Oral fish oil supplementation raises blood omega-3 levels and lowers C-reactive protein in haemodialysis patients—a pilot study

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Abstract

Background. We previously reported that haemodialysis patients have suboptimal blood levels of the cardioprotective omega-3 polyunsaturated fatty acids (n-3 PUFA) eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids. In the present pilot study, we tested the hypothesis that supplementing haemodialysis patients for 12 weeks with the American Heart Association (AHA)-recommended fish oil dose would be well tolerated and efficacious in boosting blood n-3 PUFA levels and improving cardiovascular risk biomarkers.

Methods. Twenty-seven subjects were randomized in a 2 : 1 ratio to either 1.3 g of EPA + DHA daily or placebo.

Results. At baseline, 83% of subjects consumed inadequate dietary fish and had the following erythrocyte n-3 PUFA levels (mean ± SD, % weight)—EPA: 0.3 ± 0.2, DHA: 2.9 ± 2.0, and ratio of n-6/n-3 PUFA: 4.2 ± 1.3. Supplementation induced large increases in mean blood EPA and DHA levels (% increase, P-value vs placebo group): erythrocyte—EPA: +400%, P = 0.0018, DHA: +205%, P < 0.0001; plasma—EPA: +275%, P = 0.0003, DHA: +69%, P = 0.0352. Levels in the placebo group remained relatively unchanged. The omega-3 index, a value correlating with the level of cardioprotection, increased significantly in the fish oil group. A reduction in mean C-reactive protein levels (~3.3 ± 8.1 mg/l, P = 0.0282) and a trend towards lower triglyceride levels (~24 ± 74 mg/dl, P = 0.0783) were also observed in the active vs placebo group. Minimal side effects were noted.

Conclusions. Our preliminary observations that the AHA-recommended fish oil dose is well tolerated, efficacious and may improve surrogate markers of cardiovascular disease in haemodialysis patients paves the way for larger clinical trials to confirm a clinical benefit.

Keywords: C-reactive protein; fish oil; haemodialysis; n-3; omega-3; triglyceride

Introduction

Blood levels of the long chain omega-3 polyunsaturated fatty acids (n-3 PUFAs) eicosapentaenoic (20:5n-3 or EPA) and docosahexaenoic (22:6n-3 or DHA) acids, which modulate a host of key physiological processes [1], are dependent primarily on dietary fish consumption. We previously observed that haemodialysis patients consume inadequate amounts of dietary fish and consequently have suboptimal blood n-3 PUFA levels [2]. This is important because preliminary data suggest that n-3 PUFAs may have salutary effects on a number of complications that afflict the haemodialysis population, including dialysis access thrombosis [3], hypertension [4], hypertriglyceridaemia [5] and cardiovascular outcomes [6]. Because of its putative cardiovascular benefits, the American Heart Association (AHA) and various international health organizations now recommend that persons at high cardiovascular risk, such as dialysis patients, consume up to 1 g fish oil daily as well as maintain a dietary ratio of n-6:n-3 PUFA (the ratio of pro-inflammatory fatty acid precursors) as low as 4:1 [7,8].

As reviewed by our group [1], most fish oil supplementation studies in dialysis populations have not examined in a controlled manner the dose–response relationship in blood or biochemical parameters that could be affected by such an intervention, such as coagulation, glycaemic, lipid or inflammatory indices [9]. In addition, supplementation has typically
involved supraphysiological doses of n-3 PUFAs that exceed current recommendations. In part, because of a dearth of quality data, recent National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Clinical Practice Guidelines recommend further study of this area [10].

We hypothesize that supplementing haemodialysis patients with 1.3 g of fish oil daily (i.e. approximate recommended AHA dose) would be efficacious in greatly boosting erythrocyte and plasma fatty acid n-3 PUFA content, reducing levels of inflammatory markers, and not adversely affecting blood coagulation, glycaemic or lipid parameters. We tested this hypothesis in a randomized, placebo-controlled, double-blind pilot study in an urban American chronic haemodialysis population.

Materials and methods

Study population

The study was initiated on April 2006 after obtaining written informed consent from the study participants as well as Institutional Review Board approval from Indiana University Medical Center, the R.L. Roudebush Veterans Affairs Medical Center and Dialysis Center, Inc. (DCI). All subjects were affiliated with Indiana University School of Medicine, Indianapolis, IN, USA, underwent a screening chart review prior to enrolment and were at least 18 years of age. Exclusion criteria included (i) fish oil or omega-3 supplementation in the previous 3 months; (ii) fish, corn, soybean, gelatin or vanilla allergies; (iii) current enrolment in a dietary or drug study; (iv) ongoing active illnesses involving supraphysiological doses of n-3 PUFAs that exceed current recommendations. In part, because of a dearth of quality data, recent National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Clinical Practice Guidelines recommend further study of this area [10].

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Treatment arms

Twenty-seven subjects were randomized to a fish oil or placebo arm in a 2:1 ratio (i.e. 18:9). Subjects consumed either two fish oil or placebo capsules (Ocean Nutrition Canada Ltd., Mulgrave, Nova Scotia, Canada) each day for a 12-week period. Capsules were matched for size, colour, shape and smell. The placebo capsules contained a soybean/corn oil mixture designed to mimic the fat content of the average American diet and avoid perturbation of the n-6:n-3 PUFA ratio. Each fish oil capsule was certified to contain a minimum of EPA 340 mg and DHA 170 mg, with each placebo capsule containing no EPA or DHA. Gas chromatographic analysis of four capsules (two fish oil, two placebo) revealed that the fish oil capsules contained EPA 427 mg, DHA 244 mg, oleic acid 47 mg and arachidonic acid 21 mg, while the placebo capsules contained linoleic acid 543 mg, oleic acid 258 mg, α-linolenic acid 48 mg and undetectable amounts of EPA and DHA. Both forms of capsules also contained a minimum of 2 mg of natural tocopherols as an antioxidant. Participating subjects were requested not to alter their fish consumption during the study. Baseline demographic and background data, including average weekly fish consumption, were collected. A patient survey was completed at 6 and 12 weeks to document tolerability, adverse events and medication regimens.

Laboratory tests

Fasting, pre-dialysis blood samples were drawn from the dialysis tubing of subjects immediately prior to initiating the study and at 12 weeks. International normalized ratio of prothrombin time (INR), partial thromboplastin time (PTT), platelet count, haemoglobin A1C (HbgA1C), fasting glucose, fasting lipid profile (including low-density lipoprotein (LDL) and high-density lipoprotein (HDL)) and serum albumin (albumin) were measured using standard automated laboratory techniques (Beckman Coulter LX 20, Fullerton, CA, USA; Tosoh A1C 2.2 Analyzer, Tokyo, Japan). C-reactive protein (CRP) was measured in triplicate using the Human C-Reactive Protein ELISA Kit (ADI, San Antonio, TX, USA). Oxidized LDL (OxLDL) was also measured in triplicate using the Oxidized LDL ELISA (ALPCO Diagnostics, Salem, NH, USA). Platelet function was quantified using a Platelet Function Analyzer-100 (Dade Behring, Inc., Deerfield, IL, USA) and was reported as abnormal if closure time after exposure to collagen and both epinephrine and adenosine diphosphate was prolonged.

With the exception of the blood sample to assess for platelet function (to prevent platelet activation), all blood samples were immediately placed on ice. Plasma and whole red blood cells (RBCs) were separated by centrifugation within 2 h after collection, washed several times with 0.9% saline and stored at −80°C. Lipids from plasma and RBC were extracted with chloroform/methanol (2:1, v/v) and fatty acid methyl esters (FAME) prepared by derivatization using boron trifluoride (BF3) in methanol (10% w/w, Supelco Inc. Bellefonte, PA, USA) as previously described [11]. FAME were extracted with iso-octane and analysed by a gas chromatograph (Agilent 6890 Plus, autosampler 7683, Chemstation Rev. A.08.03; Agilent Technologies, Inc., Wilmington, DE, USA) equipped with a flame ionization detector and a DB-23 fused silica capillary column (30 m, 0.53 mm i.d., 0.5 μm film thickness; Agilent) using helium as the carrier gas. FAME were identified by comparison of their retention times with authentic standards (Nu-Chek-Prep, Inc., Elysian, MN, USA) and fatty acid values expressed as weight percentages.

Randomization

Randomization was performed by a computer-generated permuted block randomization program. As in previous fish oil studies, fatty acid measurements post-intervention were used to assess adherence [12]. This is an accepted procedure because n-3 PUFA levels can only rise in appreciable amounts in the setting of exogenous consumption, since in vivo synthesis of n-3 PUFAs is very limited [13]. It was noted that in 12 subjects, changes in plasma and erythrocyte n-3 PUFA levels were inconsistent with their group assignment. Subsequent analysis of remaining study capsules confirmed that there was an error in recording to which group these subjects were assigned. However, we were able to confirm group assignment in the original 2:1 randomization ratio in all 23 subjects who completed the study by analysing
content of remaining study capsules and examining changes in both plasma and erythrocyte EPA and DHA levels.

Statistics

No parametric distribution for any of the outcome variables was assumed because of small sample size per group. Wilcoxon exact rank sum test (for continuous outcomes) and Fishers exact test (for categorical outcomes) compared the baseline characteristics as well as other primary and secondary outcomes. Only subjects who completed the study and had both baseline and final measurements were included in the analysis. A \( P \)-value of \(<5\%\) was considered statistically significant. We did not adjust \( P \)-values for multiple comparisons since all the analyses were exploratory in nature. Because this was a pilot study no power calculations were performed, and all findings need to be confirmed in a larger clinical trial. All statistical analyses were performed using SAS software (version 9.1, Cary, NC, USA).

Results

Baseline characteristics

The study’s screening and randomization procedure is presented in Figure 1. Twenty-seven subjects agreed to participate. Three subjects dropped out (one for non-compliance, one because capsules were too large, one moved), and one subject with severe pre-existing cardiac disease died of cardiac arrest. Thus, 23 subjects (15 fish oil and eight placebo) were included in the analyses (though only 14 subjects in the active group had plasma samples available to measure). As shown in Table 1, there were no significant demographic differences between the two study cohorts. Eighty-three percent of the study subjects at baseline did not meet current weekly fish consumption recommendations for individuals at high cardiovascular risk (i.e. at least two weekly servings) [7], a greater proportion than previously reported [2]. Baseline erythrocyte EPA and DHA levels (in weight %) and ratio of n-6/n-3 PUFA (mean \( \pm \) SD) for the combined cohort were \( 0.3 \pm 0.2, 2.9 \pm 2.0 \) and \( 4.2 \pm 1.3 \), respectively. Baseline combined plasma EPA and DHA levels and the ratio of n-6/n-3 PUFA were \( 0.5 \pm 0.4, 1.7 \pm 0.6 \) and \( 4.1 \pm 1.2 \), respectively.

Effects on blood fatty acid content

Fish oil supplementation induced large and statistically significant increases in erythrocyte EPA and DHA levels and reductions in the ratio of n-6/n-3 PUFA (Table 2). In addition, the omega-3 index, defined as the summation of RBC EPA and DHA content and believed to correlate with n-3 PUFA-associated cardio-protection [14], rose by 223% (Table 2, Figures 2 and 3). This index is based on cardiovascular benefits that n-3 PUFAs have provided in major observational and interventional trials. Plasma n-3 PUFA levels increased in a similar, though less dramatic, fashion (Table 3). Interestingly, supplementation was associated with a much more noticeable reduction in saturated (SATs) and monounsaturated (MONOs) fatty acids in erythrocyte membrane than plasma content. In addition, though more n-3 PUFA were available to compete with n-6 PUFA for integration into cell membranes, n-6 PUFA RBC levels in the fish oil group did not fall (see Supplementary Material, which includes complete fatty analyses of the subjects).

Effects on biochemical parameters

Table 4 summarizes the effect of supplementation on various biochemical indices of health status. A significant reduction in mean CRP levels was found in subjects receiving fish oil supplementation,
and the difference remained statistically significant even when the two major outlying values (–23, placebo group and –29 mg/l, fish oil group) were excluded from the analysis. A trend towards lower triglyceride levels was also observed. In fact, fish oil intake reduced the two highest baseline triglyceride levels (530–291 mg/dl and 315–167 mg/dl, respectively) by nearly 50%. Supplementation had no measurable effect on blood coagulation parameters, including platelet function (data not shown), or glycaemic indices and other blood lipid fractions.

**Tolerability, side effects and compliance**

Minor transient gastrointestinal complaints (i.e. nausea and burping) were noted in two subjects in the fish oil group. Compliance rates by capsule counts were 84 ± 19% (range: 46–100%) in the fish oil group and 94 ± 11% (range: 71–100%) in the placebo group.

**Discussion**

In response to mounting evidence that fish oil-derived n-3 PUFAs provide cardioprotective benefits, the American Heart Association recently released formal guidelines recommending daily consumption of 1 g fish oil for persons with established heart disease [7]. This randomized, placebo-controlled pilot study is the first in the dialysis population to rigorously test this supplementation dose for its effects on plasma and RBC PUFA content, safety and tolerability, and clinically relevant biochemical parameters.

Previous n-3 PUFA supplementation studies in dialysis populations have been limited by study design issues as previously reviewed [1]. Furthermore, nearly all such studies used supraphysiological n-3 dosing (i.e. ≥3 gm daily) that far exceed current recommendations and that could theoretically lead to adverse side effects, such as worsened glycaemic control and an increased predilection towards bleeding [9].

Our findings support previous observations that dialysis patients consume inadequate dietary fish and subsequently have suboptimal blood levels of n-3 levels [2]. This being the first interventional dialysis study to simultaneously measure plasma and RBC membrane fatty acid content, we also found that supplementation increased both plasma (reflecting short-term n-3 PUFA consumption) and RBC (reflecting longer-term n-3 PUFA consumption and myocardioocyte content [15]) n-3 PUFA levels while concomitantly improving the ratio of n-6/n-3 PUFA (which reflects the balance of precursor PUFAs for pro- and anti-inflammatory eicosanoids, respectively). Not surprisingly, the omega-3 index, a summation of erythrocyte EPA + DHA levels that correlates with cardioprotection [14], also rose dramatically in the fish oil group (Figure 3). Importantly, this increase moved the treated subjects into a range that has been found to
be cardioprotective in larger studies. The large reductions in saturated and monounsaturated fatty acids seen in erythrocyte, but not plasma, levels, as a result of supplementation is probably due either to preferential uptake of n-3 PUFA by pre-existing RBC membranes and/or simply reflects greater amounts of available n-3 PUFA that could be integrated into the membrane when it was being synthesized. All these changes occurred without any alteration in coagulation or glycaemic parameters.

N-3 PUFA supplementation also appeared to have beneficial effects on two markers of cardiovascular risk. The present investigation is the first randomized study examining the effects of fish oil therapy on CRP levels, an independent predictor of cardiovascular mortality in dialysis [16]. Our data demonstrated that fish oil supplementation reduced plasma CRP levels by approximately 24%, a statistically significant difference compared with the placebo group. Notably, CRP levels were relatively high for a clinically asymptomatic group without acute illness, but did not differ greatly from previous measurements in our population [17]. Fish oil has been found to have mixed effects on inflammatory markers, and a recent meta-analysis did not find it effective in reducing CRP levels [18]. However, this analysis included only a few small studies in healthy subjects. It is conceivable that the established anti-inflammatory effects of n-3 PUFAs [19] may be more easily detected in populations with very elevated baseline CRP levels, such as in the present study. Hypertriglyceridaemia is a component of the dyslipidaemia of kidney disease [20] as well as an established cardiovascular risk factor [21]. The trend we observed towards lower triglyceride levels

### Table 3. Effect of intervention on plasma fatty acid levels

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Fish oil cohort n = 14</th>
<th>Control cohort n = 8</th>
<th>(p^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 weeks</td>
<td>Change</td>
</tr>
<tr>
<td>OMEGA-3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18:3n-3</td>
<td>0.6 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>0.02 ± 0.16</td>
</tr>
<tr>
<td>20:5n-3 (EPA)</td>
<td>0.4 ± 0.4</td>
<td>1.5 ± 0.8</td>
<td>1.1 ± 0.6</td>
</tr>
<tr>
<td>22:5n-3</td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>0.2 ± 0.2</td>
</tr>
<tr>
<td>22:6n-3 (DHA)</td>
<td>1.6 ± 0.6</td>
<td>2.7 ± 1.0</td>
<td>1.0 ± 0.9</td>
</tr>
<tr>
<td>SATs</td>
<td>26.4 ± 1.6</td>
<td>26.4 ± 1.4</td>
<td>0.04 ± 1.73</td>
</tr>
<tr>
<td>MONOs</td>
<td>25.0 ± 3.2</td>
<td>25.1 ± 2.3</td>
<td>−0.8 ± 1.8</td>
</tr>
<tr>
<td>PUFAs</td>
<td>44.4 ± 4.0</td>
<td>45.4 ± 3.2</td>
<td>0.9 ± 3.3</td>
</tr>
<tr>
<td>Ratio of n-6/n-3 PUFA (\gamma)</td>
<td>4.4 ± 1.1</td>
<td>2.3 ± 1.4</td>
<td>−2.2 ± 1.0</td>
</tr>
<tr>
<td>Omega-3 Index (\delta)</td>
<td>2.1 ± 0.9</td>
<td>4.2 ± 1.7</td>
<td>2.1 ± 1.4</td>
</tr>
</tbody>
</table>

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### Table 4. Effects of intervention on biochemical indices

<table>
<thead>
<tr>
<th>Inflammatory markers</th>
<th>Fish oil cohort n = 15</th>
<th>Control cohort n = 8</th>
<th>(p^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Albumin (mg/dl)</td>
<td>3.3 ± 0.2</td>
<td>3.2 ± 0.3</td>
<td>−0.1 ± 0.2</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>13.8 ± 13.8</td>
<td>10.5 ± 12.7</td>
<td>−3.3 ± 8.1</td>
</tr>
<tr>
<td>OXLDL (U/l)</td>
<td>31.6 ± 13.4</td>
<td>29.6 ± 13.3</td>
<td>−2.0 ± 6.9</td>
</tr>
<tr>
<td>Lipids (mg/dl)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>145 ± 40</td>
<td>140 ± 33</td>
<td>−6 ± 33</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>140 ± 127</td>
<td>116 ± 71</td>
<td>−24 ± 74</td>
</tr>
<tr>
<td>LDL</td>
<td>73 ± 32</td>
<td>80 ± 31</td>
<td>7 ± 21</td>
</tr>
<tr>
<td>HDL</td>
<td>43 ± 13</td>
<td>39 ± 12</td>
<td>−3 ± 7</td>
</tr>
<tr>
<td>Glycemic indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1C (%)</td>
<td>5.6 ± 0.8</td>
<td>5.7 ± 0.5</td>
<td>0.1 ± 0.6</td>
</tr>
<tr>
<td>Glucose (mg/dl)</td>
<td>88 ± 13</td>
<td>88 ± 28</td>
<td>0.3 ± 26.4</td>
</tr>
<tr>
<td>Coagulation indices</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (10³/mm³)</td>
<td>217 ± 71</td>
<td>236 ± 78</td>
<td>19 ± 37</td>
</tr>
<tr>
<td>INR</td>
<td>1.1 ± 0.1</td>
<td>1.1 ± 0.3</td>
<td>0.1 ± 0.3</td>
</tr>
<tr>
<td>PTT (sec)</td>
<td>30 ± 4</td>
<td>29 ± 4</td>
<td>−1 ± 2</td>
</tr>
</tbody>
</table>

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\(\gamma\) Mean ± SD weight%.
\(\delta\) Comparison of changes between groups.
\(\gamma\): \(20:4n-6 + 22:4n-6 + 22:5n-6)/(20:5n-3 + 22:5n-3 + 22:6n-3).
\(\delta\): \(20:5n-3 + 22:6n-3).
ND, ≥70% of all data points are undetectable.

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\(a\) Baseline and 12-week values reported as mean ± SD.
\(b\) Comparison of changes between groups.
with fish oil treatment is not surprising, as fish oil, via multiple mechanisms [22], is an accepted therapy for severe hypertriglyceridaemia.

There are a number of limitations to our pilot study. First, the relatively small sample size and short follow-up period restricted statistical power (which could have prevented us from detecting statistically significant differences between groups) and limited our long-term observations on compliance, adverse effects and hard clinical outcomes. The error in recording group allocation in some subjects was an unexpected and unwelcome finding. However, we were able to identify definitively those in the n-3 PUFA group by analysing remaining study capsules and evaluating changes in plasma and erythrocyte EPA, docosapentaenoic acid (DPA, 22:5n-3) and DHA levels. This is an accepted strategy [12] since long-chain n-3 PUFA (i.e. EPA, DPA and DHA) are not synthesized in vivo to any great extent in humans, and thus plasma and blood levels are almost exclusively dependent upon dietary consumption [13]. As expected, there was a stark and obvious difference between changes in n-3 PUFA levels in individuals who had consumed fish oil and those who had not. Finally, there was an imbalance between n-3 PUFA levels at baseline between the two groups, but this is not surprising given the small size and pilot nature of this study and should not have affected our results.

In summary, this randomized controlled short-term pilot study found that the AHA-recommended fish oil supplementation dose is well tolerated and effective in boosting blood n-3 PUFA levels in long-term haemodialysis patients and is associated with improving surrogate markers of cardiovascular disease including lower CRP values and a trend towards lower triglyceride levels. Further investigation is required to better define the long-term impact of fish oil supplementation in this high-risk population.

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**Conflict of interest statement.** None declared.

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