

MODULATION OF LIPID PROFILE BY FISH OIL AND GARLIC COMBINATION

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Fish consumption has been shown to influence epidemiology of heart disease, and garlic has been shown to influence triglyceride levels. This study was undertaken to evaluate the effect of fish oil and garlic combinations as a dietary supplement on the lipid subfractions. Forty consecutive subjects with lipid profile abnormalities were enrolled in a single-blind, placebo-controlled crossover study. Each subject received placebo for 1 month and fish oil (1800 mg of eicosapentanoic acid [EPA] + 1200 mg of docosahexanoic acid) with garlic powder (1200 mg) capsules daily for 1 month. Lipid fractionation was performed prior to study initiation, after the placebo period, and after the intervention period. Subjects all had cholesterol levels >200. Subjects were instructed to maintain their usual diets.

Supplementation for 1 month resulted in an 11% decrease in cholesterol, a 34% decrease in triglyceride, and a 10% decrease in low-density lipoprotein (LDL) levels, as well as a 19% decrease in cholesterol/high-density lipoprotein (HDL) risk. Although not significant, there was a trend toward increase in HDL. There was no significant placebo effect. These results suggest that in addition to the known anticoagulant and antioxidant properties of both fish oil and garlic, the combination causes favorable shifts in the lipid subfractions within 1 month. Triglycerides are affected to the largest extent. The cholesterol lowering and improvement in lipid/HDL risk ratios suggests that these combinations may have antiatherosclerotic properties and may protect against the development of coronary artery disease. (*J Natl Med Assoc.* 1997;89:673-678.)

Key words: coronary artery disease ♦ lipid profile
♦ garlic ♦ fish oil

Research related to the beneficial cardiovascular effects of fish oil (ω 3-fatty acids) and garlic (allin) has increased tremendously in the past decade.^{1,2} Fish oil contains the ω 3-fatty acids eicosapentanoic acid (EPA) and docosahexanoic acid (DHA). The average

daily intake of human populations ranges from 0 to 10 g fish.¹ However, studies of Inuit^{3,4} and Dutch Zutphin⁵ populations drew attention to the beneficial relation between diets containing approximately 50 g of fish per day and the low incidence of coronary artery disease and mortality. Protective effects of fish oil on the recurrence of coronary stenosis following angioplasty was documented with 2 to 3 g of ω 3-fatty acids as a daily dietary supplement.⁶ Consumption of >20 g of fish/day by Dutch men was associated with a 50% reduction in stroke risk.⁷

A large spectrum of antithrombotic effects of fish oil include blood-thinning effects by incorporation into red cell membranes, causing an increase in membrane fluidity and reducing plasminogen, which

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Table 1. Patient Demographics

Characteristic	No. Patients
Total no. patients	40
Age range (years)	40 to 75
Mean age \pm SD (years)	53 \pm 13
Males	23
Mean age \pm SD (years)	47 \pm 10
Females	17
Mean age \pm SD (years)	63 \pm 11
Hypertension	14
Coronary artery disease	5
Diabetes	3
Cholesterol level >200	40
Triglyceride level >180	20
Smokers	0

Abbreviations: SD=standard deviation.

decreases blood viscosity.² The formation of eicosanoids, modulators involved in the regulation of blood vessels and inflammation, is altered by ω 3-fatty acids.¹ The resultant decrease in thromboxane A₂ and increase in prostaglandin I₃ and I₂ inhibits platelet aggregation and favors vasodilation of blood vessels. This shift also favors a decrease in the production of proinflammatory leukotrienes. The lipoprotein effects of ω 3-fatty acids are a result of its inhibition of the hepatic triglyceride-synthesizing enzyme, which reduces hepatic secretion of triglycerides and hence lowers serum triglycerides.^{8,9} No extensive studies are available on the modulation of lipid subfractions and associated lipid-related cardiovascular risk factors.

Garlic has as its principal ingredient a sulfur-containing antioxidant, allicin, in addition to other antioxidants including vitamin C, germanium, and selenium. Although at times controversial and with inconsistent effects, garlic has been the focus of medical and clinical attention because of reports on several cardiovascular risk factors.^{10,11} Garlic extracts have been reported to reduce some serum lipid levels,^{2,10-25} blood pressure,^{10,15-21,23-25} and plasma viscosity,²⁶ as well as inhibit platelet aggregation,^{17,27} increase fibrinolytic activity,^{17,27} and produce vasodilation.²⁷⁻²⁹ In contrast, certain studies were not able to substantiate the blood pressure-lowering effect¹² and absence of effects on serum lipids and lipoproteins despite matching dosages. Since the overall property profiles of both ω fish oil and garlic includes modulation, at least in part, of subfractions of the

lipids and lipoproteins, this study was undertaken to evaluate the net effect and potential synergism when ingested together at optimal daily dosages in subjects with mild to moderate hyperlipidemia in a placebo-controlled, randomized, crossover study.

MATERIALS AND METHODS

Forty consecutive volunteer subjects from the cardiology/internal medicine clinic aged 40 to 75 years with cholesterol or triglyceride levels >200 were enrolled in a randomized, placebo-controlled, crossover study. Subjects were instructed to continue their usual daily diets and activity levels during the study. Fasting baseline laboratory values were obtained for all parameters on each subject prior to the start of the study. The test arm and the placebo arm of the study each lasted 4 weeks. There was a 4-week interval for washout between termination of one arm of the study and prior to crossover to the second arm of the study.

Each subject was instructed to take daily placebo or fish oil/garlic capsules (1800 mg of EPA, 1200 mg of DHA, and 1200 mg of garlic powder). After each 4-week arm period, fasting blood samples were drawn from a peripheral vein, and lipid fractionation and chemistry analysis panels were performed.

Fish oil and garlic extract capsules were of the brand name LipoGuard (Viva America Inc, Costa Mesa, California). Fish oil was obtained from pink salmon and garlic powder was obtained from garlic cloves. Placebo tablets contained basic ingredients of inert cellulose base and filler.

Statistical analysis was performed using paired student's *t*-test with descriptive statistics in a StatMost program (DataMost Inc, Salt Lake City, Utah). *P* values <.05 were considered significant, and results were expressed as mean \pm standard deviations (SD). All subjects volunteered for the supplementation studies with informed consent. A summary of the subjects' demographics is shown in Table 1. Diets were consistent with a standard western diet.

RESULTS

Subjects with mild hyperlipidemia were enrolled in the study to evaluate the combined effect of fish oil and garlic supplementation on the lipid profile (Table 1). Fourteen of the 40 subjects had hypertension; most had at least one other clinical condition including diabetes and coronary artery disease. All subjects successfully completed the study. Only one subject complained of esophageal reflux during the

Table 2. Effect of Fish Oil/Garlic on Patients' Lipid Profiles*

	Mean \pm SD	% Change From Baseline	No. (%) Subjects Respond†	P Value Paired
Total Cholesterol				
Baseline	238 \pm 33	—	—	—
Placebo	234 \pm 34	-1	0	NS
Fish oil/garlic (4 weeks)	213 \pm 35	-11	40/40 (100)	<.01
Triglycerides				
Baseline	214 \pm 25	—	—	—
Placebo	210 \pm 23	-2	0	NS
Fish oil/garlic (4 weeks)	142 \pm 19	-34	40/40 (100)	<.05
High-Density Lipoprotein				
Baseline	43 \pm 18	—	—	—
Placebo	42 \pm 16	-2	0	NS
Fish oil/garlic (4 weeks)	43 \pm 16	0	14/40 (35)‡	NS
Low-Density Lipoprotein				
Baseline	150 \pm 29	—	—	—
Placebo	143 \pm 27	-4	0	NS
Fish oil/garlic (4 weeks)	135 \pm 36	-10	37/40 (92)	<.01

Abbreviations: SD=standard deviation and NS=not significant.
 *40 subjects enrolled as described under methods.
 †Number of subjects showing a decrease in levels.
 ‡Number of subjects showing an increase in levels.

first hour following ingestion of the capsules; otherwise, there were no reported side effects. All subjects maintained their usual standard western diet during the study.

All subjects demonstrated a significant reduction (11%; $P<.01$) in total cholesterol, while placebo effect was nonsignificant. A significant reduction (34%; $P<.01$) in total triglycerides also was observed in all subjects, with a nonsignificant change in placebo. There was a trend toward increase in high-density lipoprotein (HDL) by 32% ($P<.01$), but this trend was noted in only 35% of the subjects. The average total HDL when all subjects were considered did not show a significant change, presumably because of the strong dependence of this variable on the diet fat content during fish oil supplementation. Low-density lipoprotein (LDL) cholesterol was significantly reduced by 10% ($P<.01$) over placebo in 80% of subjects (Table 2).

The reduction in LDL probably contributes to the reduction in total cholesterol. This significant reduction in LDL is translated into a significant reduction of 18% ($P<.05$) in the LDL/HDL cardiovascular risk ratio in 90% of the subjects (Table 3).

The reduction in total cholesterol also permits a significant reduction of 19% ($P<.01$) in the other cardiovascular risk ratio, the cholesterol/HDL risk ratio (Table 3). The combined effects of reduction in total cholesterol, total triglycerides, LDL, and cardiovascular risk ratios strongly suggest a potential favorable effect on modulation and progression of atherosclerosis and cardiovascular disease.

DISCUSSION

These results demonstrate favorable alteration in lipid profile in subjects with mild hyperlipidemia during supplementation with fish oil and garlic capsules. The lipid fraction alterations are a reflection of the summation and synergism of the individual effects of garlic and fish oil in subjects who had an abnormal lipid profile and who continued their usual dietary habits during placebo and fish oil/garlic supplementation periods over a 4-week period in each regimen. An 11% reduction was noted in total cholesterol levels during fish oil/garlic supplementation. Earlier reports demonstrated 5% to 6% reduction of total cholesterol after 4 weeks of garlic supplementation alone.^{12,17}

Table 3. Effect of Fish Oil/Garlic on Patients' Cardiovascular Risk Ratios*

	Mean \pm SD	% Change From Baseline	No. (%) Subjects Respond†	P Value Paired
LDL/HDL Risk				
Baseline	4.0 \pm 0.3	—	—	—
Placebo	3.8 \pm 0.2	-5	6/40 (15)	NS
Fish oil/garlic (4 weeks)	3.3 \pm 0.2	-18	36/40 (90)	<.05
Cholesterol/HDL Risk				
Baseline	6.4 \pm 3.5	—	—	—
Placebo	6.1 \pm 2.1	-5	4/40 (10)	NS
Fish oil/garlic (4 weeks)	5.2 \pm 2.0	-19	36/40 (90)	<.05

Abbreviations: SD=standard deviation, LDL=low-density lipoprotein, HDL=high-density lipoprotein, and NS=not significant.
*40 subjects enrolled as described under methods.
†Number of subjects showing a decrease in risk ratio.

Independently, garlic extract caused significant reduction of total cholesterol and cholesterol ester accumulation by smooth muscle cells from atherosclerotic plaque.³⁰ Supplementation with fish oil alone³¹ resulted in a change that ranged from +5% increase in high-fat diets (40%) to -5% decrease in low fat diets (30%).

Triglyceride levels were consistently lowered by 34% in this study. Previous reports indicated no change and slight increases for similar periods of garlic supplementation.^{12,17} Studies with fish oil supplementation report 41% and 30% reductions in total triglycerides with high- and low-fat diets, respectively.³² The triglyceride-lowering effect of dietary fish oils on serum lipids frequently has been demonstrated³³⁻³⁷ in healthy volunteers³⁸ and in those with abnormal lipid levels,³⁹ as well as in insulin-dependent diabetics⁴⁰⁻⁴¹ and subjects with vascular disease.⁴²

The mechanism by which garlic lowers serum lipids suggests that inhibition of hydroxymethyl glutaryl coenzyme A reductase⁴³ and cholesterol biosynthesis⁴⁴ play an important role. In contrast, the effects of fish oil and ω -3 fatty acids are modulated by the inhibition of hepatic very-low-density lipoprotein (VLDL)-triglyceride synthesis⁴⁵⁻⁴⁹ and an increase in the fractional catabolic rate of VLDLs.^{37,46-49}

The fish oil/garlic combination resulted in a significant reduction (10%) in LDL-cholesterol (LDL-C). Previous studies showed that ω -3 fatty acids and fish oils may result in a small increase (5% to 8%) of LDL-C,^{31,37} including patients with insulin-dependent diabetes^{40,41} and vascular disease.⁴² Mecha-

nisms by which ω -3 fatty acids raise LDL-C include increased synthesis or removal,³⁷ with more evidence supporting the former⁵⁰ through increased triglyceride-poor smaller and denser VLDL particles that are more readily converted to LDL.^{51,52}

In addition, these VLDL particles may compete more effectively with LDL for receptor-mediated removal.⁵³ The concentration of LDL therefore might be expected to increase despite an overall reduction in triglycerides. In contrast, reports on subjects receiving garlic supplementation demonstrate a reduction as high as 9%¹² and as low as 1%.⁵⁴ The effects of garlic on LDL reduction may be mediated by its rich content of the antioxidants vitamin C, selenium, and organic germanium.⁵⁵ Selenium⁵⁶ and vitamin C^{57,58} recently have been shown to decrease LDL-C by 14% and 5.6%, respectively. The net effects of the combined effect of fish oil and garlic in this study was a significant reduction in LDL-C.

In the present study, there was no significant change in the average total HDL levels when all subjects were considered, although there was a trend toward an increase in a subgroup representing 35% of the subjects. Several studies demonstrated no effect of garlic supplementation alone on HDL.^{12,54,59} However, many studies with fish oil supplementation demonstrate a substantial increase in the HDL₂ subfraction that may be reflected as a total HDL increase (5% to 7%), particularly in low-fat diets.³¹ The lack of significant total HDL increase in the present study is probably secondary to the absence of inherent garlic effects and the small effects of fish oil supplementation on this lipid subfraction.

CONCLUSION

The proposed benefits of dietary fish oil and garlic supplementation on cardiovascular disease largely is supported by the observed significant reduction in both the LDL/HDL and cholesterol/HDL risk ratios reported in the present study. These reductions are a result of the significant reduction of the LDL and cholesterol levels. In a small group of hypercholesterolemic men, similar reductions in risk factors recently were reported.⁵⁹

From a nutritional and public health standpoint, these results suggest additive and synergistic beneficial alterations in the lipid profile that translate into significant reduction in the lipid subfraction risk ratios for cardiovascular diseases by fish oil and garlic combination. The results should be viewed as an extension of the other beneficial properties of these agents, including antioxidant activity and reduced platelet aggregability that are likely to contribute to their role in preventing coronary heart disease.

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