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Association of serum eicosapentaenoic acid to arachidonic acid ratio with microalbuminuria in a population of community-dwelling Japanese

Ako Fukami [a, *], Hisashi Adachi [b], Yuji Hirai [a], Mika Enomoto [a], Maki Otsuka [a], Eita Kumagai [a], Sachiko Nakamura [a], Ayako Yoshimura [a], Aya Obuchi [a], Yume Nohara [a], Erika Nakao [a], Kensuke Hori [a], Yoshihiro Fukumoto [a]

[a] *Department of Internal Medicine, Division of Cardio-Vascular Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan*
[b] *Department of Community Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume, Fukuoka 830-0011, Japan*

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ABSTRACT

Background: Epidemiological evidence suggests that the increased intake of omega-3 polyunsaturated fatty acids can prevent atherosclerosis-related cardiovascular diseases. Recently, serum eicosapentaenoic acid to arachidonic acid (EPA/AA) ratio has been reported to be a predictive marker of cardiovascular events. Accordingly, we examined the relationship between serum EPA/AA ratio and microalbuminuria.
Methods: We enrolled 444 residents (174 males and 270 females, mean age 66.6 ± 9.3 years) who underwent a physical examination in Uku town (fishing area) in Japan. They received blood tests including serum levels of EPA and AA, and urine test to examine microalbuminuria. Eating and drinking patterns were evaluated by a brief self-administered diet history questionnaire. Microalbuminuria was defined as a urinary albumin-to-creatinine ratio (UACR) ≥30 mg/g Cr.
Results: The mean EPA/AA ratio was 0.66 ± 0.3 in males and 0.51 ± 0.2 in females. Multiple stepwise regression analyses revealed that systolic blood pressure ($p < 0.0001$), high sensitive C-reactive protein ($p < 0.01$), serum EPA/AA ratio ($p < 0.01$, inversely), and hemoglobin A_{1c} ($p < 0.05$) were significantly associated with microalbuminuria. In the group with low serum EPA/AA ratio, the prevalence of microalbuminuria was significantly higher than the other, after the adjustments for confounding factors (odds ratio, 3.45; 95% confidence interval, 1.47–8.13; $p < 0.01$).
Conclusion: The present study demonstrated that serum EPA/AA ratio was strongly associated with microalbuminuria.

1. Introduction

Accumulated epidemiological and clinical evidences have suggested that the increased intake of omega-3 polyunsaturated fatty acids, especially eicosapentaenoic acid (EPA), can prevent atherosclerosis-related cardiovascular events [1–4]. Kromhout D et al. [1] observed the inverse dose-dependent relation between fish consumption and death by coronary heart disease. Also, it has been reported that fish consumption could protect against myocardial infarction [2] and sudden cardiac death [3]. The Japan Public Health Center-Based (JPHC) Study Cohort I also revealed that a high consumption of fish was associated with substantially reduced risk of coronary heart disease and primary nonfatal cardiac events, among middle-aged subjects [5]. Further, the Japan EPA Lipid Intervention Study (JELIS) demonstrated that administration of eicosapentaenoic acid significantly decreased the incidence of coronary artery disease in hypercholesterolemic patients [6]. Recently, it has been suggested that serum EPA to arachidonic acid (AA) ratio (EPA/AA ratio) is a predictive marker of major coronary events in a Japanese population [7].

Albuminuria is now recognized as an independent risk factor for cardiovascular morbidity and mortality in the general population [8–10]. Subclinical inflammation may link albuminuria to cardiovascular disease [11]. Accordingly, the present study aimed to

* Corresponding author.
E-mail address: fukami_ako@kurume-u.ac.jp (A. Fukami).

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Table 1
Clinical characteristics of the study subjects. Statistical significance was defined as P<0.05.

Characteristics	Total (n = 444)	Males (n = 174)	Females (n = 270)	*p*-value
Age (year)	66.5 ± 9.3	67.2 ± 8.9	66.0 ± 9.6	0.26
Body mass index (kg/m^2)	23.7 ± 3.3	24.0 ± 3.0	23.5 ± 3.5	0.06
Waist circumference (cm)	83.2 ± 9.6	84.4 ± 8.9	82.3 ± 9.9	**0.02**
Systolic blood pressure (mmHg)	137.1 ± 18.4	136.4 ± 17.5	137.4 ± 19.0	0.37
Diastolic blood pressure (mmHg)	81.4 ± 10.2	82.5 ± 10.5	80.8 ± 9.9	0.11
WBC (/μl)	5541.8.0 ± 1380.0	5864.3 ± 1387.1	5334.0 ± 1337.2	**<0.0001**
RBC (×10^4/μl)	445.0 ± 41.7	470.9 ± 40.3	428.3 ± 33.4	**<0.0001**
Hb (g/dl)	13.5 ± 1.4	14.5 ± 1.3	12.8 ± 0.9	**<0.0001**
Hct (%)	41.0 ± 3.9	43.7 ± 3.5	39.3 ± 3.1	**<0.0001**
Platelet (×10^4/μl)	20.6 ± 5.3	19.7 ± 5.0	21.2 ± 5.4	**0.005**
BUN (mg/dl)	17.4 ± 4.6	17.9 ± 4.5	17.0 ± 4.6	0.05
Creatinine (mg/dl)	0.74 ± 0.18	0.86 ± 0.18	0.66 ± 0.14	**<0.0001**
Estimated GFR (ml/min/1.73 m^2)[a]	71.3	71.3	71.4	0.96
Range	29.6–142.7	30.0–113.4	29.6–142.7	
UACR[a] (mg/g Cr)	12.8	12.2	13.3	0.18
Range	0.6–250	0.8–200	0.6–250	
Uric acid (mg/dl)	5.3 ± 1.3	6.0 ± 1.1	4.8 ± 1.1	**<0.0001**
Hemoglobin A_{1c} (NGSP) (%)	5.6 ± 0.5	5.6 ± 0.5	5.6 ± 0.5	0.91
Total cholesterol (mg/dl)	202.8 ± 34.1	194.6 ± 33.9	208.0 ± 33.3	**<0.0001**
HDL-cholesterol (mg/dl)	59.6 ± 15.3	54.9 ± 15.6	62.8 ± 14.2	**<0.0001**
LDL-cholesterol (mg/dl)	122.4 ± 32.3	116.1 ± 31.4	126.4 ± 32.3	**0.001**
Triglycerides (mg/dl)[a]	96.2	95.6	79.8	**<0.0001**
Range	25–843	25–843	33–206	
Hs-CRP (mg/dl)[a]	0.03	0.05	0.03	**0.002**
Range	0.002–1.35	0.002–0.74	0.002–1.35	
Insulin (μU/ml)[a]	4.1	4.2	3.9	0.23
Range	0.5–24.6	0.5–15.1	0.8–24.6	
Fasting plasma glucose (mg/dl)	95.6 ± 14.8	101.6 ± 16.6	92.3 ± 12.2	**<0.0001**
HOMA-IR	1.18 ± 0.8	1.29 ± 0.9	1.11 ± 0.8	**0.01**
IMT (mm)	0.78 ± 0.1	0.80 ± 0.1	0.76 ± 0.1	**<0.0001**
Eicosapentaenoic acid (μg/ml)	80.5 ± 41.8	90.6 ± 46.3	74.2 ± 37.4	**0.0001**
Arachidonic acid (μg/ml)	143.1 ± 32.9	137.6 ± 35.0	146.7 ± 30.1	**0.004**
Docosahexaenoic acid (μg/ml)	173.8 ± 54.3	179.6 ± 61.4	170.1 ± 49.0	0.11
EPA/AA ratio	0.57 ± 0.3	0.67 ± 0.3	0.51 ± 0.2	**<0.0001**
Smoking (%, yes)	7.9	17.3	1.8	**<0.0001**
Alcohol (%, yes)	15.2	39.0	2.9	**<0.0001**
Medications for				
Hypertension (%, yes)	52.0	59.1	47.4	**0.03**
Hyperlipidemia (%, yes)	38.9	32.8	42.9	**0.04**
Diabetes (%, yes)	7.2	9.8	5.6	0.11

Data are means ± standard deviation or percentage, unless otherwise indicated. Statistical analyses are performed between males and females.
Abbreviations: WBC, white blood cell count; RBC, red blood cell count; Hb, hemoglobin; Hct, hematocrit; BUN, blood urea nitrogen; GFR, glomerular filtration rate; UACR, urinary albumin-to-creatinine ratio; HDL, high density lipoprotein; LDL, low density lipoprotein; Hs-CRP, high sensitive C reactive protein; HOMA-IR, homeostasis model assessment as an index of insulin resistance; IMT, intima media thickness.
[a] Log-transformed values were used for the calculation and reconverted to anti-logarithm forms.

examine the association between serum EPA/AA ratio and microalbuminuria in community-based population in the fishing area in Japan.

2. Methods

The study complies with the Declaration of Helsinki, and was approved by the mayor and the Welfare Department of Uku town, as well as by the Ethics Committee of Kurume University. All participants gave written informed consent.

2.1. Study subjects

We have conducted annual health check-ups of residents over 40 years old in a small fishing community in Uku town, Japan. This town is an isolated island in a part of Sasebo city in Nagasaki prefecture, and total population is about 3700. This study area is a fishing community, where the average level of fish consumption is higher than farming villages. These check-ups include a review of medical history, routine physical examination, blood chemistry tests, electrocardiogram (ECG), echocardiography, and carotid artery ultrasonography. Habitual diet was assessed using a brief self-administered diet history questionnaire (BDHQ) [12]. From 2009 to 2010, a total of 451 residents (176 males and 275 females) received these health check-ups. During these 2 consecutive years, we investigated factors associated with microalbuminuria. Complete data sets were available in 444 subjects (174 males and 270 females, mean age: 66.5 ± 9.3 years old).

2.2. Data collection

The subjects' medical history, smoking habits and alcohol intake were ascertained by questionnaire. Height and weight were measured, and body mass index (BMI) (kilograms per meter squared) was calculated as an index of the presence or absence of obesity. Waist circumference was measured at the level of the umbilicus in the standing position. Blood pressure (BP) was measured twice with participants in the supine position. The second BP was taken after five deep breaths and systolic and fifth-phase diastolic pressures were used for analysis. Vigorous physical activity and smoking were avoided for at least 30 min before BP measurement. Blood samples obtained from antecubital vein in the morning in a fasting state were centrifuged and kept at −80 °C. Using these samples, we measured lipid profiles (total cholesterol,