Efficacy of Fish Oil Supplementation for Treatment of Moderate Elevation of Serum Cholesterol

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A study was performed to determine the efficacy and feasibility of using fish oil capsules for treatment of moderate hypercholesterolemia. Thirty-three subjects, randomized to fish or olive oil, took two 1-g capsules with each meal for 12 weeks. Each subject crossed over to the alternate treatment at 12 weeks. Patients maintained usual levels of exercise and diet for 24 weeks. Eight subjects dropped out. For the group starting fish oil (n = 13), the average baseline cholesterol level was 6.336 mmol/L (245.0 mg/dL) and was 6.341 mmol/L (245.2 mg/dL) after 12 weeks. High-density lipoprotein cholesterol (HDL-C) and calculated low-density lipoprotein cholesterol (LDL-C) baseline levels were 1.459 mmol/L (56.4 mg/dL) and 4.332 mmol/L (167.5 mg/dL); 1.474 mmol/L (57.0 mg/dL) and 4.479 mmol/L (173.2 mg/dL), respectively, after fish oil supplementation. In the group that began with olive oil (n = 12), baseline total cholesterol level was 6.274 mmol/L (242.6 mg/dL); HDL-C and calculated LDL-C baseline levels were 1.386 mmol/L (53.6 mg/dL) and 3.988 mmol/L (154.2 mg/dL). When mean baseline levels were compared with post–fish-oil values for the entire population, no significant change in total cholesterol or LDL-HDL ratio was obtained. Triglyceride responses to fish oil were variable. Values after olive oil treatment were neither significantly different from baseline nor different from fish oil. It was concluded that fish oil in manufacturer's recommended dosage does not appear to lower moderately elevated cholesterol levels. **J Fam Pract 1990; 30:55-59.**

Interest in using fish oil as a dietary supplement for the prevention of coronary heart disease grew from epidemiologic reports of Eskimos. These populations enjoy a lower mortality from coronary heart disease and lower total serum cholesterol[1] than counterparts eating a diet less rich in omega-3 polyunsaturated fatty acids. Because coronary heart disease is the leading cause of death in the United States, and because lowering total serum cholesterol reduces mortality from coronary heart disease,[2] fish oil appears to be a promising addition to the American diet.[3] Additionally, some patients have difficulty with dietary change, and several medications used for lowering lipids have troubling side effects. Consuming fish oil for its lipid-lowering effects seems to be an attractive alternative. The dosage necessary to achieve lipid-lowering effects, safety, and side effects have been incompletely explored.

This study was performed to assess the efficacy of using omega-3 polyunsaturated fatty acid supplementation to lower moderately elevated serum cholesterol levels. Specifically, this study tested the hypothesis that fish oil administered in manufacturer-recommended doses to hypercholesterolemic outpatients would produce a significant reduction in serum cholesterol, without other alteration in diet or lifestyle.

METHODS

Subjects

The study was conducted at the Family Health Center at University Hospital, Stony Brook, NY, and a nearby

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private physician's office. Subjects were recruited in the following fashion: All laboratory values from practice members screened for hyperlipidemia during the months of May through December 1987 were reviewed. All patients aged 20 to 60 years whose total serum cholesterol level was between the 75th and 90th percentile* for the US population by Lipid Research Clinics Prevalence Study criteria were eligible.

The following conditions represented exclusion criteria: renal, hepatic, or thyroid disease; current anticoagulant therapy; present or past abnormal bruising or bleeding, stroke, myocardial infarction, or diabetes mellitus; receiving other lipid-lowering drugs; chronic diarrhea, Crohn's disease, ulcerative colitis, malabsorption; gastrointestinal resection; fish allergy. Subjects underwent a physical examination on the first visit to rule out new diagnoses or contraindications to the study protocol.

A total of 58 subjects who met the study criteria for inclusion were asked to participate. This request was made in person or by telephone by the patient's personal physician. There were no significant differences in age, sex, or medication use between persons who refused to enroll and the study participants, nor was there a significant difference in mean serum cholesterol values of participants and nonparticipants. Thirty-three patients began the study, and 25 completed it. All subjects gave informed consent. The study was approved by the Committee on Research in Human Subjects of University Hospital.

Experimental Design

The 24-week study was a randomized, double-blind crossover, closed-label investigation comparing fish oil with olive oil in equicaloric doses. Subjects were randomized on entry using a table of random numbers and assigned (even–odd) to either of two groups. The daily diets of one half of the subjects (group A) were supplemented with two 1-g capsules of fish oil with each of three meals (supplying 1.8 g of omega-3 polyunsaturated fatty acids). The other half (group B) received olive oil on the same schedule (two 1-g capsules with each of three meals). After 12 weeks, the treatment was crossed over and continued until 24 weeks. If for some reason doses were skipped, subjects were advised not to try to make up the dose at a later time. Subjects were evaluated after 6, 12, 18, and 24 weeks and were asked to maintain their usual diet, including seafood, and activity during the course of the study. Fish oil and olive oil capsules were provided in identically labeled containers.† Adherence to the dosing regimen was monitored by conducting interviews with the subjects and by counting the number of unused capsules returned by the subjects at each visit.

Dependent Measures

Dependent measures included body weight, fasting serum levels of total cholesterol, high-density lipoprotein cholesterol (HDL-C), and triglycerides. Low-density lipoprotein cholesterol (LDL-C) was calculated using the formula LDL-C = total cholesterol − (HDL-C + triglyceride/5.) Lipid determinations were made at the beginning of week 1 (pretreatment) and the end of weeks 12 and 24 along with weight. The average time elapsed between the screening cholesterol value and that obtained at the beginning of week 1 was 31 days. Weekly portions of seafood, drug intake, exercise frequency, and side effects were monitored by a questionnaire at weeks 1, 6, 12, 18, and 24. All screening and protocol specimens used for study calculations were drawn after a 12-hour fast and processed in the University Hospital laboratories for total cholesterol and triglycerides. These determinations were made by an enzymatic-colorimetric method on a Dacos chemistry analyzer. HDL-C measurements were made at Smith-Kline Bioscience Laboratories using a phosphotungstate-magnesium precipitation on the Centrifichem-600. Measurement techniques were uniform for all subjects.

Baseline values for total cholesterol and triglycerides represent means of screening levels and pretreatment week 1 values. (Three subjects' screening values were excluded from the calculations because they were not performed at University Hospital.) For HDL-C and LDL-C where screening data were unavailable, baseline values are represented by pretreatment week 1 levels. Baseline values for body mass index are represented by their week 1 values.

Statistical Analyses

Data were entered into the Statistical Package for the Social Sciences (SPSSX) software program.[5] Changes from baseline to the values after fish oil supplementation (measured at week 12 for group A and week 24 for group B) were compared by paired *t* tests for total cholesterol, triglycerides, HDL-C, and LDL-C. These same values were compared by *t* tests for changes from baseline after olive oil treatment. Differences between mean values after olive oil and fish oil were also compared.

RESULTS

Twenty-five subjects completed the study, 15 men and 10 women. Ages ranged between 22 and 53 years (mean 40

*A "moderate risk" group was selected that would normally not require cholesterol-lowering medications but only dietary intervention as initial therapy.[4]

†Fish oil (Max EPA) and olive oil capsules were provided by R.P. Scherer, Clearwater, Fla.

TABLE 1. CHANGES IN MEAN BLOOD LIPID LEVELS AFTER FISH OIL OR OLIVE OIL SUPPLEMENTATION (GROUP A, n = 13)

	Fish Oil, Weeks 1–12							Olive Oil, Weeks 13–24				
	Baseline			12 Weeks				24 Weeks				
	mmol/L	mg/dL	(SD)	mmol/L	mg/dL	(SD)	Percent Change	mmol/L	mg/dL	(SD)	Percent Change from Crossover	Percent Change from Baseline
Total cholesterol	6.336	245.0	(28.4)	6.341	245.2	(47.4)	0.0	6.222	240.6	(43.6)	(−)1.9	(−)1.8
LDL-C	4.331	167.5	(34.5)	4.479	173.2	(48.0)	3.4	4.262	164.8	(20.7)	(−)4.8	(−)1.6
HDL-C	1.459	56.4	(21.8)	1.474	57.0	(21.1)	0.1	1.469	56.8	(21.1)	(−)0.3	0.7
Triglycerides	1.579	139.9	(135.6)	1.082	95.8	(59.0)	(−)31.5*	1.339	118.6	(74.9)	23.7	(−)15.2
LDL:HDL ratio		2.96			3.04		2.7		2.90		(−)4.2	(−)2.0

**This change from baseline is significant at P < .05; all other changes are not significant. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.*

TABLE 2. CHANGES IN MEAN BLOOD LIPIDS AFTER OLIVE OIL OR FISH OIL SUPPLEMENTATION (GROUP B, n = 12)

	Olive Oil, Weeks 1–12							Fish Oil, Weeks 13–24				
	Baseline			12 Weeks				24 Weeks				
	mmol/L	mg/dL	(SD)	mmol/L	mg/dL	(SD)	Percent Change	mmol/L	mg/dL	(SD)	Percent Change from Crossover	Percent Change from Baseline
Total cholesterol	6.274	242.6	(31.1)	6.814	263.5	(41.8)	8.6	6.411	247.9	(50.2)	(−)5.9	2.2
LDL-C	3.988	154.2	(34.4)	4.559	176.3	(40.5)	14.3	4.174	161.4	(57.6)	(−)8.4	4.6
HDL-C	1.386	53.6	(14.5)	1.425	55.1	(14.8)	2.7	1.469	56.8	(19.8)	3.1	6.0
Triglycerides	1.582	140.1	(92.3)	1.782	157.8	(144.6)	12.6	1.607	142.3	(140.2)	(−)9.8	1.6
LDL:HDL ratio		2.87			3.19		1.1		2.84		(−)9.0	(−)1.0

Note: All changes from baseline not significant. LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.

years). The body mass index mean for the study group was 26.5, with a range from 19.5 to 35.1. Seven patients had hypertension, one had angina. Medications were taken by 10 subjects. Three patients were taking calcium channel blockers, one of whom was also receiving estrogen and progesterone for menopausal symptoms. One woman took oral contraceptives. Two subjects were being treated with β-blockers for hypertension (labetalol and atenolol). Two were taking psychotropic medications—lithium carbonate, fluphenazine, benztropine, and imipramine. Two patients took theophylline, one with albuterol and the other with a thiazide diuretic. There were no changes in medications during the study. Fifteen persons took no medications.

Exercise was performed three times a week or more by seven patients. The average weekly number of seafood portions eaten by subjects was 1.8 (range 0 to 5). There was no significant change in exercise or seafood consumption in the study population over the course of 24 weeks. Although the prescribed amount of fish oil per day was 6 g, subjects took, by pill count, an average of 5 g, for an average of 1.5 g of omega-3 polyunsaturated fatty acids actually consumed per day during fish oil administration for both groups.

The blood lipid response of the subjects to fish oil administration is found in Tables 1 and 2. Baseline total cholesterol was 6.336 mmol/L (245 mg/dL) in group A, the group initially treated with fish oil, and changed to 6.341 mmol/L (245.2 mg/dL) after 12 weeks. LDL-C, HDL-C, and triglycerides in group A on fish oil changed from baseline values of 4.331 mmol/L (167.5 mg/dL), 1.459 mmol/L (56.4 mg/dL), and 1.579 mmol/L (139.9 mg/dL), to 4.479 mmol/L (173.2 mg/dL), 1.474 mmol/L (57.0 mg/dL) and 1.08 mmol/L (95.8 mg/dL), respectively.

Group B, whose mean baseline total cholesterol was 6.274 mmol/L (242.6 mg/dL), started the study on olive oil. Their total cholesterol rose to 6.814 mmol/L (263.5 mg/dL) after 12 weeks. After crossover (Table 2) to 12 weeks of fish oil supplementation, their mean total cholesterol was 6.411 mmol/L (247.9 mg/dL). HDL-C and

calculated LDL-C changed from 1.425 mmol/L (55.1 mg/dL) to 1.469 mmol/L (56.8 mg/dL) and 4.559 mmol/L (176.3 mg/dL) to 4.174 mmol/L (161.4 mg/dL), respectively. Group B triglycerides increased from 1.582 mmol/L (140.1 mg/dL) to 1.782 mmol/L (157.8 mg/dL) on olive oil, then returned to 1.607 mmol/L (142.3 mg/dL) on fish oil.

Group A mean total cholesterol was 6.341 mmol/L (245.2 mg/dL) at week 12 after fish oil. This value changed to 6.22 mmol/L (240.6 mg/dL) after 12 weeks on olive oil. This group recorded a change in LDL-C, HDL-C, and triglycerides means while on olive oil from 4.479 mmol/L (173.2 mg/dL), 1.474 mmol/L (57.0 mg/dL), and 1.082 mmol/L (95.8 mg/dL), respectively, at week 12, to 4.262 mmol/L (164.8 mg/dL), 1.469 mmol/L (56.8 mg/dL), and 1.339 mmol/L (118.6 mg/dL) on their last visit. No changes in mean lipid values for the population (N = 25) from baseline were found to be significant at the $P < .05$ level.

Reported side effects were mostly gastrointestinal and were evenly shared between the supplement groups, with the exception of bad taste and "fishy burps" reported in five persons taking fish oil. Bruising was reported in one patient taking fish oil and two taking olive oil. Fourteen persons reported no side effects on either arm of the protocol.

Eight of the original 33 subjects did not complete the study. Diarrhea caused four dropouts during the first 12 weeks (two each from groups A and B); the other four (two from each group) reported no side effects and, when asked, gave no reason for dropping out. There were no significant changes in body mass index for either group over the course of the study.

DISCUSSION

This study asked the question "Would an individual with moderate hypercholesterolemia who used fish oil capsules as sole therapy (in manufacturer-recommended doses) significantly lower serum cholesterol?" The findings suggest the answer is no. This question was tested by administering fish oil to subjects who were asked to keep diet (including seafood), exercise, and medications unchanged. Each subject served as his or her own control by the crossover design, which allowed comparison of the effects of fish oil with baseline lipid levels and with the effects of equicaloric doses of olive oil. There was no washout period between the first and second supplement. The serum lipid-altering effects of omega-3 polyunsaturated fatty acids disappear 2 weeks after discontinuation, and the maximum effects are noted within 2 weeks of supplementation;[6] therefore, the values obtained 12 weeks after crossover should reflect the influence of the crossover agent.

Olive oil was used as a comparison agent in this study because of its safety, availability, and acceptability to patients. In the small supplementary doses used,[7] there should not have been significant changes in serum lipids; these results bear out this expectation.

When used in very high dosage under controlled conditions, monounsaturated fats have been shown to have a significant cholesterol-lowering effect. Grundy[8] produced a 13% decrease in total cholesterol by substituting a liquid diet containing 28% of total calories as oleic acid for another, high in saturated fats. Both diets limited cholesterol consumption to under 100 mg. This study used less than one-tenth the above-noted monounsaturated dose as a supplement to regular diet. Cholesterol consumption was not controlled. The population was drawn from an existing medical practice and provides a test of fish oil supplements in free-living persons. The mixed sexes and different ages and body mass indexes of the study group made it possible to test the hypothesis in a true practice setting, not a metabolic unit.

The therapeutic effects of fish oil were disappointing. There was essentially no change in total cholesterol from the study population baseline level after treatment with fish oil for 12 weeks. In fact, the mean difference observed would fall within the 3% precision goal for cholesterol measurement set by the National Cholesterol Education Program (NCEP).[9]

There were a few individuals with the desired outcome—a lowered cholesterol; however, the response to fish oil was just as likely to be a rise in total cholesterol as a fall. One half the patients whose total cholesterol decreased with fish oil had an even greater drop with olive oil. The group response for HDL-C on fish oil was also insignificant. LDL-C was increased slightly, but not significantly, and not to the degree noted previously with higher dosages.[10]

This study was limited by sample size, which would make a small effect of fish oil on lipids difficult to determine. The use of potentially lipid-altering drugs by five patients might have raised these patients' baseline total cholesterol levels. Any medication effect should have remained constant, as there were no changes during the study. The total cholesterol increased 4% in these five, as compared with 1% in the entire population. This difference is not significant.

Despite the probability that patients enrolled in a study may be more motivated to tolerate side effects than others, most subjects reported no or minor side effects on an average of 5 g of fish oil actually consumed per day. Exceptions are the two who dropped out because of diarrhea while taking fish oil.

The Eskimo diet[11] contains five times the amount of fish

oil administered to these subjects. This difference in dosage, other dietary and lifestyle features, and genetic background may account for the differences in blood lipids noted in both groups.

The study population consumed an average of 1.8 portions of seafood each week. This amount is just over the US average of approximately 5 oz/wk, (personal communication, L. Leach, Iceland Seafood Corp, Camp Hill, Pa); it remained constant throughout the study. Because of this constancy and quantity, the amount of omega-3 polyunsaturated fatty acids present in the diet of the subjects did not significantly bias results.

Observation of no change in cholesterol with low-dose fish oil supplementation is in agreement with previous work. Sanders et al[12] supplemented the diet of volunteers with 4 g of omega-3 polyunsaturated fatty acids; Bronsgeest-Schoute et al[6] used doses of 1.4, 2.3, 4.1, and 8.2 g of omega-3 fatty acids. Neither found a significant change in total cholesterol. A recent review suggests that the hypocholesterolemic effects of omega-3 polyunsaturated fatty acids are seen between 5 and 20 g/d.[13] This dosage is, at a minimum, three times that used in this study and would require over 16 g of fish oil (and 144 calories) per day.

Recommendations have been recently made by the National Cholesterol Education Program[4] for evaluation and treatment of hyperlipoproteinemias. Dietary change and exercise should initiate therapy. Drug therapy should follow if there is an incomplete response to these lifestyle changes. Fish oil, as such, is not recommended as a therapy for hypercholesterolemia. These data indicate fish oil supplementation at 6 g dosage is ineffective for treatment of moderate hypercholesterolemia.

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References

1. Bang HO, Dyerberg J: Fish consumption and mortality from coronary heart disease. N Engl J Med 1985; 313:822–823
2. Lipid Research Clinics Program: The Lipid Research Clinics Coronary Prevention Trial Results: 1. Reduction in incidence of coronary heart disease due to cholesterol lowering. JAMA 1984; 251:351–363
3. Herold PM, Kinsella JE: Fish oil consumption and decreased risk of cardiovascular disease: A comparison of findings from animal and human feeding trials. Am J Clin Nutr 1986; 43:566–598
4. Report of the National Cholesterol Education Program Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults. Arch Intern Med 1988; 148:36–69
5. Statistical Package for the Social Sciences (SPSSX) Users Guide, ed 3. Chicago, SPSS, Inc 1988
6. Bronsgeest-Schoute HC, van Gent CM, Luten JB, Ruiter A: The effect of various intakes of omega-3 fatty acids on the blood lipid composition in healthy human subjects. Am J Clin Nutr 1981; 34: 1752–1757
7. Radack KL: Omega-3 fatty acids, letter. Ann Intern Med 1988; 109:81–82
8. Grundy SM: Comparison of monounsaturated fatty acids and carbohydrates for lowering plasma cholesterol. N Engl J Med 1986; 314:745–748
9. Current status of blood cholesterol measurement in clinical laboratories in the United States: A report from the Laboratory Standardization Panel of the National Cholesterol Education Program. Clin Chem 1988; 34:193–201
10. Harris WS, Dujovne CA, Zucker M, Johnson B: Effects of a low saturated fat, low cholesterol fish oil supplement in hypertriglyceridemic patients. Ann Intern Med 1988; 109:465–470
11. Bang HO, Dyerberg J, Hjorne N: The composition of food consumed by Greenland Eskimos. Acta Med Scand 1976; 200:69–73
12. Sanders TAB, Vickers M, Haines AP: Effect on blood lipids and haemostasis of a supplement of cod-liver oil, rich in eicosapentaenoic and docosahexaenoic acids, in healthy young men. Clin Sci 1981; 61:317–324
13. Yetiv JZ: Clinical applications of fish oils. JAMA 1988; 260:665–670