SRL). The high-sensitivity C-reactive protein (hs-CRP) level was measured using a nephelometric assay (Behring Diagnostic Marburg, Germany).

Statistical analysis

Data were expressed as the mean ± standard deviation for continuous variables and as percentages for discrete variables. For variables with a significantly skewed distribution, the data were expressed as the interquartile range. First, we investigated the correlations between the absolute change in the EPA/AA ratio (Δ EPA/AA ratio) and the Δ serum level of each important lipid parameter, with a view to determining which specific lipid parameter(s) contributed to the improved serum lipid profile associated with the increase in the Δ EPA/AA ratio. We then carried out univariate and multivariate analyses of the data to examine the independent lipid level-improving effect of the Δ EPA/AA ratio, using the Δ serum level of each lipid parameter that was identified as being correlated with the Δ EPA/AA ratio as a dependent variable, and the age, gender, risk factors for ASCVD, intake of lipid-modifying drugs, Δ EPA, Δ DHA, Δ AA, and the Δ EPA/AA ratio as independent variables. All variables in which Δ lipid level correlated was the Δ EPA/AA

ratio at $p < 0.05$ in the univariable regression analysis which were entered into the multivariable model. A p value less than 0.05 was considered to indicate statistical significance. All the statistical analyses were performed using the SPSS software program (SPSS Inc., Chicago, Illinois, USA) for Windows (version 12.0.1).

Results

Patients

The patient characteristics and laboratory profile are shown in Tables 1 and 2. Among the subjects enrolled in our previous cross-sectional study [8, 9], 475 subjects who underwent follow-up hematologic and blood biochemical tests at least 1 year after participation in the previous study were enrolled in the present study. Of these 475 patients, none had experienced any cardiovascular events during the 1-year interval from the previous study.

Univariable and multivariable analyses to verify the independent association of the Δ EPA/AA ratio with the Δ lipid level

Table 3 shows the simple correlations between the Δ EPA/AA ratio and the changes in the serum levels of each of the important lipid parameters, and the correlation between the former and the Δ TG/HDL-C ratio. While the Δ EPA/AA ratio was found to be inversely correlated with the Δ LDL-C, Δ TG, Δ non-HDL-C, and the Δ TG/HDL-C, it showed no correlation with any of the other lipid parameters assessed. We subsequently carried out four univariate and multivariate analyses using the Δ LDL-C, Δ TG, Δ non-HDL-C, and the Δ TG/HDL-C ratio as dependent variables, to verify whether

Table 1 Baseline patient characteristics

$N = 475$	
Male/female, *n* (%)	331 (70)/144 (30)
Age (years)	63.7 ± 12.9
BMI (kg/m^2)	24.2 ± 3.8
Hypertension, *n* (%)	370 (78)
Diabetes mellitus, *n* (%)	135(28)
HbA1c (%)	5.96 ± 0.73
Current smoking, *n* (%)	58 (12)
Dyslipidemia, *n* (%)	322 (58)
eGFR (mL/min/1.73 m^2)	69.5 ± 17.8
CKD stage ≥ 3, *n* (%)	171 (23)
Number of risk factors	2.7 ± 1.3
Coronary artery disease, *n* (%)	120 (25)
Concomitant drugs, *n* (%)	
Anti-platelets	166 (35)
ACEs/ARBs	266 (56)
β blockers	113 (24)
Calcium channel blockers	282 (60)
Lipid-modifying drugs	285 (60)

BMI Body mass index, *Hb* hemoglobin, *Hb* hemoglobin, *eGFR* estimated glomerular filtration rate, *CKD* chronic kidney disease, *ACEI* angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker

Table 2 Baseline laboratory profile

$N = 475$	
Lipids	
TC (mg/dL)	194 ± 37
LDL-C (mg/dL)	108 ± 30
HDL-C (mg/dL)	57 ± 16
TG (mg/dL)[a]	119 (90/147)
Non-HDL-C (mg/dL)	137 ± 34
MDA-LDL (U/L)	109 ± 44
Lp (a) (mg/dL)[a]	12 (6/25)
TG/HDL-C ratio[a]	2.19 (1.47/3.07)
Apolipoproteins	
apo A-1 (mg/dL)	146 ± 30
apo B (mg/dL)	89 ± 21
Inflammatory markers	
hs-CRP (mg/L)[a]	0.5 (0.3/1.3)
PUFAs (μg/mL)	
EPA[a]	63 (40/90)
DHA[a]	129 (102/160)
AA	166 ± 45
DHA/AA ratio[a]	0.808 (0.639/1.047)
EPA/AA ratio[a]	0.388 (0.248/0.599)

TC Total cholesterol, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *MDA* malondialdehyde-modified, *Lp* lipoprotein, *RLP* remnant-like particle, *apo* apolipoprotein, *hs-CRP* hypersensitive C-reactive protein, *PUFA* polyunsaturated fatty acid

[a]Median; interquartile range in parentheses

Table 3 Correlation between the ΔEPA/AA ratio and Δ serum lipid levels

	R	*p*
Δ LDL-C	−0.152	0.001
Δ HDL-C	0.015	0.744
Δ TG	−0.110	0.017
Δ Non-HDL-C	−0.124	0.008
Δ MDA-LDL	−0.038	0.430
Δ LP(a)	0.007	0.893
Δ apo A-1	0.014	0.763
Δ apo B	−0.046	0.321
Δ RLP-C	−0.056	0.225
Δ TG/HDL-C ratio	−0.115	0.013

the Δ EPA/AA ratio could be independently associated with the above-mentioned changes of the serum lipid parameters. The results revealed that the Δ EPA/AA ratio showed independent inverse associations with the Δ LDL-C, Δ TG, and Δ non-HDL-C. Furthermore, the Δ EPA/AA ratio also showed an independent inverse association with the Δ TG/HDL-C ratio as an indicator of the estimated LDL particle size (Table 4). Meanwhile, the Δ DHA and Δ AA showed a trend towards the direction of promoting atherosclerosis in univariable regression analysis.

Figure 1 shows the correlograms of the Δ EPA/AA ratio with the Δ LDL-C, Δ TG, Δ non-HDL-C, and the Δ TG/HDL-C ratio.

As seen, the Δ DHA/AA ratio showed an inverse association with Δ HDL-C and positive association with the Δ TG/HDL-C ratio (Table 5). Similarly, in univariable and multivariable analyses using Δ HDL-C and the Δ TG/HDL-C ratio as dependent variables, the Δ DHA/AA ratio was independently negatively associated with Δ HDL-C and positively associated with the Δ TG/HDL-C ratio (Table 6).

Discussion

The present longitudinal study revealed the following. Changes in the EPA/AA ratio mainly associated with dietary fish intake in daily living showed independent inverse associations with the changes in the serum levels of LDL-C, serum TG, and serum non-HDL-C. The findings suggest that increase of the EPA/AA ratio associated with regular fish intake was associated with lowering of the serum levels of the atherosclerogenic lipids. Furthermore, subjects showing elevated EPA/AA ratios also showed an increase of the LDL particle size as estimated from the serum TG/HDL-C ratio. On the other hand, there was no association of the Δ DHA/AA ratio with improvement of the lipid metabolism.

These findings may lend support to the results of the Japan Public Health Center-Based (JPHC) Study Cohort I conducted in Japanese subjects, which showed that the greater the daily dietary fish intake, the lower the incidence of myocardial infarction [3]. The conclusions were drawn theoretically in this paper, with the sole aim of verifying the research hypothesis, so that we cannot conclusively state in a strict sense that changes in the EPA/AA ratio contribute to improved serum lipid metabolism. Although the duration of observation in this study was short, the fact that Japanese people, with obviously high fish intake levels, have been exposed to this phenomenon for a long period may explain, at least in part, the low CAD morbidity rates in the Japanese population [14].

Of profound interest was that there was no appreciable serum lipid metabolism-improving effect when the assessment was made based on changes in the serum EPA level

Table 4 Univariable and multivariable analyses to verify the independent association of the Δ EPA/AA ratio with the Δ lipid level

Univariable			Multivariable	
Variable	*r*	*p* value	*β*	*p* value
1. Dependent variable: Δ LDL-C; multiple $R=0.203$, $F=9.954$, $p<0.0001$				
Age	0.096	0.036	0.071	0.135
Male gender	0.001	0.125		
BMI	−0.124	0.008	−0.106	0.026
Smoking	0.005	0.911		
Hypertension	0.034	0.463		
Diabetes mellitus	0.039	0.397		
Dyslipidemia	0.012	0.794		
Lipid-modifying drugs	0.049	0.284	–	–
Δ EPA	−0.032	0.486	–	–
Δ DHA	0.206	<0.0001	–	–
Δ AA	0.363	<0.0001	–	–
Δ EPA/AA	−0.124	0.008	−0.129	0.005
2. Dependent variable: Δ non-LDL-C; multiple $R=0.198$, $F=6.226$, $p=0.004$				
Age	0.089	0.052		
Male gender	0.072	0.116		
BMI	−0.182	0.006	−0.134	0.0036
Smoking	0.011	0.819		
Hypertension	0.054	0.244		
Diabetes mellitus	0.015	0.754		
Dyslipidemia	0.024	0.595		
Lipid-modifying drugs	0.067	0.145		
Δ EPA	−0.066	0.152	–	–
Δ DHA	0.092	0.042	–	–
Δ AA	0.302	<0.0001	–	–
Δ EPA/AA	−0.152	0.001	−0.149	0.001
3. Dependent variable: Δ TG; multiple $R=0.208$, $F=5.204$, $p=0.0004$				
Age	−0.107	0.020	−0.092	0.052
Male gender	0.063	0.174		
BMI	0.101	0.030	0.075	1.117
Smoking	0.027	0.560		
Hypertension	0.031	0.181		
Diabetes mellitus	−0.062	0.181		
Dyslipidemia	0.122	0.008	0.105	0.023
Lipid-modifying drugs	0.018	0.701		
Δ EPA	−0.062	0.183	–	–
Δ DHA	0.177	0.0001	–	–
Δ AA	0.161	0.0004	–	–
Δ EPA/AA	0.110	0.017	−0.108	0.019
4. Dependent variable: Δ TG/HDL-C ratio; multiple $R=0.196$, $F=4.529$, $p=0.001$				
Age	−0.125	0.007	−0.115	0.016
Male gender	0.059	0.208		
BMI	0.106	0.023	0.067	0.162
Smoking	0.013	0.779		

Table 4 (continued)

Univariable			Multivariable	
Variable	*r*	*p* value	*β*	*p* value
Hypertension	0.005	0.918		
Diabetes mellitus	−0.061	0.189		
Dyslipidemia	0.107	0.021	−0.115	0.016
Lipid-modifying drugs	0.008	0.858		
Δ EPA	−0.042	0.362	–	–
Δ DHA	0.205	<0.0001	–	–
Δ AA	0.127	0.0062	–	–
Δ EPA/AA	−0.115	0.013	−0.104	0.020

The abbreviations are the same as in Tables 1 and 2, *r* correlation coefficient, *β* standard partial regression coefficient

In the multivariable models, Δ EPA, Δ DHA, and Δ AA were excluded as independent variables because of their multicollinearity with the Δ EPA/AA ratio

alone, whereas, conversely, when the assessment was made based on the changes in the serum DHA level alone, the latter was demonstrated to be an independent factor adversely affecting lipid metabolism. It was shown by Itakura et al., based on subanalyses of data from the JELIS study, that changes in the serum DHA levels were directly correlated with the changes in the serum LDL-C levels [15], which is consistent with our current results. There has been no unified view concerning changes in the serum lipid profile in clinical studies of combined EPA/DHA preparations, but some relevant reports document elevation of the serum LDL-C level with intake of such preparations [16–18]. It has also been reported that the cardioprotective effects of EPA and DHA are based on different biological activities [19]: this difference may also exist in regard to their association with the lipid metabolism [17]. The present study is by no means an intervention study conducted using any n-3PUFAs, but was aimed at investigation of the effect of dietary intake at

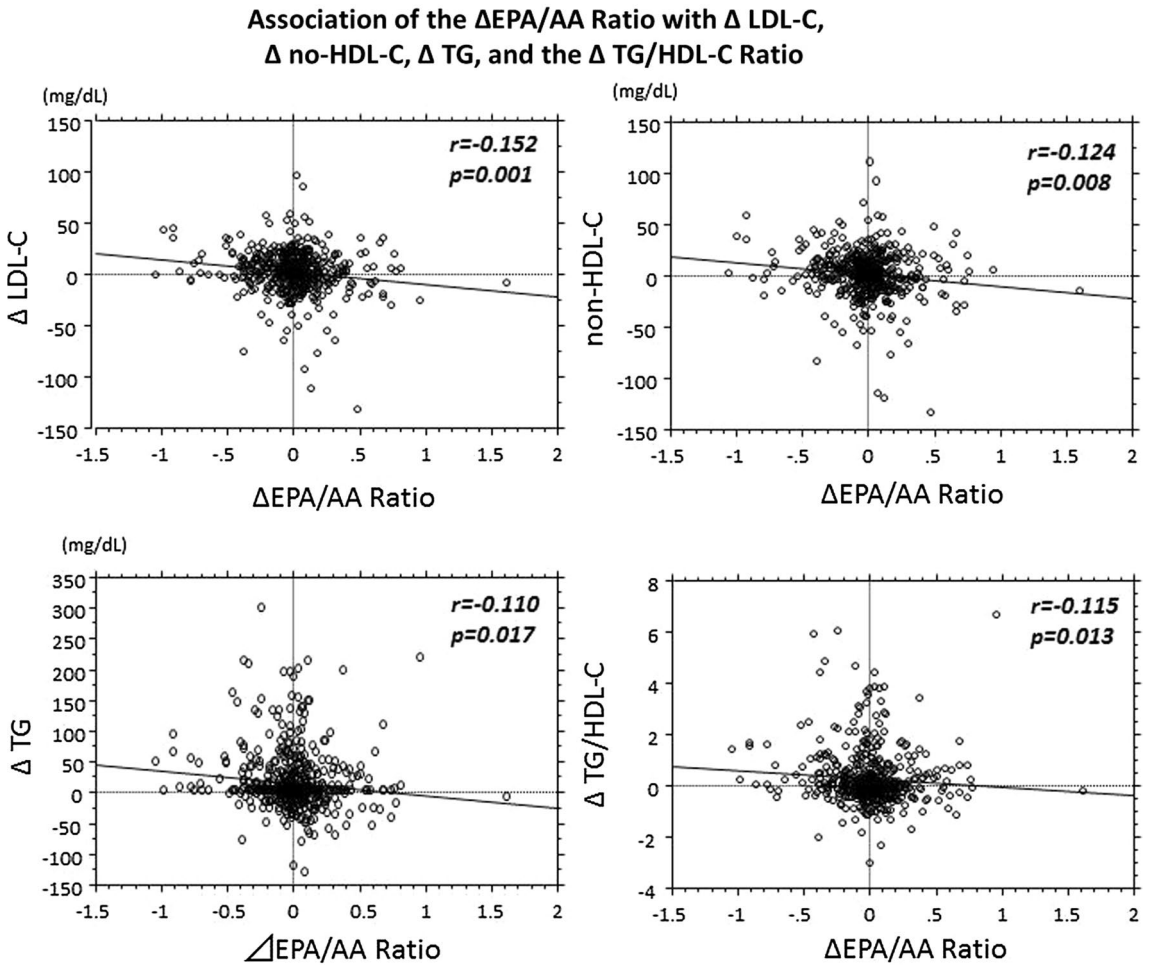

Fig. 1 Association of the ΔEPA/AA ratio with Δ LDL-C, Δ non-HDL-C, Δ TG, and the Δ TG/HDL-C ratio. The Δ EPA/AA ratio was negatively correlated with Δ LDL-C, Δ no-HDL-C, Δ TG, and the Δ TG/HDL-C ratio. Δ Absolute change from baseline, *EPA* eicosapentaenoic acid, *AA* arachidonic acid, *LDL-C* low-density lipoprotein cholesterol, *HDL* high-density lipoprotein, *TG* triglyceride

Table 5 Correlation between the ΔDHA/AA ratio and Δ serum lipid levels

	r	*p*
Δ LDL-C	−0.086	0.063
Δ HDL-C	−0.131	0.004
Δ TG	0.077	0.096
Δ non-HDL-C	0.008	0.872
Δ MDA-LDL	0.032	0.504
Δ LP(a)	0.001	0.983
Δ apo A-1	−0.050	0.277
Δ apo B	0.042	0.358
Δ RLP-C	0.075	0.120
Δ TG/HDL-C ratio	0.135	0.004

The abbreviations are the same as in Table 2, *r* correlation coefficient

Table 6 Univariable and multivariable analyses to verify the independent association of the Δ DHA/AA ratio with Δ lipid level

Univariate			Multivariate	
Variable	*r*	*p* value	*β*	*p* value
1. Dependent variable: Δ HDL-C; multiple $R=0.181$, $F=7.897$, $p=0.0004$				
Age	0.120	0.009	−0.122	0.008
Male gender	0.053	0.255		
BMI	−0.043	0.352		
Smoking	0.006	0.892		
Hypertension	0.001	0.981		
Diabetes mellitus	0.018	0.689		
Dyslipidemia	−0.048	0.297		
Lipid-modifying drugs	0.018	0.689		
Δ EPA	0.063	0.172	–	–
Δ DHA	0.076	0.102	–	–
Δ AA	0.103	0.026	–	–
Δ DHA/AA	−0.131	0.004	−0.133	0.004
2. Dependent variable: Δ TG/HDL-C; multiple $R=0.222$, $F=5.855$, $p=0.001$				
Age	−0.125	0.007	− 0.112	0.019
Male gender	0.059	0.208		
BMI	0.106	0.023	0.061	0.207
Smoking	0.013	0.779		
Hypertensin	0.005	0.918		
Diabetes mellitus	− 0.061	0.189		
Dyslipidemia	0.107	0.021	0.106	0.023
Lipid-modifying drugs	0.008	0.858		
Δ EPA	− 0.042	0.362	–	–
Δ DHA	0.205	< 0.0001	–	–
Δ AA	0.127	0.006	–	–
Δ DHA/AA	0.135	0.004	0.131	0.005

The abbreviations are the same as in Tables 1 and 2, *r* correlation coefficient, *β* standard partial regression coefficient

In the multivariable models, Δ EPA, Δ DHA, and Δ AA were excluded as independent variables because of their multicollinearity with the Δ EPA/AA ratio

low-concentrations of n-3PUFAs on the serum lipid profile. Further study is warranted.

In a population showing increased EPA/AA ratios, however, the increase of the EPA/AA ratio has a bearing upon improvement of the lipid metabolism, particularly upon lowering of the serum TG/HDL-C, an indicator of the LDL particle size, that is, upon LDL particle upsizing [20, 21]; it is of great interest that these result in suppression of the development of atherosclerosis. In other words, it may be that the anti-atherosclerotic effect of dietary fish intake can be conclusively stated solely in terms of the observed changes in the serum EPA concentrations. According to the results of the present study as well, the Δ AA showed an independent positive association with both the Δ LDL-C and Δ non-HDL-C. When viewed together with the fact that the serum EPA/AA ratio is strongly affected by the serum AA concentration, future investigations should also focus upon other constituents of a diet rich in AA content (e.g., animal food products such as egg yolk, pork liver, and dairy products) [22]. Several epidemiological studies have reported an inverse correlation between dietary fish intake and the serum TG level or prevalence of metabolic syndrome [23, 24]. This is considered to imply lowering of the serum TG level consequent upon improved intrahepatic VLDL clearance through the involvement of EPA [25].

EPA has anti-inflammatory activity, while AA has pro-inflammatory activity. Therefore, elevation of the EPA/AA ratio may result in a greater degree of amelioration of systemic inflammation, and thereby an anti-atherosclerotic effect [7, 8]. This study, however, was conducted to examine the possibility of an anti-atherogenic effect of the EPA/AA ratio, focusing on the effect of this anti-atherogenesis marker on the serum lipid profile.

While the dietary habits of the Japanese population have been becoming westernized in recent years, the possibility that the lifestyle of the Japanese per se, generally characterized by a lower intake of unsaturated fatty acids, lower caloric intake, and predominant fish intake as a source of dietary protein, compared with those of Western populations, has a great beneficial impact on the lipid metabolism may have to be taken into account [26].

Study limitations and clinical implications

First, the present study was a hospital-based longitudinal study, so further study will be necessary to investigate whether the findings can be applied to the entire population. Second, it did not investigate the relation between the amount of fish consumed and serum n-3PUFAs levels, and

since it was conducted on the basis of a 2-point blood collection, it is impossible to rule out the possibility that a bias in routine fish consumption affected the results of the analysis.

Conclusions

We demonstrated the possibility that increase of the EPA/AA ratio, but not that of the DHA/AA ratio, is associated with improved lipid metabolism. The high EPA/AA ratio derived from regular dietary fish consumption might reduce the risk of ASCVD through decreasing the atherogenic risk.

Acknowledgements This work was supported by KAKENHI Grant Number 16K09045 of the Japan Society for the Promotion of Science (JSPS). The authors would like to thank International Medical Information Center (http://www.imic.or.jp/services/translation.html) for the English language review. The authors would also like to thank Mr. Gary Cooper for his help in editing the English manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. http://www.jfa.maff.go.jp/j/kikaku/wpaper/h22_h/trend/1/t1_2_1_1.html. Accessed 11 July 2014
2. Kromhout D, Bosschieter EB, de Lezenne Coulander C (1985) The inverse relation between fish consumption and 20-year mortality from coronary heart disease. N Engl J Med 312:1205–1209
3. Iso H, Kobayashi M, Ishihara J, Sasaki S, Okada K, Kita Y, Kokubo Y, Tsugane S, JPHC Study Group (2006) Intake of fish and n3 fatty acids and risk of coronary heart disease among Japanese: the Japan Public Health Center-based (JPHC) Study Cohort I. Circulation 113:195–202
4. Mozaffarian D, Wu JH (2011) Omega-3 fatty acids and cardiovascular disease: effects on risk factors, molecular pathways, and clinical events. J Am Coll Cardiol 58:2047–2067
5. Tani S, Matsuo R, Kawauchi K, Yagi T, Atsumi W, Hirayama A (2018) A cross-sectional and longitudinal study between association of n-3 polyunsaturated fatty acids derived from fish consumption and high-density lipoprotein heterogeneity. Heart Vessels 33:470–480
6. Yokoyama M, Origasa H, Matsuzaki M, Matsuzawa Y, Saito Y, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Itakura H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Japan EPA lipid intervention study (JELIS) Investigators (2007) Effects of eicosapentaenoic acid on major coronary events in hypercholesterolaemic patients (JELIS): a randomised open-label, blinded endpoint analysis. Lancet 369:1090–1098
7. Itakura H, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y, Investigators JELIS (2011) Relationships between plasma fatty acid composition and coronary artery disease. J Atheroscler Thromb 18:99–107
8. Ohnishi H, Saito Y (2013) Eicosapentaenoic acid (EPA) reduces cardiovascular events: relationship with the EPA/arachidonic acid ratio. J Atheroscler Thromb 20:861–877
9. Hashimoto T, Ako J, Nakao K, Ozaki Y, Kimura K, Noguchi T, Yasuda S, Suwa S, Fujimoto K, Nakama Y, Morita T, Shimizu W, Saito Y, Hirohata A, Morita Y, Inoue T, Okamura A, Uematsu M, Hirata K, Tanabe K, Shibata Y, Owa M, Tsujita K, Funayama H, Kokubu N, Kozuma K, Uemura S, Toubaru T, Saku K, Ohshima S, Nakai M, Nishimura K, Miyamoto Y, Ogawa H, Ishihara M, J-MINUET investigators (2018) A lower eicosapentaenoic acid/arachidonic acid ratio is associated with in-hospital fatal arrhythmic events in patients with acute myocardial infarction: a J-MINUET substudy. Heart Vessels 33:481–488
10. Tani S, Nagao K, Hirayama A (2015) Association of atherosclerosis-related markers and its relationship to n-3 polyunsaturated fatty acids levels with a prevalence of coronary artery disease in an urban area in Japan. Heart Vessels 30:9–19
11. Tani S, Takahashi A, Nagao K, Hirayama A (2015) Association of fish consumption-derived ratio of serum n-3 to n-6 polyunsaturated fatty acids and cardiovascular risk with the prevalence of coronary artery disease. Int Heart J 56:260–268
12. Imai E, Horio M, Nitta K, Yamagata K, Iseki K, Hara S, Ura N, Kiyohara Y, Hirakata H, Watanabe T, Moriyama T, Ando Y, Inaguma D, Narita I, Iso H, Wakai K, Yasuda Y, Tsukamoto Y, Ito S, Makino H, Hishida A, Matsuo S (2007) Estimation of glomerular filtration rate by the MDRD study equation modified for Japanese patients with chronic kidney disease. Clin Exp Nephrol 11:41–50
13. Sniderman AD, Blank D, Zakarian R, Bergeron J, Frohlich J (2003) Triglycerides and small dense LDL: the twin Achilles heels of the Friedewald formula. Clin Biochem 36:499–504
14. Ueshima H (2007) Explanation for the Japanese paradox: prevention of increase in coronary heart disease and reduction in stroke. J Atheroscler Thromb 14:278–286
15. Itakura H, Yokoyama M, Matsuzaki M, Saito Y, Origasa H, Ishikawa Y, Oikawa S, Sasaki J, Hishida H, Kita T, Kitabatake A, Nakaya N, Sakata T, Shimada K, Shirato K, Matsuzawa Y (2012) The change in low-density lipoprotein cholesterol concentration is positively related to plasma docosahexaenoic acid but not eicosapentaenoic acid. J Atheroscler Thromb 19:673–679
16. Davidson MH, Maki KC, Kalkowski J, Schaefer EJ, Torri SA, Drennan KB (1997) Effects of docosahexaenoic acid on serum lipoproteins in patients with combined hyperlipidemia: a randomized, double-blind, placebo-controlled trial. J Am Coll Nutr 16:236–243
17. Leigh-Firbank EC, Minihane AM, Leake DS, Wright JW, Murphy MC, Griffin BA, Williams CM (2002) Eicosapentaenoic acid and docosahexaenoic acid from fish oils: differential associations with lipid responses. Br J Nutr 87:435–445
18. Harris WS, Ginsberg HN, Arunakul N, Shachter NS, Windsor SL, Adams M, Berglund L, Osmundsen K (1997) Safety and efficacy of Omacor in severe hypertriglyceridemia. J Cardiovasc Risk 4:385–491
19. Innes JK, Calder PC (2018) The differential effects of eicosapentaenoic acid and docosahexaenoic acid on cardiometabolic risk factors: a systematic review. Int J Mol Sci. https://doi.org/10.3390/ijms19020532
20. Maruyama C, Imamura K, Teramoto T (2003) Assessment of LDL particle size by triglyceride/HDL-cholesterol ratio in non-diabetic, healthy subjects without prominent hyperlipidemia. J Atheroscler Thromb 10:186–191
21. Quispe R, Manalac RJ, Faridi KF, Blaha MJ, Toth PP, Kulkarni KR, Nasir K, Virani SS, Banach M, Blumenthal RS, Martin SS, Jones SR (2015) Relationship of the triglyceride to high-density lipoprotein cholesterol (TG/HDL-C) ratio to the remainder of the lipid profile: the very large database of lipids-4 (VLDL-4) study. Atherosclerosis 242:243–250

22. Gabbs M, Leng S, Devassy JG, Monirujjaman M, Aukema HM (2015) Advances in our understanding of oxylipins derived from dietary PUFAs. Adv Nutr 6:513–540
23. Leaf DA, Hatcher L (2009) The effect of lean fish consumption on triglyceride levels. Phys Sportsmed 37:37–43
24. Tørris C, Molin M, Cvancarova MS (2016) Lean fish consumption is associated with lower risk of metabolic syndrome: a Norwegian cross sectional study. BMC Public Health 16:347
25. Oscarsson J, Hurt-Camejo E (2017) Omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid and their mechanisms of action on apolipoprotein B-containing lipoproteins in humans: a review. Lipids Health Dis 16:149
26. Iso H (2011) Lifestyle and cardiovascular disease in Japan. J Atheroscler Thromb 18:83–88