Original Research

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

Roxandra Bunea M.D.[1], Khassan El Farrah M.D., M.Sc.[2], Luisa Deutsch M.D., M.Sc.[2]

1. Assistant Professor, Department of Internal Medicine, McGill University; Riverview Medical Center, Montreal, Quebec, Canada.

2. JSS Medical Research, Montreal, Quebec, Canada.

Altern Med Rev 2004;9(4):420-428

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

Ruxandra Bunea, MD; Khassan El Farrah, MD, MSc; Luisa Deutsch, MD

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.

(*Altern Med Rev* 2004;9(4):420-428)

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]

Ruxandra Bunea, MD – Assistant Professor, Department of Internal Medicine, McGill University; Riverview Medical Center, Montreal, Quebec, Canada.
Correspondence address: 1586 Ave des Pins O. #302, Montreal, Quebec, Canada H3G 1B4.

Khassan El Farrah, MD, MSc – JSS Medical Research, Montreal, Quebec, Canada.

Luisa Deutsch, MD – JSS Medical Research, Montreal, Quebec, Canada.

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).

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 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

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

Table 7. Effect of a Lower Maintenance Dose of Krill Oil on Lipids

0.5 g Krill Oil	Time (d)/mg/dL		% Change	p-value
	0.00	180.00		
Total Cholesterol	235.83	192.53	18.90%	0.000
LDL	167.78	107.47	44.40%	0.000
HDL	57.22	77.71	33.40%	0.000
Triglycerides	120.50	89.89	25.40%	0.025

11.9-percent reduction of triglycerides, from 122.7 mg/dL to 112 mg/dL (p=0.113). Subjects achieved a significant reduction of triglycerides at daily doses of 2 g and 3 g daily krill oil – 28 percent (p=0.025) and 27 percent (p=0.0228) – decreasing from baseline levels of 160.4 mg/dL and 152.8 mg/dL to 116.1 mg/dL and 112.3 mg/dL, respectively. Fish oil at 3 g/day did not achieve a significant reduction of triglycerides (3.2%), decreasing from 140.9 mg/dL to 136.4 mg/dL (p=0.239). Interestingly patients in the placebo group experienced a 9.8-percent decrease in triglycerides (p=0.215).

Blood glucose levels were reduced by 6.3 percent, from 105 mg/dL to 98 mg/dL (p=0.025), in patients receiving 1 g and 1.5 g krill oil daily, and 5.6 percent, from 92 mg/dL to 88 mg/dL (p=0.011), in those receiving 2 g and 3 g krill oil daily. A daily dose of 3 g fish oil reduced blood glucose by 3.3 percent, from 90 mg/dL to 87 mg/dL (p=0.275). Placebo treatment resulted in a non-significant blood glucose increase of 0.1 percent, from 92 mg/dL to 93 mg/dL (p=0.750).

The between-group comparison showed 1 g and 1.5 g krill oil daily was significantly more effective than 3 g fish oil in reducing glucose and LDL, whereas 2 g and 3 g krill oil demonstrated a significantly greater reduction of glucose, triglycerides, and LDL compared to 3 g fish oil. Both fish oil and krill oil performed significantly better than placebo for the regulation of glucose, triglycerides, total cholesterol, and HDL.

As mentioned previously, patients receiving 1 g and 1.5 g daily krill oil continued for another 12 weeks with a lower maintenance dose of 0.5 g krill oil daily (Table 7). These patients maintained a mean total cholesterol level of 192.5 mg/dL, a reduction of 19 percent (p=0.000) from baseline. LDL was further reduced from baseline by 44 percent, a reduction from 233 mg/dL to 107.5 mg/dL (p=0.000). A moderate decrease in HDL was seen, from 36 percent increase at 90 days to 33 percent after 180 days of treatment, which was still a significant increase from baseline (p=0.000). Triglycerides were slightly decreased further to a reduction of 25 percent from baseline (p=0.000), compared to the 12-percent reduction observed after 90 days of treatment. Blood glucose decreased by 6.6 percent from baseline (p=0.20), versus the 6.3-percent decrease at 90 days.

Discussion

Arteriosclerosis is the generic term for a number of diseases in which arterial walls become thickened and lose elasticity, with atherosclerosis being considered the most important. With its effects on the brain, heart, kidneys, and other vital organs and extremities, and despite medical advancements, atherosclerotic heart disease and stroke combined remain the number one cause of morbidity and mortality in the United States, Canada, and most Western countries.[22]

In the United States, cardiovascular disease has a mortality rate of 39.9 percent for males and 43.7 percent for females, a 15-21 percent difference from malignant disease, which ranks second.[22] It is estimated that 59.7 million Americans have one or more forms of cardiovascular disease.[22] Of the population with self-reported heart disease, 56-64 percent report restricted activity, 23-37 percent require one or more disability days per week, and 28-34 percent are unemployed because of disability or illness.[22] The primary lesion of atherosclerosis is the fatty streak, which eventually evolves into a fibrous plaque. Numerous randomized trials have proven that lowering serum cholesterol slows or reverses progression of coronary artery disease (CAD) and reduces coronary events.[22-29]

A daily intake of 1-3 g EPA and DHA or 3-9 g fish oil is currently recommended to reduce the risk of cardiovascular diseases.[22,23] Nevertheless, epidemiological studies evaluating the effects of fish oil on coronary heart disease are contradictory, ranging from reverse associations to virtually no effect to a beneficial effect.[30-33] One issue in the efficacy of EPA/DHA may be the bioavailability of these fatty acids.

A recent study demonstrated *in vivo* PUFA bioavailability depends on several factors, such as the type of lipids in which they are esterified, their physical state; i.e., lipid solution or colloidal particle systems, and the presence of co-ingested lipids.[18] *In vivo* PUFA absorption was evaluated by fatty acid analysis of thoracic lymph of duct-cannulated rats after intragastric feeding of dietary fats.[19] Evidence demonstrates oral essential fatty acid supplementation in the form of phospholipids is more effective than triglycerides in increasing concentrations of long-chain PUFAs in liver and brain.[18,19] DHA is better absorbed when delivered by liposomes than by fish oil (relative lymphatic absorption equal to 91 percent and 65 percent after liposome and fish oil administration, respectively). The best bioavailability of DHA delivered by liposomes is revealed by an increase in DHA proportions in both lymphatic triacylglycerols and phospholipids, compared to a fish oil diet.[18,19]

Krill oil is a complex combination of multiple active ingredients with synergistic bioactivity. The exact mechanism of action for krill oil's lipid-lowering effects is not yet entirely clear. However, krill oil's unique biomolecular profile of omega-3 (EPA/DHA) fatty acids already incorporated into phospholipids has exhibited a lipid-lowering effect on the level of the small intestine, which distinguishes krill oil from other known lipid-lowering principals.[18,19] Werner et al demonstrated essential fatty acids in the form of phospholipids were superior to essential fatty acids as triglycerides in significantly decreasing the saturated fatty acid ratios of liver triglycerides and phospholipids (each $p < 0.05$), while significantly increasing the phospholipid concentrations of the long-chain PUFAs ($p < 0.05$).[19]

LDL oxidation is believed to increase atherosclerosis through high serum LDL levels inducing LDL particles to migrate into subendothelial space. The process by which LDL particles are oxidized begins with lipid peroxidation, followed by fragmentation to short-chain aldehydes. At the same time, lecithin is converted to lysolecithin, a selective chemotactic agent for monocytes, which become macrophages that ingest oxidized LDL. The new macrophage becomes engorged with oxidized LDL cholesteryl esters and becomes a foam cell. Groups of foam cells form a fatty streak, the earliest indication of atherosclerosis.[34,35]

The unique molecular composition of krill oil, with its abundance of phospholipids and antioxidants, may explain the significant effect of krill oil for blood lipid regulation. In comparison to fish oil, krill oil significantly lowered blood lipids at lower doses.

The effect of fish oil on cardiovascular disease is tempered by the presence of methylmercury in many fish.[33] In fact, the U.S. Food and Drug Administration has advised pregnant women and women who may become pregnant not to eat swordfish, king mackerel, tilefish, shark, or fish from locally contaminated areas.[36] Therefore, it may be prudent to obtain these essential fatty acids via supplementation. Krill oil, and most fish oil concentrates, are molecularly distilled to remove heavy metals.

Conclusion

Atherosclerotic cardiovascular disease is a major health problem in the Western world, with CAD being the leading cause of mortality in the United States. Extensive observational epidemiologic data strongly associate high CAD risk to elevated total and LDL cholesterol and low levels of HDL cholesterol. Extensive clinical trial evidence has established that favorably altering dyslipidemias produces clear improvements in CAD end points.[15-17]

The results of this clinical trial demonstrate that daily doses of 1-3 g krill oil are significantly more effective than 3 g EPA/DHA fish oil in the management of hyperlipidemia. Furthermore, a maintenance dose of 500 mg krill oil is significantly effective for long-term regulation of blood lipids. The unique molecular composition of krill oil, which is rich in phospholipids, omega-3 fatty acids, and diverse antioxidants, surpasses the profile of fish oils and offers a superior approach toward the reduction of risk for cardiovascular disease.

References

1. Horrobin DF. The role of essential fatty acids and prostaglandins in the premenstrual syndrome. *J Reprod Med* 1983;28:465-468.
2. Simopoulos AP. Omega-3 fatty acids in health and disease and in growth and development. *Am J Clin Nutr* 1991;54:438-463.
3. Alvin PE, Litt IF. Current status of the etiology and management of dysmenorrhea in adolescence. *Pediatrics* 1982;70:516-525.
4. Cameron IT, Fraser IS, Smith SK. *Clinical Disorders of the Endometrium and Menstrual Cycle*. Oxford, United Kingdom: Oxford University Press; 1998:359.
5. Drevon CA. Marine oils and their effects. *Nutr Rev* 1992;50:38-45.
6. Hansen HS. Dietary essential fatty acids and *in vivo* prostaglandin production in mammals. *World Rev Nutr Diet* 1983;42:102-134.
7. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-1 and tumor necrosis factor by mononuclear cells. *N Engl J Med* 1989;320:265-271.
8. Hansen HS, Olsen SF. Dietary (n-3)-fatty acids, prostaglandins and prolonged gestation in humans. *Prog Clin Biol Res* 1988;282:305-317.
9. Lee TH, Mencia-Huerta JM, Shih C, et al. Effects of exogenous arachidonic, eicosapentaenoic and docosahexaenoic acids on the generation of 5-lipoxygenase pathway products by ionophore-activated human neutrophils. *J Clin Invest* 1984;74:1922-1933.
10. Deutch B. Menstrual pain in Danish women correlated with low n-3 polyunsaturated fatty acid intake. *Eur J Clin Nutr* 1995;49:508-516.
11. Deutch B. Painful menstruation and low intake of n-3 fatty acids. *Ugeskr Laeger* 1996;158:4195-4198. [Article in Danish]
12. Harel Z, Biro FM, Kottenhahn RK, Rosenthal SL. Supplementation with omega-3 polyunsaturated fatty acids in the management of dysmenorrhea in adolescents. *Am J Obstet Gynecol* 1996;174:1335-1338.
13. Salem N Jr, Niebylski CD. The nervous system has an absolute molecular species requirement for proper function. *Mol Membr Biol* 1995;12:131-134.
14. Dewailly E, Blanchet C, Lemieux S, et al. n-3 Fatty acids and cardiovascular disease risk factors among the Inuit of Nunavik. *Am J Clin Nutr* 2001;74:464-473.
15. Holub BJ. Clinical nutrition: 4. Omega-3 fatty acids in cardiovascular care. *CMAJ* 2002;166:608-615.
16. Harris WS. Fish oils and plasma lipid and lipoprotein metabolism in humans: a critical review. *J Lipid Res* 1989;30:785-807.
17. Jeppesen J, Hein HO, Suadicani P, Gyntelberg F. Triglyceride concentration and ischemic heart disease: an eight-year follow-up in the Copenhagen Male Study. *Circulation* 1998;97:1029-1036.
18. Cansell M, Moussaoui N, Denizot A, Combe N. Influence of the physicochemical form of polyunsaturated fatty acids on their *in vivo* bioavailability; 94th Annual AOCS Meeting & Expo PHO1: Phospholipids for Improving Bioavailability Chair: Michael Schneider, Consultant, Germany.
19. Werner A, Havinga R, Kuipers F, Verkade HJ. Treatment of EFA deficiency with dietary triglycerides or phospholipids in a murine model of extrahepatic cholestasis. *Am J Physiol Gastrointest Liver Physiol* 2004;286:G822-G832.

20. Health and Welfare Canada. Promoting Healthy Weights: A Discussion Paper. Minister of Supply and Services Canada: Ottawa, Ontario. 1988
21. Garrow JS, Webster J. Quetelet's index (W/H2) as a measure of fatness. *Int J Obes* 1985;9:147-153.
22. Krauss RM, Eckel RH, Howard B, et al. AHA Dietary Guidelines: revision 2000: A statement for healthcare professionals from the Nutrition Committee of the American Heart Association. *Stroke* 2000;31:2751-2766.
23. de Lorgeril M, Salen P, Martin JL, et al. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: final report of the Lyon Diet Heart Study. *Circulation* 1999;99:779-785.
24. Guallar E, Aro A, Jimenez FJ, et al. Omega-3 fatty acids in adipose tissue and risk of myocardial infarction: the EURAMIC study. *Arterioscler Thromb Vasc Biol* 1999;19:1111-1118.
25. Kromhout D, Bosschieter EB, de Lezenne Coulander C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 1985;312:1205-1209.
26. Daviglus ML, Stamler J, Orencia AJ, et al. Fish consumption and the 30-year risk of fatal myocardial infarction. *N Engl J Med* 1997;336:1046-1053.
27. Hu FB, Bronner L, Willett WC, et al. Fish and omega-3 fatty acid intake and risk of coronary heart disease in women. *JAMA* 2002;287:1815-1821.
28. Ascherio A, Rimm EB, Stampfer MJ, et al. Dietary intake of marine n-3 fatty acids, fish intake, and the risk of coronary disease among men. *N Engl J Med* 1995;332:977-982.
29. Morris MC, Manson JE, Rosner B, et al. Fish consumption and cardiovascular disease in the Physicians' Health Study: a prospective study. *Am J Epidemiol* 1995;142:166-175.
30. Gillum RF, Mussolino M, Madans JH. The relation between fish consumption, death from all causes, and incidence of coronary heart disease: the NHANES I Epidemiologic Follow-up Study. *J Clin Epidemiol* 2000;53:237-244.
31. Wood DA, Riemersma RA, Butler S, et al. Linoleic and eicosapentaenoic acids in adipose tissue and platelets and risk of coronary heart disease. *Lancet* 1987;1:177-183.
32. Guallar E, Hennekens CH, Sacks FM, et al. A prospective study of plasma fish oil levels and incidence of myocardial infarction in U.S. male physicians. *J Am Coll Cardiol* 1995;25:387-394.
33. Salonen JT, Seppanen K, Nyyssonen K, et al. Intake of mercury from fish, lipid peroxidation, and the risk of myocardial infarction and coronary, cardiovascular, and any death in eastern Finnish men. *Circulation* 1995;91:645-655.
34. Bruckert E, Giral P, Tellier P. Perspectives in cholesterol-lowering therapy: the role of ezetimibe, a new selective inhibitor of intestinal cholesterol absorption. *Circulation* 2003;107:3124-3128.
35. Cuchel M, Schwab US, Jones PJ, et al. Impact of hydrogenated fat consumption on endogenous cholesterol synthesis and susceptibility of low-density lipoprotein to oxidation in moderately hypercholesterolemic individuals. *Metabolism* 1996;45:241-247.
36. Center for Food Safety and Applied Nutrition. Consumer advisory: an important message for pregnant women and women of childbearing age who may become pregnant about the risks of mercury in fish. College Park, MD: Food and Drug Administration, March 2001. (Accessed November 1, 2002).