

Reduction of postprandial triglyceridemia in humans by dietary n-3 fatty acids

William S. Harris,¹ William E. Connor, Nargis Alam, and D. Roger Illingworth

Division of Endocrinology, Metabolism, and Clinical Nutrition, Department of Medicine, Oregon Health Sciences University, Portland, OR 97201

Abstract Long chain n-3 fatty acids present in fish oils have been shown to reduce fasting plasma triglyceride and very low density lipoprotein levels in normal and hyperlipidemic human subjects. The present studies were designed to examine whether dietary n-3 fatty acids influence chylomicron formation and metabolism in healthy volunteers. In the first study seven subjects were fed either saturated fat, vegetable oil, or fish oil-based diets for 4 weeks each, and test meals containing 50 g of the background fat were administered after the second week of each diet. The postprandial rise in triglyceride levels was significantly lower following the fish oil test meal as compared to the saturated fat or vegetable oil test meals. In the second study, six subjects eating their usual home diets were given two fat tolerance tests. The first contained saturated fat and the second, given 1 week later, contained fish oil. There was no difference in the postprandial triglyceride response between the fish oil and the saturated fat meals. A third study was then conducted with eight volunteers in which saturated fat and fish oil test meals were administered during saturated fat and fish oil background diets in a crossover design. The presence of fish oil in the background diet reduced postprandial lipemia regardless of the type of fat in the test meal. Although there was no effect of the fish oil diet on the lipoprotein lipase and hepatic lipase activity of postheparin plasma measured in vitro, stimulation of in vivo lipolysis was not ruled out. **Our results suggest that chronic (but not acute) intake of fish oil may inhibit the synthesis or secretion of chylomicrons from the gut. However, accelerated clearance due to decreased VLDL competition cannot be excluded.—Harris, W.S., W.E. Connor, N. Alam, and D.R. Illingworth. Reduction of postprandial triglyceridemia in humans by dietary n-3 fatty acids. *J. Lipid Res.* 1988. 29: 1451–1460.**

Supplementary key words fish oils • chylomicrons • very low density lipoproteins • fatty acids • hypotriglyceridemic agents

A dramatic reduction in the concentration of plasma triglyceride has been the most consistent effect noted in people consuming diets rich in long chain n-3 polyunsaturated fatty acids from fish oils (reviewed in ref. 1). We have previously found that dietary fish oil reduced the triglyceride levels by 33% in normal subjects and 64 to 80% in patients with moderate and severe hypertriglyceridemia (2-4). In these studies, 30-

40% of calories were derived from fish oil. However, significant decreases in plasma triglyceride and very low density lipoprotein (VLDL) levels have been reported with as little as 20 ml of cod liver oil per day or 10 g of MaxEPA, a fish oil concentrate (5, 6).

The present investigations were designed to further elucidate the mechanisms responsible for the hypotriglyceridemic effect of dietary fish oils. Reductions in the plasma concentrations of triglyceride may be attributable to decreased secretion of triglyceride-rich lipoproteins from the liver (VLDL) or small intestine (VLDL and chylomicrons) into plasma, increased rates of their removal, or a combination of these. The two enzymes responsible for the intravascular hydrolysis of triglyceride are lipoprotein lipase (LPL) and hepatic triglyceride lipase (7, 8). To assess whether dietary fish oils may influence triglyceride removal from VLDL and chylomicrons, we have measured the activities of both of these enzymes in postheparin plasma after a diet high in n-3 fatty acids.

We have previously shown that a diet rich in fish oil caused a dramatic blunting of the normal rise in plasma triglyceride levels following a fatty meal (3). To determine whether this effect was the result of the presence of fish oil in the test meal or in the background diet, we have examined the effects of n-3 fatty acids on postprandial triglyceride levels. Our results suggest that the presence of n-3 fatty acids in the background diet alone will reduce postprandial triglyceride levels regardless of the type of fat administered in the meal itself.

Abbreviations: VLDL, very low density lipoproteins; LDL, low density lipoproteins; HDL, high density lipoproteins; LPL, lipoprotein lipase; apoB, apolipoprotein B; EPA, eicosapentaenoic acid; FFA, free fatty acids.

¹Reprint requests should be sent to Dr. Harris' current address: Lipid and Arteriosclerosis Prevention Clinic, Department of Medicine, University of Kansas Medical Center, Kansas City, KS 66103.

METHODS

Subjects

Twenty one normolipidemic subjects (11 males and 10 females) volunteered for these experiments. They ranged in age from 21 to 54 years (mean, 33 yr). None of the subjects was obese (over 120% of ideal body weight), and none was taking medication known to affect lipid metabolism. The baseline diets of the study subjects remained stable and no participant made any significant changes in daily exercise between study periods. Informed consent was obtained from each subject before entering the study. The protocol had been approved by the Human Research Committee of the Oregon Health Sciences University.

Study protocols

Three studies were designed to test the effects of n-3 fatty acids upon postprandial triglyceride metabolism (fat tolerance). The three different protocols used are outlined in **Table 1**. In Study I, we compared fat tolerance when the fat in the background diet was the same as the fat fed in the test meal. Three different types of fat were studied in each of the seven subjects in this first study: saturated fats versus polyunsaturated vegetable oil versus salmon oils (see Diets for details). The results of this study led us to design Study II in which six subjects consuming their normal home diets were given two fat tolerance test meals one week apart. The first contained saturated fats and the second, fish oil. Study III was designed to determine whether the presence of n-3 fatty acids in the background diet, the test meal, or both influenced the postprandial triglyceridemic response. In this study, each of the eight subjects was given four separate fat tolerance tests: two (one saturated fat and one fish oil

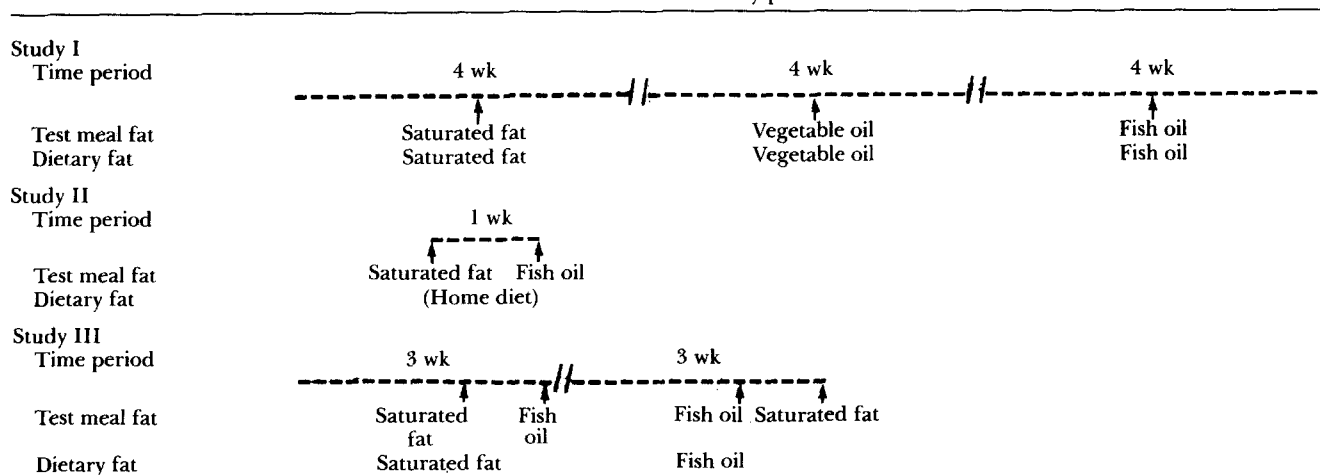
test) when the subjects were consuming the background diet rich in saturated fat and the other two during the fish oil dietary phases.

Diets

All diets (except those in Study II) were prepared and fed in the Clinical Research Center. They contained both mixed foods (fruits, vegetables, grains) and a liquid formula (protein and fat), and were composed of 30–40% of calories as fat, 15% as protein, and 55–45% as carbohydrate as described previously (2, 3). The cholesterol intake for each subject remained constant during each dietary period (125 mg/1000 kcal), but ranged from 300 to 500 mg/day from subject to subject. The primary sources of protein were fish fillets (salmon or black cod) which were given during the fish oil diet, and casein which was given during the saturated fat and the vegetable oil diets.

The fatty acid compositions of the fats that were used in the experimental diets are described in **Table 2**. The saturated fat diet contained a mixture of peanut oil and cocoa butter and was designed to simulate the fatty acid composition of the typical American diet (9). A mixture of safflower oil and corn oil was given during the polyunsaturated vegetable oil diet and either salmon oil or MaxEPA (R.P. Scherer Co., Troy, MI) provided the n-3 fatty acids during the fish oil phases of Study I and Study III, respectively. The salmon oil diet provided about 24 g of n-3 fatty acids per day, and the MaxEPA diet about 28 g per day, both based upon a 2,500 kcal diet. No other foods or alcohol were allowed during the study periods except calorie-free beverages. Compliance was estimated by observation of food intake, close daily contact with the subjects, weight stability, and the presence of n-3 fatty acids in the plasma of the subjects during the fish oil phases (data not presented here).

TABLE 1. Study protocols^a



^aDietary sequences were randomized in studies I and III; arrows indicate when the fat tolerance meals were given.

The fat tolerance test meals given to induce postprandial lipemia varied only in the type of fat (saturated fat, fish oil or vegetable oil) which they contained. Each meal provided a total of 800 kcal and was made up of 50 g of the test fat, 42 g of carbohydrate (dextrimaltose, cornstarch, and sucrose), and 43 g of protein (calcium caseinate). The cholesterol content was 170 mg. The salmon oil meal contained 11 g of n-3 fatty acids and the MaxEPA meal about 16 g. Fifty g of fat was chosen because this was considered to be both a typical and physiological level (9). The meals were given as a liquid formula at 8–9 AM in the morning and were consumed over a 10–15-min period.

Study procedures

Experimental diets were fed for 4 weeks each in Study I, and for 3 weeks in Study III. They were randomly allocated throughout the study. The assays for postheparin plasma lipolytic activity were done at the end of the third week of the fish oil and saturated fat periods of Study I. The fat tolerance tests were conducted after the second week of each dietary period in Study I, and after the second and the third weeks in Study III. In Study II, the saturated fat tolerance test was given 1 week before the fish oil test.

Fat tolerance meals were administered in the morning following a 12–14-hr fast. Blood samples were drawn to determine baseline triglyceride levels, then the subjects drank the test formula. Further blood samples were drawn every other hour (every hour in Study III) for the next 8 hr. The subjects were allowed only calorie-free beverages throughout the 8 hr of the test. After the final blood samples were drawn, the

subjects were given their food for the rest of the day. Physical activity for each subject was similar during each fat tolerance test.

Laboratory methods

Postheparin lipolytic activity was determined in fasting plasma samples obtained 15 min after the intravenous injection of sodium heparin (beef lung, Upjohn Co., Kalamazoo, MI) at a dose of 100 units/kg body weight. Blood samples were collected into chilled tubes, cooled on ice, and the plasma was separated by centrifugation at 4°C. Total and protamine-resistant postheparin lipolytic activity (the latter is equal to hepatic triglyceride lipase) was determined by modification of the methods of Krauss, Levy, and Fredrickson (7) and Glad et al. (8). Briefly, the procedure involved incubating postheparin plasma with [$1-^{14}\text{C}$] triolein and heat-inactivated serum (a source of apolipoprotein C-II). After a 30-min incubation (with and without protamine), the reaction was stopped and the amount of radioactive oleic acid liberated was measured. The procedure has been described in detail previously (10).

Plasma cholesterol, triglyceride, and lipoprotein lipid levels were measured with an AutoAnalyzer II (Technicon Instruments, Tarrytown, NY) using Lipid Research Clinics methods (11). The fatty acid composition of chylomicron triglyceride was measured in one subject from Study II after a fish oil fat tolerance test. Chylomicrons were isolated by overlaying 3 ml of plasma with 3 ml of physiological saline followed by centrifugation in a Beckman 40.3 rotor at 0.67×10^6 g-min (11). The fatty acid compositions of the diets and chylomicron triglyceride were determined by combined thin-layer and capillary gas-liquid chromatography as previously described (12).

TABLE 2. The fatty acid composition of the three experimental fats^a

Fatty Acid	Saturated Fat	Vegetable Oil	Fish Oil	
			MaxEPA	Salmon
		*% of total fatty acids		
16:0	19	12	17	15
16:1(n-7)	1	0	9	6
18:0	17	3	3	6
18:1(n-9)	40	26	15	23
18:2(n-6)	18	54	2	3
20:1(n-9)	0	0	2	10
20:5(n-3)	0	0	17	9
22:1(n-11)	0	0	1	9
22:5(n-3) + 22:6(n-3)	0	0	15	11
Saturated	36	16	30	25
Monounsaturated	41	27	29	48
n-6 Polyunsaturated	18	54	2	3
n-3 Polyunsaturated	<1	<1	34	20
Iodine no. ^b	69	121	198	167
P/S Ratio	0.5	3.4	1.2	0.9

^aSources of fats: saturated fat, cocoa butter and peanut oil; vegetable oil, safflower and corn oils; MaxEPA, R.P. Scherer, Co., Troy, MI; salmon, Oregon Aqua Foods, Astoria, OR.

^bIodine numbers were calculated from fatty acid composition.

Data analysis

The postprandial rise in plasma triglyceride levels was assessed by two methods. The triglyceridemic response was defined as the average of the two highest postprandial triglyceride levels minus the baseline (fasting) triglyceride level according to the method of Patsch et al. (13). This method provides an estimate of the magnitude of the plasma triglyceride rise without regard for the time course of the rise. Secondly, the average rise in plasma triglyceride levels at each hour after the meal was also computed and compared between treatments.

Statistical comparisons were also carried out by two methods. When only two comparisons were involved, the Student's t-test for paired observations was used. When the subjects were studied under three or more conditions (e.g., Study III), an analysis of variance with repeated measures was performed followed by the Newman-Keuls test for differences between groups. These methods are described in Winer's text (14).

RESULTS

Study I

The effects of salmon oil on the plasma lipid and lipoprotein cholesterol levels of the subjects in Study I are given in Table 3. Plasma triglyceride levels on the day the test meals were given were 72 ± 19 , 76 ± 37 , and 46 ± 11 mg/dl on the saturated fat, vegetable oil, and fish oil phases, respectively. Comparing these values with those in Table 3, it can be seen that plasma triglyceride levels had stabilized by the second week of the 4-week trial.

The total postheparin plasma lipolytic activity, as well as the activities of hepatic triglyceride lipase and LPL, were measured in Study I. Total lipase activity (in $\mu\text{mol FFA released/hr per ml}$) was 11.6 ± 2.9 for

the saturated period and 11.7 ± 2.6 for the fish oil period. Corresponding values for hepatic lipase and lipoprotein lipase were 6.5 ± 1.9 and 5.1 ± 2 on the saturated diet and 6.4 ± 1.5 and 5.3 ± 2 on the fish oil diet, respectively. These differences were not statistically significant.

The postprandial triglyceride response to meals containing 50 g of the respective dietary fats was reduced with the fish oil diet compared to both the saturated diet and the polyunsaturated vegetable oil diet (Fig. 1). The rise in plasma triglyceride was significantly less during the fish oil diet at 4 hr after the test meal. In addition, the triglyceridemic response during the fish oil diet was significantly reduced compared to the two other dietary fats (Fig. 2). There was no difference in the triglyceridemic responses between the vegetable oil diet and the saturated fat diet.

Study II

Fish oil was not fed chronically during Study II, so fasting triglyceride levels were the same at the time of each fat tolerance test (77 ± 38 and 70 ± 30 mg/dl for saturated fat and fish oil, respectively). There was no significant difference in either the shape of the fat tolerance curves or the magnitude of the triglyceridemic response between the fish oil and the saturated fat meals (73 ± 34 vs 59 ± 46 mg/dl, respectively) (Fig. 3). Indeed, there was a nonsignificant tendency toward higher and more prolonged rises in plasma levels with the fish oil meal. These results indicate that the fish oil fatty acids were well absorbed by the small intestine and incorporated into chylomicron triglycerides.

Study III

The effects of feeding n-3 fatty acids from MaxEPA during Study III are given in Table 3. MaxEPA caused a significant lowering of total, VLDL, and LDL cholesterol levels, and a trend toward lower HDL levels.

TABLE 3. The effects of MaxEPA (30% of calories) on plasma lipids and lipoproteins in studies I^a and III

Diet	Plasma Cholesterol				Plasma Triglyceride	
	Total	VLDL	LDL	HDL	Total	VLDL
Study I (n = 7)						
Saturated fat	191 ± 38	12 ± 5	127 ± 43	53 ± 10	76 ± 22	
Vegetable oil	174 ± 41	12 ± 5	115 ± 37	54 ± 8	75 ± 21	
Salmon oil	170 ± 39	6 ± 2	111 ± 43	54 ± 11	50 ± 17	
Significance ^b	***	****	**	NS	***	
Study III (n = 8)						
Saturated fat	185 ± 40	14 ± 9	129 ± 41	40 ± 16	80 ± 36	51 ± 35
MaxEPA	126 ± 25	5 ± 2	94 ± 30	32 ± 3	45 ± 15	7 ± 6
Significance	$P < 0.01$	$P < 0.05$	$P < 0.01$	NS	$P < 0.01$	$P < 0.025$

^aTaken from reference 2.

^b**Saturated fat vs vegetable oil, $P < 0.05$; ***saturated fat vs fish oil, $P < 0.05$; ****vegetable vs fish oil, $P < 0.05$.

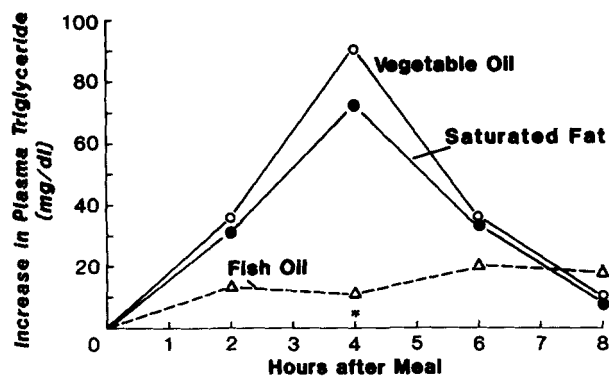


Fig. 1. Study 1: The increase in plasma triglyceride levels following the ingestion of 50 g of fat. Saturated fat test meal given during the saturated fat diet (closed circles); vegetable oil test meal given during the vegetable oil diet (open circles); salmon oil test meal given during the salmon oil diet (triangles). Mean fasting triglyceride levels were 72 ± 19 , 76 ± 37 , and 46 ± 11 mg/dl before the saturated fat, vegetable oil, and salmon oil, respectively, test meals were administered. Statistical comparison of the plasma triglyceride increases at the designated hours: *, $P < 0.05$; **, $P < 0.01$; ***, $P < 0.005$. No symbol, not significant (for all figures).

Total and VLDL triglyceride levels were also reduced significantly.

In order to separate the effects of the fat in the background diet from the fat in the test meal, the fish oil and the saturated fat test meals were both given during each of the two background diets. The four combinations of experimental conditions can be compared to each other in six ways. Four of these are presented graphically in Fig. 4. These figures show the fat tolerance curves when the same meal was tested during the two different background diets (Fig. 4A and 4B), and when the two different test meals were given during the same background diet (Fig. 4C and 4D).

The fish oil background diet produced significantly lower triglyceridemic responses than the saturated fat background diet, regardless of the type of fat given in the test meal (Fig. 5). This is also evident in Figs. 4A and 4B. The former depicts the postprandial rise in triglyceride levels following the saturated test meal given during the saturated and the fish oil background diets. The same comparison is made in Fig. 4B using fish oil in the test meal. In both cases, the triglyceridemic responses were lower during the fish oil background diet. Moreover, the two different test meals did not produce significantly different triglyceridemic responses when they were given during the same background diet (Fig. 5). Differences in responses appeared only when the same test meals were taken during different background diets. The results of Study III confirmed the observations made in the first two studies, and again demonstrated that fish oils are absorbed just as efficiently as saturated fats in subjects consuming the typical American diet.

Compared to the saturated fat test meal, the fish oil test meal appeared to cause a slower rise in triglyceride levels when given to subjects eating the fish oil background diet, as evidenced by the lower triglyceride increases at 2 and 3 hr after the meal (Fig. 4C). In addition, postprandial triglyceride levels stayed elevated somewhat longer following the fish oil test meal on both the fish oil and saturated fat background diets (Figs. 4C and 4D).

The fatty acid composition of chylomicron triglycerides at 1 and 4 hr after the fish oil test meal is given in Table 4. The test was given during the subject's normal background diet. The concentration of n-3 fatty acids in the chylomicron triglycerides approached those in the test oil at 4 hr, confirming that these fatty acids are well absorbed and incorporated into chylomicrons.

DISCUSSION

The regular ingestion of relatively large amounts of n-3 fatty acids from fish oils consistently lowers plasma triglyceride levels (present in VLDL) in normal subjects (2,3) and in hypertriglyceridemic patients (4). The present study was conducted to examine the effects of dietary fish oils on the concentrations of exogenous triglyceride-containing lipoproteins (chylomicrons) in the plasma of normal subjects. We found that the presence of fish oil in the background diet reduced the extent of postprandial lipemia, and that this effect was independent of the type of fat ingested.

Several possible mechanisms can be proposed to explain these effects, and they will be discussed indi-

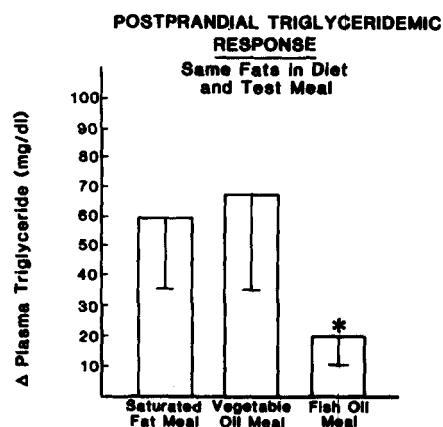


Fig. 2. Study I: Triglyceridemic response to three dietary fats when the fat in the test meal was the same as the fat in the background diet. Mean fasting triglyceride levels were 72 ± 19 , 76 ± 37 , and 46 ± 11 mg/dl before the saturated fat, vegetable oil, and salmon oil, respectively, test meals were administered; *, $P < 0.05$ vs both saturated fat and vegetable oil.

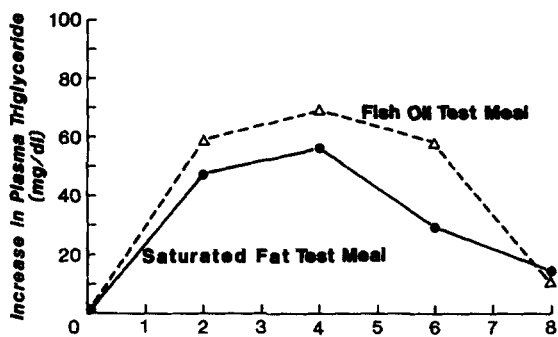


Fig. 3. Study II: The increase in plasma triglyceride levels following the ingestion of 50 g of fat. Background diets were fed ad libitum; saturated fat test meal (circles); MaxEPA test meal (triangles). Mean fasting triglyceride levels were 77 ± 38 and 70 ± 30 mg/dl before the saturated fat and fish oil test meals, respectively.

vidually. The reduced postprandial triglyceride levels observed with fish oil feeding may have resulted from a decrease in the rate or efficiency of n-3 fatty acid absorption. Bottino, Vandenberg, and Reiser (15) have suggested that the unique configuration of triglycerides containing n-3 fatty acids may prevent their interaction with lipolytic enzymes via steric hinderance. They showed that the in vitro hydrolysis of whale oil

triglycerides by pancreatic lipase was retarded. Chen et al. (16) studied fish oil absorption in the lymph-cannulated rat model. When they infused (intraduodenally) free EPA, they found that it was absorbed equally as well as oleic acid. However, when they infused fish oil (esterified EPA), they found that it was absorbed more slowly than corn oil (17). These results infer a slower rate of intraluminal hydrolysis of triglycerides containing n-3 fatty acids by pancreatic lipase.

These findings contrast with the in vivo observations of the present study in which a fish oil test meal produced a normal postprandial rise in triglyceride levels during the control background diet. In addition, fish oils did not cause fat malabsorption. None of our subjects lost weight, had steatorrhea, or an increased frequency of bowel movements. Fecal fat levels (measured in ten subjects) were within normal limits (less than 5 g/day) during the fish oil period. Although the reason(s) for this apparent discrepancy between the human studies, and the animal and in vitro data are not known, the latter studies may not have completely mimicked the in vivo situation in which a multitude of enzymes, cofactors, and gastrointestinal hormones all play a role in fat absorption. Similarly, the decrease in postprandial triglyceride levels during chronic fish oil feeding observed in the present study may have resulted

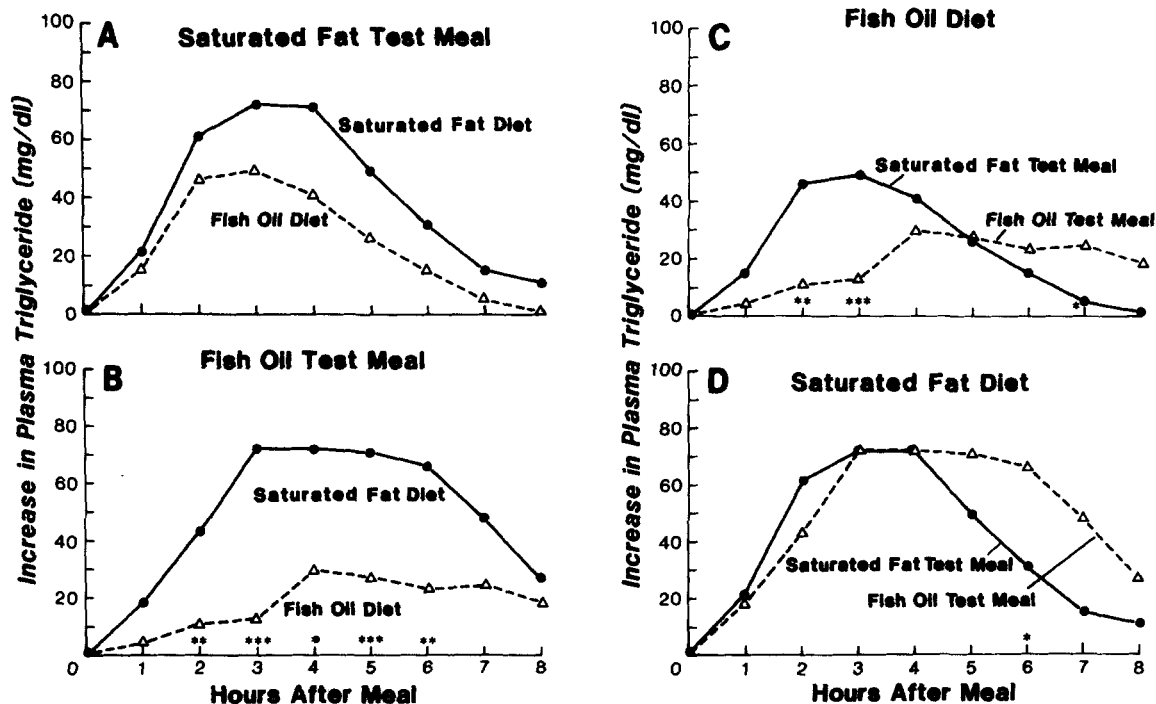


Fig. 4. Study III: The increase in plasma triglyceride levels following the ingestion of 50 g of fat. The same test meals given during different background diets: A) saturated fat meal during the saturated fat diet (circles) and during the fish oil diet (triangles); B) fish oil meal during the saturated fat diet (circles) and during the fish oil diet (triangles). Different meals given during the same background diets: C) fish oil background diet with the saturated fat meal (circles) and the fish oil meal (triangles); D) saturated fat background diet with the saturated fat meal (circles) and the fish oil meal (triangles). Fasting triglyceride levels were 80 ± 36 and 45 ± 15 mg/dl before the test meals were given during the saturated fat and fish oil periods, respectively. Significance is described in Fig. 1.

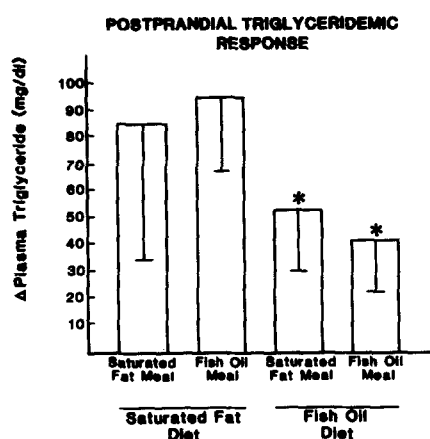


Fig. 5. Study III: The plasma triglyceridemic response to dietary fats when the fat in the test meal was either the same as or different from the fat in the background diet. Fasting triglyceride levels were 80 ± 36 and 45 ± 15 mg/dl before the test meals were given during the saturated fat and fish oil periods, respectively; *, $P < 0.05$ vs both of the responses observed during the saturated fat background diet.

from other changes in the intraluminal or digestive environment, or from potential changes in gastrointestinal motility.

Fish oils may affect the formation of chylomicron particles in the enterocyte. Although this has not been specifically investigated, several previous studies have examined the effects of n-3 fatty acids on hepatic VLDL production and have demonstrated a decrease in VLDL triglyceride and apolipoprotein B production (18–26). Since triglyceride resynthesis takes place in the enterocyte during fat absorption (27), it is possible that this process is likewise inhibited by n-3 fatty acids. Such an inhibition would lead to a reduced rate of formation of chylomicrons secondary to a reduction in endogenous triglyceride synthesis from newly absorbed free fatty acids and monoglycerides, and would produce lower postprandial chylomicronemia. As in the liver, this effect would only become evident after chronic treatment with fish oil, not after a single meal. (Chronic treatment would gradually modify cell membrane fatty acid composition which may alter enzyme activities as discussed below.) This explanation fits with the observations of the present study in which

fat absorption was inhibited only when subjects were chronically consuming diets rich in n-3 fatty acids; both control and fish oil absorption was normal when n-3 fatty acids were not in the background diet. Future studies will be needed to probe this hypothesis.

The third possible explanation for our results is that the decreased postprandial triglyceride levels observed with chronic fish oil feeding are due to an increased rate of triglyceride removal. There are several mechanisms by which this could occur: 1) enhanced activity of LPL or hepatic triglyceride lipase; 2) facilitated interaction of chylomicrons with these enzymes secondary to the presence of n-3 fatty acids in the particles themselves or in endothelial cell membranes; or 3) greater interaction of chylomicrons with these enzymes because of reduced substrate competition from VLDL.

Our data do not support the first possibility; neither the activity of LPL nor hepatic triglyceride lipase was stimulated by fish oil feeding when measured in vitro in postheparin plasma. Similar findings have been reported in rats (28) and chickens (29) fed fish oil.

The second possibility, that n-3 fatty acids in the chylomicrons accelerate their clearance, has been studied in rats by Chen et al. They found that, both in vitro (30) and in vivo (31), chylomicron removal rates were not enhanced when the particles contained n-3 fatty acids. In the present study, we found that the fish oil test meal produced normal (or even elevated compared to control) postprandial increases in triglyceride levels. Thus, the presence of n-3 fatty acids in the chylomicrons does not accelerate their clearance.

Changes in the fatty acid composition of cell membranes can affect the activity of membrane-bound enzymes (32–34). Such an effect might alter lipogenic (as noted above) or lipolytic enzymes. Whether n-3 fatty acids affect the activity of LPL in vivo is not known. Although kinetic data from human studies have indicated that diets rich in n-3 fatty acids do not enhance VLDL triglyceride removal rates (18,19), this does not necessarily mean that chylomicron triglyceride removal is also not stimulated by fish oil inges-

TABLE 4. The fatty acid composition of chylomicron triglycerides following a MaxEPA test meal

Fatty Acid	Chylomicron Triglycerides		MaxEPA
	1 hr ^a	4 hr ^a	
16:0	20.8	17.7	17
16:1(n-7)	6.2	7.3	9
18:0	3.9	3.1	3
18:1(n-9)	24.5	14.9	15
18:2(n-6)	14.3	6.6	2
20:5(n-3)	7.6	14.1	17
22:6(n-3)	5.0	8.3	11

^aTime after ingestion of test meal containing 50 gm of MaxEPA.

tion. Such a mechanism has not been ruled out. Nevertheless, available data do not suggest that the reduced postprandial triglyceridemia seen with fish oil feeding is caused by enhanced lipolytic activity.

Finally, it is well known that elevated plasma triglyceride (VLDL) levels interfere with chylomicron clearance (35–38). This presumably results from increased competition for LPL between these two lipoprotein particle types. Thus, the fish oil-induced reduction in postprandial lipemia may simply reflect a more rapid removal of chylomicrons because less VLDL is present to compete for hydrolysis of triglycerides.

As attractive as this explanation may be, there is one major difficulty with it. In the studies reported here, the mean fasting triglyceride levels during the saturated fat phases were only about 76 mg/dl, and during the fish oil phases they were about 45 mg/dl. In order to explain the reduced postprandial triglyceridemia by this mechanism, one must assume that LPL was, to a physiologically significant extent, saturated at a triglyceride level of 76 mg/dl, and that it became significantly less saturated at the lower triglyceride value. This assumption has not been directly investigated. Nestel (38), Grundy and Mok (35), Denborough and Paterson (36) and Patsch et al. (13) have all studied the relationship between fasting triglyceride levels and postprandial triglyceride levels. They have clearly shown that individuals who have high fasting triglyceride levels (200 to 500 mg/dl) also have exaggerated postprandial triglyceride responses. In most of these studies, very few individuals with low triglyceride levels (<100 mg/dl) were included, and thus no judgement can be made about changes in chylomicron clearance as a function of triglyceride levels in this low range. Patsch et al. (13) were the only ones to compare the triglyceridemic response to a fat load in subjects with fasting levels less than 125 mg/dl. Although they showed a statistically significant ($r=0.45$) correlation between the fasting triglyceride level and the triglyceridemic response to the test meal, this was between subjects; not in the same subjects studied longitudinally. These investigators did not show that lowering triglyceride levels from 80 to 50 mg/dl in the same person accelerated chylomicron removal rates. Until studies are done to directly assess the effects of low, fasting triglyceride levels on chylomicron metabolism, it cannot be concluded that the improved fat tolerance in the fish oil studies resulted from reduced competition from VLDL.

Regardless of the mechanism, the reduction in chylomicrons (and presumably chylomicron remnants) may be cardioprotective since the latter have been implicated in atherogenesis (39–43). Recent angio-

graphic studies have demonstrated a high frequency of lipoprotein remnant particles in the plasma of patients with coronary artery disease (44). Patients with type III hyperlipoproteinemia have increased levels of triglyceride-rich lipoprotein remnants and are at increased risk for atherosclerosis. These data support the view that increased plasma concentrations of chylomicron remnant particles may play a role in the atherogenic process. The reported rarity of coronary heart disease among populations ingesting large amounts of n-3 fatty acids (e.g., Greenland Eskimos) may, in part, be the result of lower levels of chylomicron remnant particles (45). Further studies are warranted to examine the effects of n-3 fatty acids on chylomicron remnant production and metabolism as well as on the intestinal synthesis of triglycerides and apolipoproteins. ■

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