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Original article

Effects of a fish-based diet and administration of pure eicosapentaenoic acid on brachial-ankle pulse wave velocity in patients with cardiovascular risk factors

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ABSTRACT

Background and purpose: Brachial-ankle pulse wave velocity (baPWV) and ratio of plasma eicosapentaenoic acid to arachidonic acid (EPA/AA ratio) are surrogate markers for coronary artery disease (CAD). We aimed to evaluate the effects of a fish-based diet and administration of EPA on baPWV and plasma EPA/AA ratio.

Methods and results: The changes in baPWV and plasma EPA/AA ratio were compared before and after a 6-month fish-based diet in 191 patients with cardiovascular risk factors. A fish-based diet resulted in significant increment of plasma EPA/AA ratio (0.40 ± 0.18 vs. 0.49 ± 0.27, $p < 0.001$), with baPWV remaining unchanged. Multivariate analysis revealed that systolic blood pressure (SBP) (6-month SBP-baseline SBP) and CAD were positively associated with increased baPWV (CAD: odds ratio = 2.040, $p = 0.0436$, SPB: odds ratio = 1.056, $p = 0.0003$). When the patients were divided into three groups: CAD, low-risk, and high-risk with no prior history of CAD according to the number of risk factors at baseline, comparison among the three groups disclosed an inter-group difference in the magnitude of change in baPWV (low-risk: -35 ± 164 cm/s, high-risk: -14 ± 190 cm/s, CAD: 39 ± 164 cm/s, $p = 0.0071$ for trend). In 191 patients who had received a 6-month fish-based diet, 21 patients (primarily CAD patients) sequentially received high purity EPA (1800 mg/day) for 6 months. It resulted in marked increment of plasma EPA/AA ratio (0.65 ± 0.57 vs. 1.19 ± 0.46, $p < 0.001$), accompanied by significant reduction in baPWV (1968 ± 344 cm/s vs. 1829 ± 344 cm/s, $p = 0.0061$). There was a significant negative correlation between changes in baPWV and changes in plasma EPA/AA ratio in patients with a fish-based diet and sequential administration of EPA ($r = -0.446$, $p = 0.017$).

Conclusion: A fish-based diet was effective against increased baPWV only in low-risk patients, with slight increment of plasma EPA/AA. In high-risk patients and CAD patients, administration of EPA for preventing progression of baPWV endorsed the validity of high purity EPA administration recommended in the current guidelines.

Introduction

Heart-type fatty acid binding protein, troponin T, and pentraxin 3 are biomarkers for the diagnosis of acute coronary syndrome [1]. Brachial-ankle pulse wave velocity (baPWV) which reflects arterial stiffness serves as a predictor of the onset of cardiovascular events in primary or secondary prevention [2,3].

As far as secondary prevention for patients with coronary artery disease (CAD) is concerned, we may say that the residual risk has not yet been sufficiently suppressed [4]. Multi-faceted approaches including glycemic control, blood pressure control, lipid lowering with statin therapy [5], aspirin therapy, angiotensin-converting enzyme inhibitors, and lifestyle modifications, now seem desirable to reduce the residual risk in patients with CAD. Recently, close attention has been paid to eicosapentaenoic acid (EPA), one of the omega-3 polyunsaturated fatty acids (PUFA), that has been proven to reduce the risk of major coronary events [6]. Research on EPA

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dates back to the 1970s, when a study revealed that Inuit, living in Greenland and ingesting seals or the like as the main diet, had a lower prevalence of cardiovascular disease than Caucasians, accompanied by a high plasma level of EPA [7]. Since then, reports have been published, demonstrating the effectiveness of multiple omega-3 PUFA in preventing cardiovascular events, including sudden cardiac death [8,9]. Statins and omega-3 PUFA are the most favorable lipid-lowering interventions with reduced risks of overall and cardiac mortality [9].

The addition of EPA to statin therapy provides further benefits in preventing cardiovascular events, mainly through cholesterol-independent mechanisms, in patients with hypercholesterolemia, especially for the secondary prevention of CAD [6]. Therefore, the guidelines published in 2012 by the Japan Atherosclerosis Society state that administration of EPA in addition to statin deserves consideration for high-risk patients with dyslipidemia [10].

EPA has anti-atherosclerotic effects and reduces baPWV, a marker for arterial stiffness [11]. EPA is taken up into the cell membrane in the form of phospholipid, resulting in formation of biologically active substances [prostaglandin (PG) I_3, thromboxane A_3, and leukotriene B_5). EPA is thus expected to exert vasoprotective activity. On the other hand, PG, formed from arachidonic acid (AA), is known to induce vascular smooth muscle contraction, thrombus formation, and inflammation, thus antagonizing the PG formed from EPA [12]. The ratio of EPA to AA (EPA/AA ratio) in cell membrane and plasma serves as an overall marker of the actions of multiple types of PG conflicting with each other. There is a recent trend toward utilization of plasma EPA/AA ratio as "a new risk marker" for cardiovascular disease [13,14].

Not much has been done to clarify the effects of a fish-based diet on baPWV from the viewpoint of plasma EPA/AA ratio.

This study was undertaken to elucidate the factors associated with increased baPWV, and to verify whether a fish-based diet and sequential treatment of pure EPA affected baPWV and plasma EPA/AA ratio in patients with cardiovascular risk factors.

Methods

Study population

We assessed a consecutive series of 257 outpatients with cardiovascular risk factors managed for eligibility (Fig. 1). Inclusion criteria were CAD, hypertension, dyslipidemia, and diabetes. Exclusion criteria were therapy of EPA, peripheral artery disease, aortic valve disease, aortic aneurysm, aortic dissection, artificial vascular graft, obstructive cardiomyopathy, and atrial fibrillation. We excluded medication changes during the study. We enrolled 191 patients in the present study, with informed consent and the ethics committee approval.

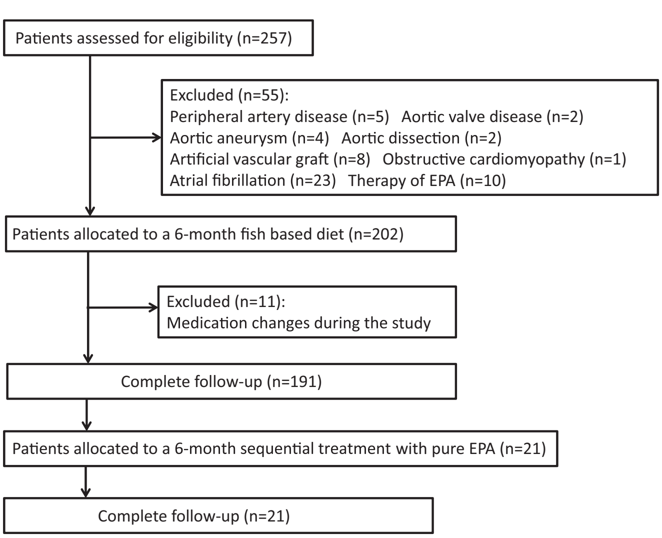

Fig. 1. Flow chart of the study population. EPA, eicosapentaenoic acid.

Baseline data measurements

Blood low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride (TG), creatinine (Cr), HbA1c (Japan Diabetes Society), and plasma PUFA [EPA, AA, and docosahexaenoic acid (DHA)] were measured. Systolic blood pressure (SBP), baPWV, and ankle/brachial index (ABI) were measured at right brachial and both ankles with a blood pressure pulse wave testing device (BP-203RPE II form PWV/ABI; Omron Healthcare Co., Ltd, Tokyo, Japan), which has been described detail previously [15]. SBP and baPWV of the side with ABI less than 0.9 were excluded and the higher baPWV was included. Carotid maximum intima-media thickness (IMT) was measured by ultrasonography.

Fish-based diet and administration of pure EPA

The protocol of a fish-based diet consisted of a 6-month dietary intervention period. Fish-based diet was assessed at baseline with self-administered food-frequency questionnaires (FFQ). The dietician instructed each patient and his/her family members about the daily intake of fish by a food model. During the fish-base intervention period, the study subjects were instructed to eat no less than 1.0 g/day omega-3 PUFA derived from fish which is the recommended dose for CAD patients by the American Heart Association (AHA) [16]. The adherence to a fish-based diet was evaluated at the end of a 6-month period by a dietician.

After a 6-month fish-based diet, subsequent oral administration of pure EPA (1800 mg/day) for 6 months was provided to CAD and high-risk patients with dyslipidemia according to Japan Atherosclerosis Society guidelines [10].

BaPWV and plasma PUFA were measured at the end of the 6-month fish-based diet and at the end of 6-month oral administration of pure EPA.

Definitions

Estimated glomerular filtration rate (estimated GFR, $mL/min/1.73\,m^2$) was calculated using the equation given below.

$$GFR(male) = 194 * serumCr^{-1.094} * age^{-0.287}$$

$$GFR(female) = GFR(male) * 0.739$$

Left ventricular hypertrophy (LVH) was defined as thickness ≥13 mm by echocardiography.

Changes from baseline to those after the 6-month fish-based diet are abbreviated as Δ.

Factors determining ΔbaPWV were explored, by dividing the patients into two groups, increased baPWV (ΔbaPWV > 0 cm/s) and decreased baPWV (ΔbaPWV ≤ 0 cm/s), and comparing baseline risk factors, percentage of low-risk/high-risk/CAD, and concomitant drugs between the two groups.

The patients were divided into CAD patients (CAD) and non-CAD patients at baseline. We defined age ≥45 years (male) or ≥55 years (female), hypertension, diabetes, and HDL-C <40 mg/dl, as risk factors. The non-CAD group was subdivided into high-risk (possessing 3 or more major risk factors) and low-risk (possessing 2 or fewer major risk factors) according to the number of risk factors. ΔbaPWV was compared among the three groups that are CAD, high-risk and low-risk.