Prostaglandins, Leukotrienes and Essential Fatty Acids 86 (2012) 29–34

Contents lists available at SciVerse ScienceDirect

Prostaglandins, Leukotrienes and Essential Fatty Acids

journal homepage: www.elsevier.com/locate/plefa

Effect of omega-3 fatty acids on the modification of erythrocyte membrane fatty acid content including oleic acid in peritoneal dialysis patients

W.S. An [a,e,*], S.M. Lee [a], Y.K. Son [a], S.E. Kim [a], K.H. Kim [a], J.Y. Han [b], H.R. Bae [c], Y. Park [d]

[a] Department of Internal Medicine, Dong-A University College of Medicine, Busan, Republic of Korea
[b] Department of Laboratory Medicine, Dong-A University College of Medicine, Busan, Republic of Korea
[c] Department of Physiology, Dong-A University College of Medicine, Busan, Republic of Korea
[d] Department of Food and Nutrition, Hanyang University, Seoul, Republic of Korea
[e] Dong-A University Hospital Regional Clinical Trial Center, Dong-A University College of Medicine, Busan, Republic of Korea

ARTICLE INFO

Article history:
Received 19 June 2011
Received in revised form
21 October 2011
Accepted 22 October 2011

Keywords:
Erythrocyte membrane
Monounsaturated fatty acid
Oleic acid
Omega-3 fatty acids
Peritoneal dialysis

ABSTRACT

Erythrocyte membrane fatty acids (FA), such as oleic acid, are related to acute coronary syndrome. There is no report about the effect of omega-3 FA on oleic acid in peritoneal dialysis (PD) patients. We hypothesized that omega-3 FA can modify erythrocyte membrane FA, including oleic acid, in PD patients. In a double-blind, randomized, placebo-controlled study, 18 patients who were treated with PD for at least 6 months were randomized to treatment for 12 weeks with omega-3 FA or placebo. Erythrocyte membrane FA content was measured by gas chromatography at baseline and after 12 weeks. The erythrocyte membrane content of eicosapentaenoic acid and docosahexaenoic acid was significantly increased and saturated FA and oleic acid were significantly decreased in the omega-3 FA supplementation group after 12 weeks compared to baseline. In conclusion, erythrocyte membrane FA content, including oleic acid, was significantly modified by omega-3 FA supplementation for 12 weeks in PD patients.

1. Introduction

Patients who are maintained with dialysis therapy have a high incidence of coronary artery disease [1,2]. Supplementation with omega-3 fatty acid (FA) lowers the risk of cardiovascular death in patients with myocardial infarction [3]. Furthermore, omega-3 FA supplementation significantly reduces myocardial infarction as a secondary outcome in hemodialysis (HD) patients [4]. This cardioprotective effect of omega-3 FA can be explained by anti-inflammatory, anti-oxidative, or anti-thrombotic effects. In addition, omega-3 FA modulates cell membrane receptors and affects signal transduction and eicosanoid metabolism [5–7]. Altering membrane FA composition plays an important role in cellular function by changing the microenvironment of transmembrane proteins and inflammatory mediators interact with transmembrane receptors involved with cell signaling systems [8,9].

The erythrocyte membrane content of FA has been shown to correlate with the FA content of the myocardium [10]. Therefore, cardiac FA content can be easily measured by the estimation of erythrocyte membrane FA content. The risk of cardiovascular disease or sudden cardiac death is significantly reduced in subjects with high omega-3 index and omega-3 FA, such as eicosapentaenoic acid (EPA), in the erythrocyte membrane [11,12]. In contrast, high levels of erythrocyte membrane total trans-FA, trans-oleic acid, and arachidonic acid (AA) are associated with an increased risk of cardiovascular disease [13,14]. Erythrocyte membrane monounsaturated FA (MUFA) content, including oleic acid, is significantly higher in patients with acute coronary syndrome than control subjects [13,15,16]. The erythrocyte membrane oleic acid content was also higher in dialysis patients who have high risks of cardiovascular disease compared to control subjects [17,18]. Therefore, the modification of erythrocyte membrane FA content is very important with respect to cardiovascular disease. In a previous study, erythrocyte membrane omega-3 index was shown to be increased and the MUFA content was decreased after 12 weeks of omega-3 FA supplementation in HD patients [19]. However, there are no reports about the effect of omega-3 FA on the erythrocyte membrane FA composition in peritoneal dialysis (PD) patients, who have higher erythrocyte membrane MUFA and oleic acid content compared to HD patients [17,18].

In this study we hypothesized that omega-3 FA supplementation for 12 weeks can modify erythrocyte membrane FA content, including MUFA and oleic acid, in PD patients. In addition, we evaluated the effect of omega-3 FAs on inflammation and the lipid profile in PD patients.

* Corresponding author at: Department of Internal Medicine, Dong-A University, 3Ga-1, Dongdaesin-Dong, Seo-Gu, Busan 602-715, Republic of Korea.
Tel.: +82 51 240 2811; fax: +82 51 242 5852.
E-mail address: anws@dau.ac.kr (W.S. An).

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doi:10.1016/j.plefa.2011.10.009

2. Patients and methods

2.1. Study design and patients

We conducted a randomized, double-blind, placebo-controlled, intervention study in a single Dong-A University dialysis center between June 2009 and December 2009. Twenty four PD patients, 20–80 years of age, who wanted to participate in the study, were evaluated by review of medical records. Patients with a history of active infection within 3 months, fish oil or omega-3 FA supplementation within 3 months, a history of fish, gelatin, omega-3 FA, and/or olive oil allergies, a history of hospital admission within 3 months, a history of bleeding within 3 months, thrombocytopenia, current use of warfain, an albumin level < 2.5 g/dL, malignancy and/or liver cirrhosis were excluded. Eighteen patients who were treated with PD for at least 6 months due to end-stage renal failure were randomized to treatment for 12 weeks with omega-3 FA (Omacor®, 3 g/day; Pronova, Sandefjord, Norway) or placebo (olive oil, 3 g/day). One gram of Omacor contained 460 mg of EPA and 380 mg of docosahexaenoic acid (DHA). The dose of omega-3 FA was based on a prior study in which at least 3 g/day of omega-3 FA supplementation was used in dialysis patients [20]. Randomization was performed using a random table. The enrolled PD patients received 4 exchanges per day using a standard regimen (8 L/day). This study was approved by the Dong-A University Hospital Institutional Review Board. The present study was conducted in accordance with the Helsinki Declaration and written informed consent from the study participants was obtained.

2.2. Survey of food consumption

PD patients were asked for the average frequency and portion size of food consumption at the point of initiating the study and after 12 weeks. We interviewed patients at 12 weeks intervals. The semi-quantitative food frequency questionnaire contained 121 foods used in the Korean Cancer Research Survey. Three-dimensional food models and full-scale photographs were used to assist subjects in estimating the portion size. Nutrient intake was estimated by the Computer Aided Nutritional Analysis Program (Can-Pro 3.0, The Korean Nutrition Society), which provides 1823 food items.

2.3. Laboratory measurements

Routine laboratory tests, including hemoglobin, glucose, blood urea nitrogen (BUN), creatinine, albumin, calcium, phosphorus, iron, total iron biding capacity (TIBC), C-reactive protein (CRP), and lipids were obtained using fasting blood samples and the body mass index (BMI) were determined. Plasma oxidized LDL (Mercodia, Uppsala, Sweden), leptin (human leptin; R&D Systems Inc., Mineapolis, MN, USA), and adiponectin (human adiponectin; R&D Systems Inc.) were measured by enzyme-linked immunosorbent assays. Blood samples were obtained by venipuncture from PD patients. Samples were immediately placed on ice. Plasma and erythrocytes were promptly separated by centrifugation and stored at -70 °C until assayed.

2.4. Gas chromatography procedure

The isolated erythrocytes were methylated by the addition of boron trifluoride (BF_3) methanol–benzene for 10 min at 100 °C. Fatty acid methyl esters were analyzed by gas chromatography (Shimadzu 2010AF, Shimadzu Scientific Instrument, Japan) with a 100-m SP2560 capillary column (Supelco, Bellefonte, PA, USA). Fatty acids were identified by comparison with known standards (GLC-727; Nu-Chek Prep, Elysian, MN, USA). The omega-3 index is a measure of EPA and DHA in erythrocyte membranes. Erythrocyte membrane FA content is expressed as weight percentages.

2.5. Statistical analysis

Data are presented as the mean $\pm$ SD, with the exception of CRP, leptin and dietary consumption data, which are expressed as the mean $\pm$ SE. On the basis of a minimum sample size of 6 per group, the trial had a statistical power of 80% to detect a difference between the two groups in the change of erythrocyte membrane MUFA with an alpha level of 0.05. This erythrocyte membrane MUFA change, 3.6 ± 2.7% per 12 weeks, was based on previous study [19]. The non-parametric Mann–Whitney U test was used to compare baseline data between the omega-3 FA supplementation and placebo groups. The non-parametric Wilcoxon exact rank sum test was used to compare baseline data to the 12 weeks data. Fourteen patients who completed the study and had baseline and final measurements were included in the analysis. P values < 0.05 were considered statistically significant. All statistical calculations were performed with SPSS software (version 17.0; SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Baseline characteristics

Four patients of 18 PD patients were withdrawn during this study. One patient complained of nausea and one patient chose to discontinue the study among the omega-3 FA supplementation group. PD peritonitis was developed in one patient and one patient declined blood sampling at 12 weeks among the placebo group. Fourteen PD patients (omega-3 FA supplementation group [$n = 7$] and placebo group [$n = 7$]) completed this study and were included in the analyses. The mean age of the patients was

Table 1
Clinical and biochemical characteristics of the study population.

	Placebo	Omega-3	P-value
Number	**7**	**7**	
Age (years)	**52.6 ± 12.1**	**51.6 ± 8.7**	**0.949**
Gender (male/female)	**3/4**	**4/3**	**1.000**
Duration (months)	**43.4 ± 33.8**	**50.4 ± 16.8**	**0.371**
DM (%)	**3 (47.9)**	**4 (57.1)**	**1.000**
BMI (kg/m^2)	**24.6 ± 2.8**	**22.6 ± 4.2**	**0.338**
Calcium (mg/dL)	**8.4 ± 1.0**	**8.8 ± 0.8**	**0.405**
Phosphorus (mg/dL)	**4.3 ± 1.1**	**3.6 ± 1.1**	**0.259**
Hemoglobin (g/dL)	**10.5 ± 1.7**	**9.3 ± 1.0**	**0.180**
Glucose (mg/dL)	**103.6 ± 28.5**	**113.1 ± 45.7**	**0.848**
BUN (mg/dL)	**57.9 ± 19.5**	**55.0 ± 19.3**	**0.654**
Creatinine (mg/dL)	**8.8 ± 2.0**	**11.3 ± 3.9**	**0.138**
Protein (g/dL)	**6.9 ± 0.8**	**6.7 ± 0.8**	**0.368**
Albumin (g/dL)	**3.8 ± 0.4**	**3.7 ± 0.4**	**0.521**
CRP (mg/dL) ± SE	**0.22 ± 0.09**	**0.83 ± 0.48**	**0.747**
Total cholesterol (mg/dL)	**198.1 ± 47.2**	**171.1 ± 45.9**	**0.201**
Triglyceride (mg/dL)	**197.7 ± 75.7**	**148.1 ± 63.3**	**0.201**
HDL cholesterol (mg/dL)	**41.7 ± 9.6**	**45.6 ± 23.0**	**0.522**
LDL cholesterol (mg/dL)	**111.6 ± 39.9**	**92.0 ± 37.4**	**0.249**
Oxidized LDL (mg/dL)	**16.0 ± 19.1**	**20.5 ± 17.4**	**0.482**
Iron (ug/dL)	**99.0 ± 93.7**	**68.0 ± 23.2**	**0.935**
TIBC (ug/dL)	**276.9 ± 52.5**	**248.4 ± 42.2**	**0.201**
Leptin (ng/mL) ± SE	**16.5 ± 8.0**	**14.7 ± 5.9**	**0.749**
Adiponectin (ug/mL)	**32.5 ± 26.2**	**28.5 ± 20.2**	**0.848**

Omega-3, omega-3 fatty acid supplementation; DM, diabetes mellitus; BMI, body mass index; BUN, blood urea nitrogen; CRP, C-reactive protein; HDL, high density lipoprotein; LDL, low density lipoprotein; TIBC, total iron binding capacity.
Values are expressed as mean ± SD.