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Secular trend of serum docosahexaenoic acid, eicosapentaenoic acid, and arachidonic acid concentrations among Japanese—A 4- and 13-year descriptive epidemiologic study

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ABSTRACT

Cross-sectional studies have shown age-related increases in blood docosahexaenoic and eicosapentaenoic acid and decreases in arachidonic acid. We describe serum docosahexaenoic, eicosapentaenoic, and arachidonic acid concentrations over 13 years (1997–2012) across four study waves and serum fatty acid composition over 4 years (2006–2012) between two study waves according to age groups by sex in the same subjects. We included 443 men and 435 women aged 40–79 years at baseline. Serum arachidonic acid concentrations increased in all sex and age groups over 13 years, and eicosapentaenoic or docosahexaenoic acid concentrations increased in males and females who were younger and middle-aged at baseline. Only serum arachidonic acid composition increased over 4 years in men and women who were 40–69 years at baseline, even after adjustment for arachidonic acid intake. These findings suggest a secular increase trend in serum arachidonic acid levels over 13 years among randomly selected community-dwelling middle-aged and elderly Japanese.

1. Introduction

Docosahexaenoic acid (DHA) of the n-3 polyunsaturated fatty acids (PUFA) and arachidonic acid (ARA) of the n-6 PUFA are the predominant long-chain PUFA of membrane phospholipids in mammalian brain and neural tissues [1,2]. These PUFA and eicosapentaenoic (EPA) have been shown to participate in numerous cellular functions affecting membrane fluidity, membrane enzyme activities, and eicosanoid synthesis [3]. Several studies, including our previous cohort study [4], have shown age-related changes in blood fatty acids (FA), as increases in DHA and EPA and decreases in ARA occur over time [5–8]. We hypothesized that serum DHA, EPA, and ARA changed in a steady pattern with aging.

Recently, a large descriptive study of 160,000 male and female patients in the United States indicated that erythrocyte-saturated and mono- and polyunsaturated FA levels were generally stable across the human lifespan (10–90 s), whereas the omega-3 index (EPA+DHA) increased by about 1.5 percentage points across decades and stabilized after age 70 [9]. However, most previous studies were cross-sectional studies [4–8]; it is thus unknown whether there are age effects on serum FA in the same population.

In this descriptive epidemiologic study of community-dwelling middle-aged and elderly Japanese subjects, we describe serum DHA, EPA, and ARA concentrations for 13 years (1997–2013) according to age groups categorized by the age at first participation in the study, and examine trends in serum DHA, EPA, and ARA concentrations among them. To eliminate the effects of total FA on serum FA concentrations – because DHA, EPA, and ARA concentrations might depend on the total FA concentration – we also describe FA compositions for 4 years between two study waves (fifth wave, 2006–2008; and seventh wave, 2010–2012) according to age groups by sex in the same subjects.

2. Materials and methods

2.1. Study subjects

Data for this survey were collected as part of the National Institute for Longevity Sciences Longitudinal Study of Aging (NILS-LSA). In this project, the normal aging process has been assessed over time using detailed questionnaires and medical checkups,

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anthropometric measurements, physical fitness tests, and nutritional examinations. Participants in the NILS-LSA included randomly selected age- and sex-stratified individuals from the pool of residents in the NILS neighborhood areas of Obu and Higashiura in Aichi Prefecture. Details of the NILS-LSA study have been reported elsewhere [10].

The initial survey of NILS-LSA included 2267 men and women aged 40–79 years, including almost 300 men and 300 women for each decade of life. They have been followed up every 2 years from the first wave (November 1997–April 2000), second wave (April 2000–May 2002), third wave (May 2002–May 2004), fourth wave (June 2004–July 2006), fifth wave (July 2006–July 2008), sixth wave (July 2008–July 2010), and seventh wave (July 2010–July 2012). Each wave was conducted for 2 years; the total length of the first through seventh waves was 15 years. However, in individuals, the entire follow-up period was 13 years.

When participants could not be followed up (e.g., they transferred to another area, dropped out for personal reasons, or died), new age- and sex-matched subjects were randomly recruited. All waves included nearly 1200 men and 1200 women.

Serum DHA, EPA, and ARA levels were assessed in the first, second, third, fifth, and seventh waves. In this study, we selected participants who participated in the first (1997–2000), third (2002–2004), fifth (2006–2008), and seventh (2010–2012) waves as values could be followed up every 4 years from the first wave. Among them, 549 men and 523 women participated in all four waves. We excluded participants who fasted <12 h, who were unable to supply a sufficient volume of blood at least one time ($n=67$), or who did not complete all nutritional assessments ($n=127$). Thus, a total of 878 Japanese (443 men and 435 women) between 40 and 79 years of age at the first wave were available for analysis. The mean ($\pm$ standard deviation) interval between first and seventh wave, and fifth to seventh wave for each participant was 13.7 ($\pm$ 0.6), and 4.0 ($\pm$ 0.3) years, respectively.

The study protocol was approved by the Committee of Ethics of Human Research of the National Center for Geriatrics and Gerontology (No. 369-2). Written informed consent was obtained from all subjects.

2.2. Blood sampling and FA analysis

Upon enrollment in the survey, venous blood was collected early in the morning after at least 12-h fasting. Blood samples were centrifuged at 3500*g* for 10 min. Serum was separated by a single technician, and it was refrigerated for up to few hours in the first to third waves, or frozen at -80 °C in the fifth to seventh waves, before analysis for FA content. Serum FA composition was measured by gas-liquid chromatography at a clinical laboratory (SRL, Tokyo, Japan). Briefly, total lipids in the serum were extracted using the Folch procedure and FA were then methylated with BF_3/methanol. Transesterified FA was then analyzed using a gas chromatograph (GC-17A; Shimadzu, Kyoto, Japan) with a capillary column Omegawax 250 (Supelco, Bellefonte, PA). In all waves, lipids and FA profiles were measured by the same method at the same clinical laboratory (SRL, Tokyo, Japan).

In the first and third waves, serum DHA, EPA, and ARA concentrations were assessed. In the fifth and seventh waves, to gain a more detailed serum lipid profile, serum concentrations of 24 kinds of FA including DHA, EPA, and ARA concentrations were assessed as follows: lauric (12:0), myristic (14:0), palmitic (16:0), stearic (18:0), arachidic (20:0), behenic (22:0), lignoceric (24:0), myristoleic (14:1n-5), palmitoleic (16:1n-7), oleic (18:1n-9), eicosenic (20:1n-9), erucic acid (22:1n-9), nervonic (24:1n-9), alpha-linoleic (18:3n-3), eicosapentaenoic (20:5n-3), docosapentaenoic (22:5n-3), docosahexaenoic (22:6n-3), linoic (18:2n-6), gamma-linoleic (18:3n-6), eicosadienoic (20:2n-6), dihomo-γ-linoleic (20: 3n-6), arachidonic (20:4n-6), docosatetraenoic (22:4n-6), and 5-8-11 eicosatrienoic (20:3n-9) acids. In the fifth and seventh waves, the weight of each FA (μg/mL) as the FA concentration was identified by comparison with known standards, and the weight percentage of each FA among total FA (wt% total) was quantified by the total weight for all FA. Mean serum FA compositions among the study subjects in the fifth and seventh waves by sex are shown in Supplementary Table 1.

For grouped FA, we defined saturated FA as the sum of (12:0), (14:0), (16:0), (18:0), (20:0), (22:0), and (24:0); monounsaturated FA as the sum of (14:1n-5), (16:1n-7), (18:1n-9), (20:1n-9), (22:1n-9), and (24:1n-9); n-3 series polyunsaturated FA as the sum of (18:3n-3), (20:5n-3), (22:5n-3), and (22:6n-3); n-6 series polyunsaturated FA as the sum of (18:2n-6), (18:3n-6), (20:2n-6), (20: 3n-6), (20:4n-6), and (22:4n-6); and polyunsaturated FA as the sum of n-3 and n-6 series polyunsaturated FA and (20:3n-9).

Intra- and inter-assay precision and accuracy values (coefficient of variation [CV]) were 3.2 and 5.8 CV% for ARA, 2.7 and 6.9 CV% for EPA, and 1.9 and 6.9 CV% for DHA, respectively.

2.3. Nutritional assessments

Nutritional intakes were assessed using a 3-day dietary record after participation in all waves. The dietary record was completed over 3 continuous days (both weekend days and 1 weekday) [11], and most subjects completed it at home and returned records within 1 month. Food was weighed separately on a scale (1-kg kitchen scale; Sekisui Jushi, Tokyo, Japan) before being cooked or portion sizes were estimated. Subjects used a disposable camera (27 shots; Fuji Film, Tokyo, Japan) to take photos of meals before and after eating. Dietitians used these photos to complete missing data and telephoned subjects to resolve any discrepancies or obtain further information when necessary. Averages for 3-day food and nutrient intakes were calculated according to the fifth edition of the Standard Tables of Foods Composition in Japan and other sources [11]. Alcohol intake in the previous year was assessed using a food frequency questionnaire; trained dieticians interviewed subjects using this questionnaire.

2.4. Other measurements

Medical history of heart disease, stroke, hypertension, hyperlipidemia, and diabetes (past and current), education (≤ 9, 10–12, or ≥ 13 years of school), and smoking status (yes/no) were collected using questionnaires. Body mass index was calculated as weight in kilograms divided by the square of height in meters.

2.5. Statistical analysis

All statistical analyses were conducted using Statistical Analysis System software version 9.3 (SAS Institute, Cary, NC, USA) and were done separately by sex. To simplify the analysis, participants were categorized into four age groups (40–49, 50–59, 60–69, and 70–79 years) according to age at first participation.

Comparisons between continuous variables were performed by analysis of variance and trend test. Linear regression models were constructed using the PROC GLM procedure to examine the association between mean nutritional intake, FA concentration adjusted for corresponding FA intake, crude serum FA concentration, and four waves according to age group, respectively.

Serum FA compositions (wt%) were determined as a weight percentage of total FA (μg/ml). To eliminate the effects of total FA on serum FA concentrations, the paired *t*-test was performed for comparisons between FA compositions in the fifth and seventh waves according to age group by sex. To further adjust for FA intake on serum FA composition, FA composition adjusted for corresponding FA intake was estimated by linear regression models in the fifth and seventh waves according to age group by sex.