Evaluation of the Effects of Neptune Krill Oil on the Clinical Course of Hyperlipidemia

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Abstract

OBJECTIVE: To assess the effects of krill oil on blood lipids, specifically total cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). METHODS: A multi-center, three-month, prospective, randomized study followed by a three-month, controlled follow-up of patients treated with 1 g and 1.5 g krill oil daily. Patients with hyperlipidemia able to maintain a healthy diet and with blood cholesterol levels between 194 and 348 mg/dL were eligible for enrollment in the trial. A sample size of 120 patients (30 patients/group) was randomly assigned to one of four groups. Group A received krill oil at a body mass index (BMI)-dependent daily dosage of 2-3 g daily. Patients in Group B were given 1-1.5 g krill oil daily, and Group C was given fish oil containing 180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA) per gram of oil at a dose of 3 g daily. Group D was given a placebo containing microcrystalline cellulose. The krill oil used in this study was Neptune Krill Oil (NKO®), provided by Neptune Technologies & Bioresources, Laval, Quebec, Canada. OUTCOME MEASURES: Primary parameters tested (baseline and 90-day visit) were total blood cholesterol, triglycerides, LDL, HDL, and glucose. RESULTS: Krill oil 1-3 g/day (BMI-dependent) was found to be effective for the reduction of glucose, total cholesterol, triglycerides, LDL, and HDL, compared to both fish oil and placebo. CONCLUSIONS: The results of the present study demonstrate within high levels of confidence that krill oil is effective for the management of hyperlipidemia by significantly reducing total cholesterol, LDL, and triglycerides, and increasing HDL levels. At lower and equal doses, krill oil was significantly more effective than fish oil for the reduction of glucose, triglycerides, and LDL levels.

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Introduction

The balance of polyunsaturated essential fatty acids (PUFAs) in the body is critical for the maintenance of healthy cell membranes and hormone regulation. During the last few decades the fatty acid content of the U.S. diet has shifted so it now contains much higher levels of omega-6 and less omega-3 fatty acids. When long-chain omega-6 fatty acids predominate in the phospholipids of cell membranes, the production of pro-inflammatory type-2 prostaglandins (PGs) and type-4 leukotrienes (LTs) are encouraged; whereas, the presence of omega-3 fatty acids promotes the production of anti-inflammatory PGs and LTs.[1,2]

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Omega-6 fatty acids, mainly arachidonic acid, have been shown to initiate an inflammatory process by triggering a flux of inflammatory PGs and LTs.[3,4] Omega-3 fatty acids, mainly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), compete with the omega-6 species for the enzyme prostaglandin synthetase. Omega-3 fatty acids trigger secretion of less potent 5-series LTs and anti-inflammatory PGs of the 3 series (PE_3, PI_3 and thromboxanes-A_3).[4-9] Consequently, supplementation with EPA and DHA promotes the production of less potent PGs and LTs, resulting in a decrease in the formation of inflammatory mediators.[10-13]

The exact mechanism of action by which omega-3 fatty acids favorably modify cardiovascular disease and associated disorders is not yet fully confirmed. Evidence suggests an increased intake of EPA and DHA results in an increase of EPA and DHA in tissue, cellular lipids, and circulatory lipids.[14] In parallel, they result in a simultaneous reduction of omega-6 fatty acids in the body.[14] This fatty acid shift is predominantly marked in cell membrane-bound phospholipids and results in alteration of the physicochemical properties of cell membranes. This favorably modifies cellular functions, including cell signaling, gene expression, biosynthetic processes, and eicosanoid formation.[15]

Human studies have revealed the ability of EPA and DHA to significantly reduce circulating levels of blood triglyceride and very low-density lipoprotein (VLDL), which have been associated with increased risk of cardiovascular disease.[16,17]

Krill oil is extracted from Antarctic krill, *Euphausia superba*, a zooplankton crustacean rich in phospholipids carrying long-chain omega-3 PUFAs, mainly EPA and DHA. Krill oil also contains various potent antioxidants, including vitamins A and E, astaxanthin, and a novel flavonoid similar to 6,8-di-c-glucosylluteolin, but with two or more glucose molecules and one aglycone.

Krill oil has a unique biomolecular profile of phospholipids naturally rich in omega-3 fatty acids and diverse antioxidants significantly different from the usual profile of fish oils. The association between phospholipids and long-chain omega-3 fatty acids highly facilitates the passage of fatty acid molecules through the intestinal wall, increasing bioavailability and ultimately improving the omega-3:omega-6 fatty acid ratio.[18,19]

Materials and Methods

A 12-week, double-blind, randomized trial was conducted comparing krill oil to high EPA and DHA (3:2 ratio) fish oil and placebo. Eligible patients were 18-85 years and had at least a six-month diagnosis of mildly high to very high blood cholesterol (193.9-347.9 mg/dL) and triglyceride levels (203.8-354.4 mg/dL). Patients with familial hypercholesterolemia, severely high cholesterol (>349 mg/dL), pregnancy, known or suspected allergy to fish or seafood, known alcohol or drug abuse within the previous year, known coagulopathy or receiving anticoagulant therapy, or co-morbidity that would interfere with study results were excluded from the study.

Enrolled patients were randomly assigned to one of four groups:

▲ Group A: Krill oil (2-3 g once daily)
Body Mass Index (BMI) < 30 – 2 g/day
BMI > 30 – 3 g/day

▲ Group B: Krill oil (1-1.5 g once daily)
BMI < 30 – 1 g/day
BMI > 30 – 1.5 g/day
Follow-up 500 mg/day for 90 days

▲ Group C: Fish oil (3:2) containing 180 mg EPA and 120 mg DHA per gram (3 g once daily)

▲ Group D: placebo (3 g once daily)

Patients were allowed to continue lipid-lowering medications at the usual daily dose and asked to report any change in dosage. Natural health products were discontinued for a two-week washout period prior to study initiation and thereafter for the study duration. Patients were asked to record concomitant medications taken daily.

Table 1. Results of Krill Oil (1.0 g/day) on Lipids

1.0 g Krill Oil	Time (d)/mg/dL		% Change	p-value
	0.00	90.00		
Total Cholesterol	235.83	204.12	-13.44%	0.000
LDL	167.78	114.05	-32.03%	0.000
HDL	57.22	82.35	43.92%	0.000
Triglycerides	120.50	107.21	-11.03%	0.114

Table 2. Results of Krill Oil (1.5 g/day) on Lipids

1.5 g Krill Oil	Time (d)/mg/dL		% Change	p-value
	0.00	90.00		
Total Cholesterol	231.19	199.49	-13.71%	0.000
LDL	164.74	105.93	-35.70%	0.000
HDL	58.76	83.89	42.76%	0.000
Triglycerides	126.70	111.64	-11.89%	0.113

The primary parameters tested were blood glucose, cholesterol, triglycerides, low-density lipoprotein (LDL), and high-density lipoprotein (HDL). Fasting blood lipids and glucose were analyzed at baseline as well as 30 and 90 days after study initiation for all groups, and at 180 days for the 30 patients in Group B.

Statistical Rationale and Analysis

A sample size of 120 patients (30 patients/group) provided 90-percent power to detect a 15-percent change in total cholesterol from baseline to three months.

Within-group differences reflecting changes over time for the same patient were assessed for statistical significance with the Paired Student's t-test. Between-group differences were assessed with planned comparisons of one-way analysis of variance.

Results

One-hundred-twenty patients with a mean age of 51 years (standard deviation 9.46) and ranging between 25 and 75 years were enrolled in the trial. BMI, a tool indicating weight status in adults, was calculated according to the metric formula ([weight in kilograms/(height in centimeters) x (height in centimeters)] x 10,000).[20,21] Of the 120 patients enrolled, 30 (25%) had moderate-to-severe obesity, with a BMI higher than 30. Sixty-four (53%) subjects were overweight, and 26 (22%) were normal weight, with a BMI between 25 and 30 and lower than 25, respectively. Women had a higher

mean BMI (28.2±5.1) compared to men (25.4±3.9) ($p<0.001$).

Among the 60 patients in the two groups receiving krill oil, 42 (70%) had a BMI of 30 or less. In Group A, 19 patients received 2 g krill oil daily and the remaining 11 received 3 g daily. In Group B, 23 patients were treated with a daily dose of 1 g krill oil and 7 with 1.5 g. All patients in Group B continued for an additional 90 days with a maintenance dose of 500 mg krill oil daily.

Baseline analysis of demographic criteria, laboratory data including total cholesterol and triglyceride levels, comorbidity, and concomitant medication at baseline showed no significant differences among the four groups (p=0.102-0.850).

Table 3. Results of Krill Oil (2.0 g/day) on Lipids

2 g Krill Oil	Time (d)/mg/dL		% Change	p-value
	0.00	90.00		
Total Cholesterol	247.42	202.58	-18.13%	0.000
LDL	182.86	114.43	-37.42%	0.000
HDL	51.03	79.25	55.30%	0.000
Triglycerides	160.37	116.07	-27.62%	0.025

Table 4. Results of Krill Oil (3.0 g/day) on Lipids

3 g Krill Oil	Time (d)/mg/dL		% Change	p-value
	0.00	90.00		
Total Cholesterol	250.52	205.67	-17.90%	0.000
LDL	172.81	105.16	-39.15%	0.000
HDL	64.18	102.45	59.64%	0.000
Triglycerides	152.77	112.27	-26.51%	0.028

After 12 weeks of treatment, patients receiving 1 or 1.5 g krill oil daily had a 13.4-percent and 13.7-percent decrease in mean total cholesterol, from 236 mg/dL and 231 mg/dL to 204 mg/dL (p=0.000) and 199 mg/dL (p=0.000), respectively (Tables 1 and 2). The group of patients treated with 2 or 3 g krill oil showed a significant respective reduction in mean total cholesterol of 18.1 and 18 percent. Levels were reduced from a baseline of 247 mg/dL and 251 mg/dL to 203 mg/dL (p=0.000) and 206 mg/dL (p=0.000), correspondingly (Tables 3 and 4). In comparison, people receiving 3 g fish oil had a mean reduction in total cholesterol of 5.9 percent, from a baseline 231 mg/dL to 218 mg/dL (p=0.000) (Table 5). Those enrolled in the placebo group showed a 9.1-percent increase in mean total cholesterol, from 222 mg/dL to 242 mg/dL (p=0.000) (Table 6).

Table 5. Results of Fish Oil (3.0 g/day) on Lipids

3 g Fish Oil	Time (d)/mg/dL		% Change	p-value
	0.00	90.00		
Total Cholesterol	231.15	217.55	-5.88%	0
LDL	121.67	117.83	-4.56%	0.141
HDL	56.64	59.03	4.22%	0.002
Triglycerides	140.87	136.44	-3.15%	0.239

Table 6. Results of Placebo on Lipids

Placebo	Time (d)/mg/dL		% Change	p-value
	0.00	90.00		
Total Cholesterol	221.91	242.01	9.06%	0.000
LDL	136.47	154.25	13.03%	0.000
HDL	56.83	56.70	4.00%	0.850
Triglycerides	143.53	129.36	-9.88%	0.215

An analogous effect on LDL levels was observed in all groups. Krill oil at a daily dose of 1 g, 1.5 g, 2 g, or 3 g achieved significant reductions of LDL of 32, 36, 37, and 39 percent, respectively (p=0.000). Baseline levels were decreased in the krill oil 1-g/day group from 168 mg/dL to 114 mg/dL, in the 1.5-g/day group from 165 mg/dL to 106 mg/dL, and in the 2- and 3-g/day groups from 183 mg/dL and 173 mg/dL to 114 mg/dL and 105 mg/dL, respectively. The laboratory results of patients treated daily with 3 g fish oil did not achieve a significant reduction in LDL (4.6%), with blood levels decreased from 122 mg/dL at baseline to 118 mg/dL (p=0.141) after 12 weeks. Patients receiving placebo showed a negative effect, with a 13-percent increase in LDL levels, from 137 mg/dL to 154 mg/dL (p=0.000).

HDL was significantly increased in all patients receiving krill oil (p=0.000) or fish oil (p=0.002). HDL levels increased from 57.2 mg/dL to 82.4 mg/dL (44% change) at krill oil 1 g/day; 58.8 mg/dL to 83.9 mg/dL (43% increase) for krill oil 1.5 g/day; 51 mg/dL to 79.3 mg/dL (55% increase) at krill oil 2 g/day; and from 64.2 mg/dL to 102.5 mg/dL (59% increase) at a daily krill oil dose of 3 g. Fish oil taken at 3 g/day increased HDL from 56.6 mg/dL to 59.03 mg/dL (4.2% increase). No significant decrease of HDL (p=0.850) was observed within the placebo group, with levels of HDL remaining almost stable, 56.8 mg/dL to 56.7 mg/dL.

Krill oil taken 1 g/day reduced blood triglycerides by a non-significant 11 percent, from 120.5 mg/dL to 107.2 mg/dL (p=0.114). A daily dose of 1.5 g krill oil resulted in a non-significant

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