IJC Metabolic & Endocrine 10 (2016) 1–6

Contents lists available at ScienceDirect

IJC Metabolic & Endocrine

journal homepage: http://www.journals.elsevier.com/ijc-metabolic-and-endocrine

Circulating eicosapentaenoic acid to oleic acid ratio and risk for cardiovascular events in patients with coronary artery disease: A sub-analysis of the SHINANO registry☆

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ARTICLE INFO

Article history:
Received 4 October 2015
Accepted 8 November 2015
Available online 10 November 2015

Keywords:
Coronary artery disease
Omega-9 monounsaturated fatty acid
Omega-3 polyunsaturated fatty acid
Major adverse cardiovascular event

ABSTRACT

Background: The omega-3/omega-6 polyunsaturated fatty acid (PUFA) ratio, particularly the eicosapentaenoic acid (EPA)/arachidonic acid (AA) ratio, is associated with cardiovascular disease. However, the clinical impact of omega-9 monounsaturated fatty acids (MUFAs) on cardiovascular disease is not well understood. In this study, we evaluated whether the PUFA/MUFA ratio, especially the EPA/oleic acid (OA) ratio, predicted clinical outcomes in patients with coronary artery disease (CAD) who underwent percutaneous coronary intervention (PCI).

Methods: The SHINANO registry was a prospective, observational, multicenter cohort study that enrolled 1923 consecutive patients with CAD. From this registry, we identified 182 patients for whom fatty acids were measured on admission and stratified them according to the median EPA/OA ratio. The primary endpoint was major adverse cardiovascular events (MACEs), including cardiovascular death, nonfatal myocardial infarction, ischemic stroke, heart failure, and PCI for a de novo lesion within 1 year.

Results: Patients' mean age was 72 ± 9 years, 24% were women, and 28% had acute coronary syndrome. The 1-year follow-up was completed in 181 patients (99.5%). There were 59 cases of MACE. In the Kaplan–Meier analysis, the MACE incidence was significantly higher in patients with an EPA/OA ratio of ≤0.1169 than in those with a ratio of ≥0.1170 (39.6% vs. 25.3%, $p = 0.041$). In a multivariate Cox regression analysis, an EPA/OA ratio ≥0.1170 was associated with a lower incidence of MACE (hazard ratio, 0.53; 95% confidence interval, 0.31–0.91; $p = 0.020$).

Conclusions: We demonstrated that the EPA/OA ratio predicted MACE in patients with CAD who underwent PCI.

1. Introduction

Many epidemiologic and clinical studies have demonstrated that the long-term intake of omega-3 polyunsaturated fatty acids (PUFAs) is associated with decreased mortality related to coronary artery disease (CAD) [1,2]. In particular, large amounts of eicosapentaenoic acid (EPA) and/or docosahexaenoic acid (DHA) are reported to decrease the risk of cardiovascular events and death [3–5].

Omega-9 monounsaturated fatty acids (MUFAs) are one type of fatty acid and are different from PUFAs on the basis of having only one double bond. Omega-9 MUFAs must be obtained from food, and oleic acid (OA) is the major component found in food. Although high-omega-9 MUFA diets have been reported to have cardioprotective effects in some epidemiologic studies [6], several meta-analyses and epidemiologic studies found no significant association between MUFA and CAD [7–9]. One experimental study demonstrated that a diet high in MUFA caused atherosclerosis equivalent to that observed from diets high in saturated fatty acids [10]. Few studies have assessed the relationship between the PUFA/MUFA ratio and cardiovascular events. Thus, the aim of this study was to evaluate whether the PUFA/MUFA ratio could predict adverse events in patients who underwent percutaneous coronary intervention (PCI).

Abbreviations: AA, arachidonic acid; ACS, acute coronary syndrome; CAD, coronary artery disease; CKD, chronic kidney disease; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; HF, heart failure; LA, linoleic acid; LV, left ventricular; LVEF, left ventricular ejection fraction; MACE, major adverse cardiovascular event; MI, myocardial infarction; MUFA, monounsaturated fatty acid; OA, oleic acid; PCI, percutaneous coronary intervention; PUFA, polyunsaturated fatty acid; SHINANO, The Shinshu Prospective Multi-center Analysis for Elderly Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention; STEMI, ST-segment elevation myocardial infarction; VIF, variance inflation factor.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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http://dx.doi.org/10.1016/j.ijcme.2015.11.001

2. Methods

2.1. Study population

This retrospective cohort analysis used integrated data for the period from August 2012 to July 2013, obtained from the SHINANO (The Shinshu Prospective Multi-center Analysis for Elderly Patients with Coronary Artery Disease Undergoing Percutaneous Coronary Intervention) registry. The design of the SHINANO registry has previously been described in detail [11]. In brief, the SHINANO registry was a prospective, multicenter, observational registry of patients undergoing PCI with any coronary heart disease, including stable angina, ST-segment elevation myocardial infarction (STEMI), non-STEMI, and unstable angina, from 16 collaborating hospitals located in the Nagano prefecture in Japan. It is registered with the University Hospital Medical Information Network Clinical Trials Registry, as accepted by the International Committee of Medical Journal Editors (UMIN-ID; 000010070). This registry had no exclusion criteria and was an all-comer registry. The study protocol was developed in accordance with the Declaration of Helsinki and was approved by the ethics committee of each participating hospital. All patients provided written informed consent before participating in the study.

From among the 1923 patients registered in the SHINANO registry, we identified 182 patients for whom circulating fatty acids were measured and who did not take EPA treatment on admission. Clinical events for patients were retrospectively tracked for 1 year (Fig. 1). The primary endpoint of this study was the incidence of major adverse cardiovascular events (MACEs), including cardiovascular death, nonfatal myocardial infarction (MI), ischemic stroke, heart failure, and any PCI for 1 year.

2.2. Measurement of fatty acids

Fasting blood samples were collected, and the serum levels of fatty acids were measured at an external laboratory (SRL Inc., Tokyo, Japan). We evaluated the levels of omega-3 PUFAs (EPA and DHA), omega-6 PUFAs (arachidonic acid [AA] and linoleic acid [LA]), and omega-9 MUFA (oleic acid [OA]) in this study. Plasma was stored at −20 °C until analysis. Using a screw-capped glass tube, 100 μL of plasma and 1 μg of C17:0 as an internal standard were mixed with 2 mL of methanolic 5% hydrochloric acid and tightly capped. After shaking, the mixture was incubated for 2 h at 100 °C. After cooling to room temperature, the methyl derivatives were extracted twice with 2 mL of *n*-hexane, dried under a stream of nitrogen, and finally dissolved in 1 mL of *n*-hexane supplemented with 0.05% butylated hydroxytoluene as an antioxidant. The extract was stored at 120 °C until analysis. The methylated fatty acids were analyzed using a capillary gas chromatograph (QP5050A, Shimadzu, Kyoto, Japan). The concentration of each fatty acid was expressed as μg/mL. To assess the relationship between adverse events and the PUFA/MUFA ratios, we calculated the ratios of omega-3 to omega-6 (EPA/AA and DHA/AA) and the ratio of omega-3 to omega-9 (EPA/OA). All participants were stratified based on the median of the serum EPA/AA, DHA/AA, DHA/OA, and EPA/OA ratios.

2.3. Definitions

Nonfatal MI was defined as a 2-fold or greater increase in creatine phosphokinase, troponin-T levels ≥0.1 ng/mL, or new Q waves in ≥2 contiguous leads on electrocardiography [12]. Ischemic stroke was defined as the presence of a new neurological deficit lasting for at least 24 h with definite evidence on magnetic resonance imaging or computed tomography [13]. Heart failure (HF) was based on a previous diagnosis of HF, history of hospitalization for HF, or current treatment for HF. Diabetes was defined as HbA1C ≥6.5%, fasting plasma glucose ≥200 mg/dL, or treatment with oral hypoglycemic agents or insulin. Hypertension was defined as systolic blood pressure (BP) ≥140 mm Hg, diastolic BP ≥90 mm Hg, or ongoing therapy for hypertension. Dyslipidemia was defined as a serum total cholesterol concentration ≥220 mm Hg, a low-density lipoprotein cholesterol concentration ≥140 mm Hg, or current treatment with lipid-lowering therapy. Chronic kidney disease (CKD) was defined as an estimated glomerular filtration rate <60 mL/min/1.73 m^2 (calculated using the Modification of Diet in Renal Disease formula) [14]. Left ventricular ejection fraction (LVEF) was assessed by echocardiography using the Teichholz method, and LVEF ≤40% indicated left ventricular (LV) systolic dysfunction [15].

2.4. Statistical analysis

Continuous variables are presented as the mean ± standard deviation, whereas dichotomous variables are described as numbers and percentage. Differences between the patients in each group according to the median fatty acid ratios were compared using the chi-squared test for categorical variables and unpaired Student *t*-tests or Wilcoxon

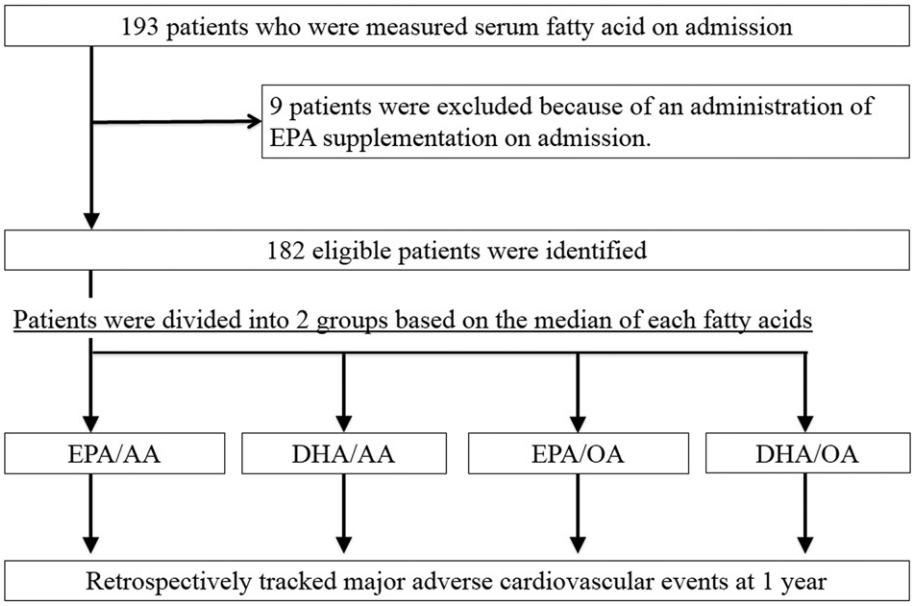

Fig. 1. Patient flow chart.