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Evaluating the Effects of Prescription Fish Oil, Supplemental Fish Oil and a Krill Oil Blend on Serum Lipids/Lipoproteins and the Omega-3 Index: A Pilot Study

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Abstract

Numerous preparations containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are commercially available. We examined changes in serum lipids/lipoproteins and the omega-3 index with various EPA/DHA formulations. Dyslipidemic subjects (N=10/arm) were randomized to daily doses of prescription fish oil (3360 mg EPA+DHA), supplemental fish oil (3340 mg EPA+DHA) or a krill oil blend (960 mg EPA+DHA); in a 6-week, open-label trial. The fish oil preparations produced significant ($p<0.05$) and comparable reductions in triglycerides (~25%); whereas the krill oil blend (KOB) resulted in a modest increase. Other lipoprotein changes were similar across treatments. The fish oil products each produced similar elevations in the omega-3 index, and more than the KOB, although all agents produced significant changes from baseline. When evaluated per gram of EPA+DHA dosed, the KOB increased the omega-3 index 2-fold more than the fish oil groups.Overall, the fish oil preparations provided comparable and favorable changes in triglycerides and the omega-3 index, which were significantly greater than those observed with the KOB.

Keywords: Omega-3 fatty acids; Eicosapentaenoic acid; Docosahexaenoic acid; Krill oil; Serum lipoproteins; Red blood cell membranes; Omega-3 index

Abbreviations and Symbols: CHD: Coronary Heart Disease; CVD: Cardiovascular Disease; DHA: Docosahexaenoic acid; EPA: Eicosapentaenoic acid; FA: Fatty Acid; GI: Gastrointestinal; HDL-C : High Density Lipoprotein Cholesterol; LDL-C: Low Density Lipoprotein Cholesterol; RBC: Red Blood Cell

Introduction

The consumption of the omega-3 fatty acids (FA), eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have demonstrated numerous health benefits including lower rates of cardiovascular disease (CVD) [1]. Common sources of EPA+DHA include fish oil and krill oil. Fish oil is extensively utilized and available as a nutritional supplement or prescription. Krill oil (*Euphausiasuperba*) is another supplemental source but the EPA+DHA content is markedly less per serving compared to fish oil. Fatty acid form is also a key factor differentiating these agents. In fish oil,omega-3 FA are present as triglycerides, whereas in krill oil, 30-65% of theseFA are incorporated in phospholipids [2]. In most prescription products, omega-3 FA are provided as ethyl esters. Previous data have suggested phospholipids are more efficient at delivering EPA+DHA,[3,4] and ethyl esters can be poorly absorbed if taken without food [5]. This difference in chemical for may therefore impact the absorption and bioavailability of the EPA+DHA, and potentially the subsequent cardioprotective effects of these products.

The primary effect of fish oil derived EPA+DHA on the lipid panel is triglyceride reduction [1]. This dose-dependent response can produce a 20-50% decrease in triglycerides with up to 4 grams of EPA+DHA daily, whereas modest increases in high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) are generally observed [1,6]. Conversely, the impact of krill oil or a krill oil blend (KOB) on lipid parameters has not been comprehensively evaluated.

The omega-3 index is inversely related to coronary heart disease (CHD) risk [7]. This biomarker measures the EPA+DHA content in red blood cell (RBC) membranes as a percentage of total FA. Based on epidemiological and randomized controlled trial data, an omega-3 index of <4% is considered high risk, 4-8% moderate risk, and >8% is low risk, for CHD mortality in adults [8].

Numerous studies have established the effects of fish oil on lipids and lipoproteins, but few data are available directly examining supplemental and prescription agents or evaluating a KOB. To our knowledge, no studies have been performed comparing these commonly available forms - prescription fish oil, supplemental fish oil and a KOB; or directly compared supplemental to prescription fish oil. The primary aim of our pilot study was to examine the three commonly utilized omega-3 preparations on major lipids/lipoproteins and the omega-3 index. Secondary analyses were performed evaluating major parameters per gram of EPA+DHA dosed. Our findings indicate that prescription and supplemental fish oil produced comparable effects on triglyceride reduction and elevations in the omega-3 index, which was significantly greater than that observed with the KOB. However, our secondary analysis suggested an efficient incorporation of EPA/DHA with the KOB.

Material and Methods

This was a 6-week, single-site, three arm, open-label, parallel design pilot study. Thirty subjects (N=10/arm) were randomized to daily doses of a prescription ethyl ester product (Lovaza® - 3360 mg EPA+DHA), a fish oil supplement (Spring Valley® - 3340 mg EPA+DHA) or a KOB

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(Arctic Pure® - 960 mg EPA+DHA), for 6 weeks. Fasting blood samples were drawn at visit 1 (baseline) and visit 2 (week 6). Subjects were instructed to take each dose with food and to maintain their current dietary habits. Agastrointestinal (GI) questionnaire was administered to subjects at baseline and end of study [9]. Adherence was determined at visit 2 by pill count, and subjects with a >20% non-adherence rate were excluded from data analyses. The study was approved by the University of Kansas Medical Center institutional review board.

Adult subjects with triglycerides of 120-300 mg/dL, and between the ages of 18 and 80 years, were eligible for enrollment. Key exclusion criteria included chronic renal, GI, endocrine, or hepatic disease, previous sensitivity to seafood or fish oil, currently receiving lipid-altering agents, current or recent use of omega-3 supplements, or the consumption of ≥2 oily fish meals weekly.

Table 1 contains detailed product information. The specific supplemental fish oil and KOB agents were selected because of reviews by Consumer Labs® indicating "passing" for claimed amounts of omega-3 FA [10]. We had additional analyses performed by Consumer Labs® on the actual KOB study product; indicating an overall testing score of "pass" for multiple evaluations. This product, similar to many marketed krill oil preparations, also contained a lesser amount of fish oil; thereby we termed it a "krill oil blend". The manufacturer reported a fish oil content of 30-48% and krill oil of 50-65%; an analysis in our laboratory indicated that, of the total EPA+DHA present, 47% was in phospholipids, 22% in triglycerides and 30% were non-esterified (i.e., free FA). By comparison, the EPA+DHA distribution in pure krill oil (e.g., Superba®, Aker Biomarine Antarctic) was 74%, 14% and 10%, respectively. Study doses - our intent for the fish oil arms was to provide comparable EPA+DHA between agents, and utilize the FDA approved dose of prescription omega-3 acid ethyl esters (3340 mg EPA+DHA/day). For the KOB, our goal was to provide ~30% of the EPA+DHA intake to that of fish oil, without excessive pill burden (>8 caps).

Laboratory analyses

The method for determining the omega-3 index was previously described in detail by Harris et al. [11] Lipoprotein and lipid measurements including total cholesterol, triglycerides, LDL-C (direct), HDL-C, and non-HDL-C, and the omega-3 index, were collected at visits 1 and 2 under fasting conditions.

Statistical analysis

Statistical Analysis Software 9.2 was used for all statistical procedures. Baseline comparisons of quantitative variables between groups were analyzed with non-parametric, 2-sided *t*-tests and categorical variables by Chi-Square tests. Group differences in change scores were determined using linear mixed models and normality was determined using the model residuals. Covariates that were tested were age, sex and race, but they did not change outcomes. Data is presented as least squared means and standard error of the mean.

Study product	Daily study dose	Daily EPA dose	Daily DHA dose	Daily EPA+DHA dose
[a]Prescription fish oil	2 caps twice daily (4.0 g oil)	1860 mg	1500 mg	3360 mg
[b]Supplemental fish oil	[c]2 caps twice daily (5.6 g oil)	2588 mg	1012 mg	3340 mg
[c]Krill oil blend	4 caps twice daily (4.0 g oil)	600 mg	360 mg	960 mg

[a]Omega-3 fatty acids provided as ethyl esters
[b]One cap was omitted twice weekly in unit-dose packaging to provide a comparable weekly amount of EPA+DHA to prescription fish oil
[c]Also provided 6 mg astaxanthin daily; manufacturer reported 50-65% krill oil + 30-48% fish oil
DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Table 1: Content of the omega-3 fatty acid study products.

Results

A total of 30 subjects completed the study. Baseline characteristics were similar among groups, except baseline triglycerides were higher in the prescription fish oil group (Table 2). Based on total doses, the fish oil preparations produced comparable and significant reductions in triglycerides; whereas the KOB caused a modest increase (Table 3). No significant differences in other lipoproteins were observed between groups; including each treatment producing modest increases in LDL-C and HDL-C concentrations. When analyzed per gram of EPA/DHA consumed, the KOB produced a greater increase in LDL-C compared to supplemental fish oil, and a notable HDL-C increase of 8%, but overall changes were comparable to the fish oil products.

All products significantly increased the omega-3 index and reduced omega-6 FA from baseline (Table 4). The increase in the omega-3 index was similar between the prescription and supplemental fish oil products, and these were significantly more than the KOB (Table 4). On a per gram of EPA+DHA basis, the KOB increased the omega-3 index approximately 2-fold more (55%) than prescription or supplemental fish oil (26%), while no differences were noted between the latter two groups(Table 5).

No major adverse events were reported. Overall, GI complaints were minimal and considered mild to moderate. Although not statistically significant, subjects receiving the supplemental fish oil and KOB did complain of fishy aftertaste, and more belching symptoms were noted with the supplemental fish oil compared to prescription fish oil.

Discussion

The primary impact from the EPA+DHA preparations on the lipid profile were the favorable and comparable triglyceride reductions noted for the fish oil groups; whereas the KOB produced a modest increase (Table 3). No other clinically relevant changes between groups were observed when evaluating total doses. Since the EPA+DHA content are markedly less per serving with the KOB, we also analyzed changes per gram of omega-3 FA intake (Table 3). This approach resulted in the KOB significantly increasing LDL-C compared to supplemental fish oil and a moderate but insignificant increase in HDL-C compared to the fish oil products.

For triglyceride reduction, doses>2000 mg/day of EPA+DHA are generally required [1]. This threshold was met with each of the fish oil agents (~3350 mg); however the KOB provided only 960 mg/day. The present study suggests our krill oil product may exhibit greater bioavailability compared to fish oil (per gram EPA+DHA omega-3 index analysis). Nonetheless, the requisite EPA+DHA for triglyceride lowering may still have been insufficient, thereby limiting the impact of the KOB on this parameter. Previous studies using pure krill oil indicates modest triglyceride reductions of ~5-10% [12-14].

Earlier data have suggested krill oil produces a 2-3 fold greater increase (e.g. 9% vs. 3%) in HDL-C compared to fish oil [12,13]. In the present study, HDL-C increases were similar across treatments with total doses. This comparable effect may be explained by the triglyceride reduction with the fish oil products and the resultant HDL-C increase. When evaluated per gram of EPA+DHA dosed, the KOB produced an 8% increase in HDL-C compared to smaller increases in the fish oil groups. A possible explanation involves the presence of astaxanthin (carotenoid) and higher amounts of phospholipids in the KOB, each

Parameter, mean (SD)	Arm 1 Prescription Fish Oil (N = 10)	Arm 2 Supplemental Fish Oil (N =10)	Arm 3 Krill Oil Blend (N = 10)
Age (years)	41 ± 13	45 ± 14	51 ± 11
Gender			
Female	6	5	8
Male	4	5	2
Race			
White	8	9	7
Black	0	1	2
Other	2	0	1
Weight (kg)	82.9 ± 7.5	76.6 ± 9.7	79.0 ± 15.4
Body mass index (kg/m^2)	29.3 ± 3.1	26.8 ± 3.4	27.5 ± 4.1
Waist circumference (cm)	94.0 ± 7.3	89.0 ± 9.1	89.7 ± 10.4
Blood pressure, mm Hg	123 ± 16	122 ± 15	134 ± 20
Systolic	80 ± 11	77 ± 8	85 ± 14
Diastolic			
Omega-3 index (%)	4.1 ± 1.3	4.3 ± 1.6	4.4 ± 1.1
Lipoproteins (mg/dl)			
Total cholesterol	232 ± 48	222 ± 49	227 ± 59
Triglycerides*	213 ± 79[a]	149 ± 34	156 ± 38
HDL-C	56 ± 17	56 ± 18	51 ± 12
LDL-C	129 ± 41	128 ± 41	140 ± 52
Non-HDL-C	175 ± 48	166 ± 49	176 ± 56

No significant differences between groups except triglyceride concentrations (non-parametric, ANOVA 2-way comparison)
*Group means different at baseline (p≤0.05)
[a]Outlier removed for analysis
HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Table 2: Baseline subject characteristics of study groups.

Parameter	Prescription Fish Oil 3360 mg EPA+DHA	Supplemental Fish Oil 3340 mg EPA+DHA	Krill Oil Blend 960 mg EPA+DHA	Group P-value
Total cholesterol				
% Δ overall	3 ± 3	0 ± 3	4 ± 3	0.90
% Δ per gram EPA+DHA	1 ± 2	0 ± 2	4 ± 2	0.59
Low-density lipoprotein cholesterol				
% Δ overall	11 ± 4	2 ± 4	9 ± 4	0.56
% Δ per gram EPA+DHA	3 ± 2	1 ± 2*	8 ± 2	0.35
High-density lipoprotein cholesterol				
% Δ overall	7 ± 4	8 ± 4	7 ± 4	0.97
% Δ per gram EPA+DHA	2 ± 2	2 ± 2	8 ± 2	0.09
Triglycerides				
% Δ overall	-24 ± 8*[Ia]	-28 ± 7*[I]	2 ± 7	0.01[a]
% Δ per gram EPA+DHA	-7 ± 5[a]	-9 ± 4	3 ± 4	0.09[a]
Non-high-density lipoprotein cholesterol				
% Δ overall	1 ± 4	-2 ± 4	3 ± 4	0.84
% Δ per gram EPA+DHA	1 ± 3	-1 ± 3	3 ± 3	0.72

*Different than krill oil blend (p<0.05)
[I]Different from baseline (p<0.05)
[a]Outlier removed for analysis.
DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Table 3: Lipoprotein changes of the omega-3 preparations (LS Means ± SEM).

with known HDL-C increasing properties [13,15].

We primarily analyzed changes in the omega-3 index with total doses consumed (Table 4).The higher doses from the fish oil groups produced similar and significantly greater overall increases in the omega-3 index and EPA plasma concentrations compared to the KOB, whereas no differences in DHA levels were observed between groups. This provides novel findings as the cardioprotection derived from the EPA/DHA was comparable between the prescription and the supplemental fish oil. In contrast, the KOB did not produce a comparable increase in the omega-3 index to the fish oil given at >3x the total dose. Although, we must consider our KOB contained between 30-48% fish oil (of unknown omega-3 content); suggesting that perhaps an exclusively krill oil product may have produced greater changes in measured parameters.

Our data indicate that both prescription and supplemental fish oil were comparable at increasing the omega-3 index, and superior to a KOB when the daily EPA+DHA intake is >3-fold. We are not aware of other studies demonstrating similar effects on the omega-3 index with supplemental and prescription fish oil. When analyzed per gram (EPA+DHA), the KOB suggested efficiency at incorporating into RBC. These later findings are consistent with data from other studies. Ulven et al. [13] compared plasma EPA+DHA concentrations when subjects were randomized to krill oil or fish oil. Although those in the krill oil group received a lower daily dose of EPA+DHA (543 mg) compared to subjects receiving fish oil (864 mg), the increase in omega-3 FA was comparable. Similarly, Maki et al. [12] examined the same question in overweight and obese adults. After 4 weeks of treatment the increase in plasma EPA was greater with krill oil while DHA levels were similar between groups. Another study initially reported greater increases in omega-3 FA with krill oil compared to fish oil, [4] but a subsequent commentary questioned their results [16].

Clinical Application

The findings from our pilot study require additional examination in larger randomized controlled trials using a longer study period. Despite this, our data and previous studies provide some insight on appropriate utilization of the various omega-3 preparations in clinical practice. The two major uses of these products in the cardiovascular arena are for cardio protection and triglyceride reduction [1]. The supplemental and prescription fish oil products in the present study provided comparable triglyceride reductions and elevations in the omega-3 index, with minimal adverse effects. Choosing between prescription and supplemental fish oil is a common clinical dilemma but minimal data are available to inform the question. The present study indicates the two products produced comparable clinical effects, and in certain clinical circumstances may be interchangeable. If supplemental agents are substituted for prescription products, therapeutic monitoring (e.g. triglyceride concentrations) is warranted. However, given the numerous supplemental fish oil products available, possible variability between batches, and lack of FDA oversight, therapeutic equivalence between prescription and supplemental fish oil cannot be stated.

Similar to previous data evaluating krill oil, [12,13] the KOB yielded no triglyceride reduction in the present study, which may be a result of insufficient dosing. However, utilizing higher doses, given the low omega-3 content per serving, may not be practical. For instance, in the present study, eight capsules were needed to obtain 960 mg of EPA+DHA (120 mg/cap). Thus, a triglyceride lowering dose would likely require several more capsules. Such a dose would likely pose a pill burden to the patient. Conversely, krill oil may be an alternative to fish oil for increasing the omega-3 index and the associated cardioprotective effects. Our secondary analysis, per gram of EPA+DHA dosing, suggests a 2-fold greater increase in this biomarker with a KOB compared to fish oil. However, these findings must be interpreted with caution as comparable doses were not utilized and key pharmacokinetic parameters impacting EPA/DHA absorption

Variable (%)	Prescription Fish Oil (3360 mg)	Supplemental Fish Oil (3340 mg)	Krill Oil Blend (960 mg)	Group P-value
	PrePost Change	*Pre Post Change*	*Pre PostChange*	
Omega-3 Index	4.1 ± 1.3 7.3 ± 1.23.2 ± 0.9*,i	4.3 ± 1.67.6 ± 1.73.3 ± 0.8*,i	4.4 ± 1.26.5 ± 1.42.2 ± 1.0i	0.01
EPA	0.4 ± 0.192.0 ± 0.51.6 ± 0.5*,i	0.5 ± 0.32.5 ± 0.62.1 ± 0.5*,i	0.4 ± 0.21.4 ± 0.41.0 ± 0.4i	<0.0001
DHA	3.7 ± 1.1 5.3 ± 0.81.7 ± 0.7i	3.8 ± 1.45.1 ± 1.11.3 ± 0.5i	3.9 ± 1.05.1 ± 1.11.2 ± 0.7i	0.23
Total Omega-6	35.4 ± 1.0 31.4 ± 1.3-4.1 ± 1.0i	34.5 ± 2.330.9 ± 1.5-3.6 ± 1.3i	34.7 ± 2.731.9 ± 2.5-2.8 ± 1.2i	0.07
Arachidonic acid	15.5 ± 1.013.5 ± 1.1-1.9 ± 0.8*,i	15.4 ± 1.414.0 ± 1.2-1.4 ± 0.5i	15.0 ± 1.414.1 ± 1.6-1.0 ± 1.0i	0.04

*Change score different than krill oil blend (Tukey-adjusted p<0.05)
iDifferent from baseline (p<0.05)
DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Table 4: Overall effect on selected red blood cell fatty acids of three omega-3 products (LS means ± SEM).

Variable	Prescription Fish Oil	Supplemental Fish Oil	Krill Oil Blend	Group P-value
	Percent change per gram EPA+DHA (LS Mean ± SEM)			
Omega-3 Index (%)	26 ± 5%*	26 ± 5%*	55 ± 5%	0.003
EPA (%)	121 ± 23%*	165 ± 23%*	250 ± 22%	0.013
DHA (%)	16 ± 4%*	12 ± 4%*	35 ± 4%	0.004
Total Omega-6 (%)	-3 ± 1%*	-3 ± 1%*	-9 ± 1%	<0.0001
Arachidonic Acid (%)	-4 ± 1%	-3 ± 1%	-7 ± 1%	0.08

*Different than krill oil blend (Tukey-adjusted p<0.05)
DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid

Table 5: Percent change per gram intake of EPA+DHA/day, while controlling for baseline (LS Means ± SEM).

may not be linear. The amount of krill oil based EPA+DHA required to achieve an optimal omega-3 index should be a focus of future study.

The limitations to our study include the small sample size, open-label design and short duration. More importantly, the krill oil product we used was a blend of fish oil and krill oil which may not represent the effects of pure krill oil; but, from an informal review of available products, likely represents a substantial portion of what consumers are utilizing.

Conclusion

To summarize, we found that supplemental and prescription fish oil produced comparable reductions in triglycerides and increases in the omega-3 index; both of which were greater than a KOB. When evaluated per gram of EPA+DHA consumed, the KOB provided an efficient increase in the omega-3 index. Future studies should be designed to directly compare common EPA/DHA preparations, including a pure krill oil product, and enroll a larger study population with a longer duration. Presently, the appropriate utilization of prescription and supplemental fish oil for cardiovascular effects include triglyceride reduction and increasing the omega-3 index. Conversely, few data support the use of krill oil for triglyceride reduction; however products studied, including a KOB, have effectively increased the omega-3 index.

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Conflicts of Interest

Dr. Backes: Research grant-Kowa Pharmaceuticals; Speakers bureau-Kowa Pharmaceuticals, Astra Zeneca, Abbvie, and Sanofi

Dr. Ruisinger: Research grant-Kowa Pharmaceuticals

Dr. K. Harris:Employee-OmegaQuant

Dr. C. Gibson: None

Dr. W. Harris:Employee – HDLab; Ownership interest – OmegaQuant; Consultant/Advisory board – Aker Biomarine, Omthera, Amarin

Dr. Moriarty:Research grant – Amgen, Kowa Pharmaceuticals, Lilly USA, Novartis Pharmaceuticals, Bejing Peking University WBL Biotech Co. LTD, Sanofi-Aventis; Speakers bureau–Amarin; Consultant/Advisory board – Sanofi-Aventis

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