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Predictors of change in omega-3 index with fish oil supplementation in peripheral artery disease

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ABSTRACT

Background: The omega-3 index represents the red blood cell (RBC) content of two major long-chain n-3 polyunsaturated fatty acids (PUFAs), eicosapentaenoic acid, and docosahexaenoic acid. We sought to determine factors associated with a favorable response to fish oil treatment and to characterize changes in RBC PUFAs associated with fish oil supplementation.
Methods: This study was a secondary analysis of the OMEGA-PAD I trial, a randomized, double-blinded, placebo-controlled trial investigating short-duration, high-dose n-3 PUFA oral supplementation on endothelial function and inflammation in subjects with peripheral arterial disease. Patients with mild to severe claudication received either 4.4 g of fish oil providing 2.6 g of eicosapentaenoic acid and 1.8 g of docosahexaenoic acid daily ($n = 40$) or placebo capsules ($n = 40$) for 1 mo. The RBC fatty acid content was measured by gas chromatography and expressed as a percent of total fatty acids. The change in omega-3 index was calculated as the difference between pre- and post-supplementation in the fish oil and placebo groups. Univariate analysis identified predictors of change in omega-3 index, with these variables included in our multivariable model.
Results: In the fish oil group, there was an increase in the omega-3 index (5.1± 1.3% to 9.0± 1.8%; $P < 0.0001$), whereas there was no change in the control group. Factors associated with a favorable response (i.e., greater than the median change of 4.06%) included a lower body mass index and higher concentrations of low-density lipoproteins. Other demographic and/or lifestyle factors such as age, race, or smoking status were unrelated to the response. Oral n-3 PUFA supplementation also decreased the n-6 PUFA content in RBCs.
Conclusions: Short-term, high-dose n-3 PUFA supplementation increases the omega-3 index to a greater extent in patients with a lower body mass index and higher total and low-density lipoprotein cholesterol levels.

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Introduction

Peripheral arterial disease (PAD), a chronic inflammatory condition affecting the vasculature, continues to be associated with a high risk of cardiovascular events and mortality compared with coronary artery disease (CAD), despite the wide availability of medical and interventional therapies.[1] Current nutritional guidelines from the American Heart Association and American College of Cardiology recommend a diet rich in oily fish for individuals with cardiovascular disease, including PAD.[2] Evidence demonstrates that n-3 polyunsaturated fatty acid (PUFA) plays a role in reducing systemic inflammation[3] and protecting against the development of atherosclerosis.[4] A widely used biomarker of n-3 PUFA status is the omega-3 index, which represents the level of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) in red blood cell (RBC) membranes.[5] This marker is a well-documented surrogate of the EPA + DHA status of other tissues.[6-8] The omega-3 index is inversely associated with a high-risk CAD profile[9] and inflammatory markers[10] and has been proposed as an actual risk factor for death from CAD.[5] Therefore, a relatively low membrane concentration of *n*-3 PUFA may contribute to the development and progression of PAD.[11]

We have previously reported that in patients with PAD, a higher omega-3 index was associated with older age, elevated body mass index (BMI), and prior fish oil supplementation, whereas a history of smoking correlated with a lower omega-3 index.[12] We also demonstrated the ability of high-dose, short duration n-3 PUFA supplementation to increase the omega-3 index in patients with PAD.[13] Determining those factors involved in a robust response to n-3 PUFA supplementation could help guide treatment considerations in patients with PAD. The goal of this analysis was, therefore, to identify factors associated with a favorable response to fish oil treatment. We also aimed to characterize changes in other RBC fatty acids with n-3 PUFA supplementation.

Materials and methods

The methods of the OMEGA-PAD I (NCT01310270) trial, a randomized, double-blinded, placebo-controlled trial designed to assess the impact of high-dose, short-term *n*-3 PUFA supplementation on endothelial function and inflammation in patients with symptomatic PAD, have been previously published.[14] The present study is a secondary analysis using data from that trial to investigate baseline omega-3 indices in PAD patients, absolute change in the omega-3 index after a 1-mo course of high-dose *n*-3 PUFA supplementation, and predictors of omega-3 index response. Eighty patients with stable, mild, or severe claudication (Rutherford Class 1-3) received either 4.4 g of fish oil capsules consisting of 2.6 g of EPA and 1.8 g of DHA daily ($n = 40$) or placebo capsules ($n = 40$) for 1 mo. The placebo capsules were the same shape and color as the fish oil capsules, and the same quantity of capsules was taken daily by all participants in both cohorts. The omega-3 index was analyzed according to the HS-Omega-3 index methodology.[15]

Statistical analysis

Baseline clinical and demographic characteristics of the intervention and placebo groups were compared using chi-square tests for categorical variables and unpaired *t*-tests for continuous variables. Changes in RBC PUFA composition from pre- to post-intervention were compared within and between intervention groups using paired *t*-tests for within-group comparisons and unpaired *t*-tests for between group comparisons. Within only the intervention group, factors associated with a change in omega-3 were examined for two levels of response: (1) a difference greater than the median response and (2) a difference greater than the 75th percentile response.

Table 1 – Baseline clinical profile of the study population.

	Fish ($n = 40$)	Placebo ($n = 40$)	*P* value
General characteristics			
Age (y)	68 ± 7	69 ± 9	0.41
Male	39 (98)	39 (98)	1.0
Caucasian	27 (68)	31 (78)	0.32
BMI (kg/m)	28 ± 5	27 ± 4	0.17
Index ABI	0.73 ± 0.12	0.71 ± 0.14	0.74
Rutherford			
Mild claudication	10 (25)	10 (25)	0.75
Moderate claudication	10 (25)	12 (30)	
Severe claudication	20 (50)	18 (45)	
Omega Index (%)	5 ± 2	5 ± 1	0.13
Comorbidities			
CAD	13 (33)	22 (55)	**0.04**
Hypertension	38 (95)	35 (88)	0.24
Hyperlipidemia	32 (80)	36 (90)	0.21
Diabetes mellitus	11 (28)	14 (35)	0.47
PAD risk factors			
History of smoking	38 (95)	36 (90)	0.40
Total cholesterol (mg/dL)	175 ± 48	161 ± 37	0.15
Triglycerides (mg/dL)	157 ± 99	150 ± 69	0.71
HDL cholesterol (mg/dL)	45 ± 14	44 ± 12	0.77
LDL cholesterol (mg/dL)	100 ± 42	87 ± 33	0.12
Statin therapy	31 (77.5%)	37 (92.5%)	0.12
HbA1c (%)	6.2 ± 1.0	6.1 ± 1.2	0.85
Vitamin D (ng/mL)	24 ± 11	23 ± 12	0.64
Inflammation			
hsCRP (mg/L)	4.3 ± 4.6	4.2 ± 4.1	0.91
IL-6 (pg/mL)	1.3 ± 0.7	1.4 ± 0.7	0.59
ICAM-1 (ng/mL)	250 ± 77	281 ± 101	0.13
TNF-α (pg/mL)	2.0 ± 0.6	2.3 ± 0.8	0.05
Fibrinogen	389 ± 77	389 ± 105	0.99

Bold value is statistically significant.
ABI = ankle brachial index; HbA1c = hemoglobin A1c; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; ICAM-1 = intercellular adhesion molecule 1; IL-6 = interleukin 6; TNF-α = tumor necrosis factor α.