Effects of Fish Oil Supplementation on Glucose and Lipid Metabolism in NIDDM

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Fish oils, containing omega-3 fatty acids (ω3FAs), favorably influence plasma lipoproteins in nondiabetic humans and prevent the development of insulin resistance induced by fat feeding in rats. We studied the effects of fish oils in 10 subjects (aged 42–65 yr) with mild non-insulin-dependent diabetes mellitus (NIDDM). Subjects were fed a standard diabetic diet plus *1*) no supplementation (baseline), *2*) 10 g fish oil concentrate (30% ω3FAs) daily, and *3*) 10 g safflower oil daily over separate 3-wk periods, the latter two supplements being given in radom order by use of a double-blind crossover design. At the end of each diet period, fasting blood glucose (FBG), insulin, and lipids were measured, and insulin sensitivity was assessed with a hyperinsulinemic-euglycemic clamp performed with [3-^{3}H]glucose. FBG increased 14% during fish oil and 11% during safflower oil supplementation compared with baseline ($P < .05$), whereas body weight, fasting serum insulin levels, and insulin sensitivity were unchanged. The absolute increase in FBG during each supplementation period correlated with the baseline FBG (fish oil, $r = .83$, $P < .005$; safflower oil, $r = .75$, $P = .012$). Fasting plasma triglyceride levels decreased during fish oil supplementation in the 4 subjects with baseline hypertriglyceridemia (>2 mM) but were not significantly reduced overall. There was no significant change in fasting plasma total, high-density lipoprotein, and low-density lipoprotein cholesterol levels. In summary, dietary fish oil supplementation adversely affected glycemic control in NIDDM subjects without producing significant beneficial effects on plasma lipids. The effect of safflower oil supplementation was not significantly different from fish oil, suggesting that the negative effects on glucose metabolism may be related to the extra energy or fat intake. These data indicate that fish oil supplementation should be used with caution in subjects with NIDDM. *Diabetes* 38:1314–19, 1989

The regular consumption of even small amounts of fish has been correlated with a reduced mortality from coronary artery disease (CAD;1–4). This phenomenon has been ascribed to the beneficial effects of the two major long-chain polyunsaturated omega-3 fatty acids (ω3FAs), eicosapentaenoic acid (EPA; C20:5ω3) and docosahexaenoic acid (DHA; C22:6ω3), on lipoprotein metabolism (5–8), platelet function (9–11), and leukotriene production (12), although other mechanisms may contribute (13–15). Non-insulin-dependent diabetes mellitus (NIDDM) is associated with hyperlipoproteinemia, enhanced platelet aggregability, and a marked predisposition to development of atherosclerotic complications, especially CAD (16). Because the resultant mortality in NIDDM subjects is twice that of nondiabetic subjects, increased consumption of ω3FAs may be of benefit.

Another issue is whether dietary ω3FAs influence the abnormal glucose metabolism of individuals with NIDDM. Greenland Eskimos, whose diet contains large amounts of fish (17), have a low prevalence of CAD and NIDDM despite their relative obesity (18,19); this suggests that fish oils might have a preventive influence on NIDDM and CAD. Such an effect could result from changes in insulin-stimulated glucose uptake, which is characteristically impaired in NIDDM (20). We have shown that a diet rich in safflower oil produces a similar impairment of insulin action in rats (21), which is prevented by substitution of some of the linoleic acid (an ω6 fatty acid) with ω3FAs derived from fish oil (22). If the same effect occurs in humans, fish oil could be a valuable adjunct to therapy for NIDDM.

In this study, we evaluated the potential benefits of dietary fish oil supplementation in subjects with mild NIDDM. Effects

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on glycemic control, insulin sensitivity, and plasma lipids were assessed after 3-wk periods of dietary supplementation with a fish oil concentrate and safflower oil in random order. Comparison was made with safflower oil so the specific effects of fish oil could be separated from any effects of additional calories or unsaturated fatty acids.

RESEARCH DESIGN AND METHODS

Subjects. After a complete explanation of the protocol, 10 subjects with NIDDM gave written informed consent to the study, which was approved by the St. Vincent's Hospital Ethics and Research Committee. Six were treated with diet alone, and 4 were treated with diet and 2.5 or 5 mg glyburide daily. Subjects had no clinical or biochemical evidence of kidney or liver disease or any diabetic microvascular complications. One had stable ischemic heart disease, and 2 had hypertension controlled with medicine. Clinical details are shown in Table 1. The mean ± SE fasting plasma triglyceride and cholesterol levels were 2.41 ± 0.46 and 6.03 ± 0.38 mM, respectively, at entry into the study.

Protocol. Subjects were studied over 12 wk, during which they consumed a standard diabetic diet and took their usual medicine. The dosage of hypoglycemic agents was held constant throughout the study. The initial 3 wk served as a baseline during which no additional therapy was taken. Subjects were then instructed to supplement their basic diet with 10 g fish oil concentrate daily and 10 g safflower oil daily over separate 3-wk periods, with a randomized double-blind crossover design with an intervening 3-wk washout period. Fasting blood samples were taken weekly during each diet period for measurement of glucose, insulin, C-peptide, and lipid concentrations. Insulin sensitivity was assessed with a hyperinsulinemic-euglycemic clamp at the end of the baseline and both oil supplementation periods.

Diets and dietary assessment. On recruitment into the study, each subject was given individual dietary counseling, and a standard diet low in fat and high in complex carbohydrate and fiber was prescribed to be consumed throughout the study. Subjects were instructed to avoid eating fish. Self-recorded 4-day food records, obtained on recruitment and at the end of each diet period, were used to monitor dietary composition. This data was analyzed with the Computerized Dietary Analysis Package developed by the Commonwealth Scientific and Industrial Research Organisation of Australia, which is based on British food-composition tables (23).

TABLE 1
Clinical details of subjects at entry into the study

Subject	Sex	Age (yr)	Body mass index (kg/m²)	Duration of diabetes (yr)	Fasting blood glucose (mM)
1	M	62	31	0.3	4.9
2	M	49	34	1.5	5.0
3	F	58	36	1	8.4
4	M	56	29	1.5	6.8
5	M	64	22	6	5.7
6	M	57	25	4	8.7
7	M	63	26	4	6.1
8	M	43	33	3.5	7.1
9	F	56	27	3.5	10.0
10	F	64	25	10	4.4
Mean ± SE		57 ± 2	29 ± 1	3.5 ± 0.9	6.7 ± 0.6

Oil capsules. The fish oil supplement was provided as unlabeled 1-g capsules of a commercially available fish oil extract, MaxEPA (Scherer, Melbourne, Australia), containing ~18% EPA and 12% DHA as triacylglycerols and 6 mg cholesterol/g. The safflower oil supplement, which was cholesterol free, was provided in similar 1-g capsules.

Euglycemic clamp. At the end of each diet period, a hyperinsulinemic-euglycemic clamp was performed as previously described (24). At 0800–0900, after a 10- to 12-h overnight fast, an intravenous cannula was inserted into an antecubital vein for infusion of insulin, glucose, and [3-^{3}H]glucose. Another cannula was inserted into a dorsal vein of the contralateral hand and warmed to ~50°C with a heating pad to provide arterialized venous blood for sampling. A continuous infusion of [3-^{3}H]glucose (25 μCi/h) was then begun and continued throughout the study. One hundred twenty minutes after the tracer infusion was started, 68 mU · kg^{-1} · h^{-1} purified porcine insulin (Actrapid, Novo, Copenhagen) was infused until the end of the study. A variable-rate glucose infusion was adjusted according to glucose measurements taken every 5 min to clamp the blood glucose level at 5 mM. Plasma samples were taken at 10-min intervals during the basal 120 min and at 15-min intervals during the clamp for measurement of glucose levels and [3-^{3}H]glucose specific activity. Samples were taken for measurement of serum insulin levels at 0, 60, and 120 min basally and at 25, 45, 70, and 90 min during the clamp.

Analytical methods. Blood and plasma glucose concentrations were measured by the glucose oxidase method with a glucose analyzer (YSI, Yellow Springs, OH). Serum insulin, C-peptide, and plasma [3-^{3}H]glucose specific activity were determined as previously described (25). Serum nonesterified fatty acids were measured with an acyl-CoA oxidase–based colorimetric kit (WAKO NEFA-C, Wako, Osaka, Japan). Plasma cholesterol and triglyceride concentrations were estimated with automated enzymatic methods (26,27); the interassay coefficients of variation (C.V.) were 3.6 and 5.9%, respectively. High-density lipoprotein cholesterol (HDL-chol) was determined after precipitation of other lipoprotein classes with phosphotungstic acid/magnesium chloride (28); interassay C.V. was 7.8%. Plasma fatty acid composition was assessed after extraction of total lipids with chloroform/methanol. The fatty acid methyl esters were extracted with hexane and analyzed by gas-liquid chromatography with a flame-ionization detector (8).

Calculations. The disappearance (R_d) and appearance (R_a) rates of glucose in the plasma were calculated from the [3-^{3}H]glucose specific activities with the non-steady-state equations of Steele (25,29). Basal R_a, which is equivalent to basal hepatic glucose output, was estimated during the 80- to 120-min period of the tracer infusion before insulin administration. During the clamp, the peripheral glucose disposal rate (R_d) and the hepatic glucose output were estimated over the final 45 min. The hepatic glucose output (HGO) was calculated as the difference between the rate of exogenous glucose infusion (GIR) and the derived R_a (i.e., HGO = R_a − GIR). Negative values were interpreted as complete suppression of HGO and treated as 0. Low-density lipoprotein cholesterol (LDL-chol) levels were de-

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rived with the formula LDL-chol = total chol − [(0.458 × triglyceride) + HDL-chol], with all parameters expressed in millimoles per liter.

Data analysis and statistics. The results obtained during the initial baseline diet period and on completion of the fish oil and safflower oil supplementation periods were analyzed. Statistical comparisons were performed with analysis of variance or paired *t* tests as appropriate. Statistical significance was taken as $P < .05$. Values are presented as means ± SE.

RESULTS

Dietary composition was similar during each study period (Table 2). All subjects tolerated the oil capsules without significant adverse effects, although three experienced mild dyspeptic symptoms that did not affect their participation in the study. Eight subjects noted an aftertaste that allowed them to correctly identify the fish oil capsules; however, the investigators remained blind until the end of the study. Body weight increased marginally during both periods of dietary supplementation compared with baseline (baseline, 84.4 ± 5.2 kg; safflower oil, 85.6 ± 5.3 kg; fish oil, 84.9 ± 5.3 kg; NS).

Glucose metabolism. Fasting blood glucose (FBG) levels increased significantly during both periods of oil supplementation compared with the baseline period (Fig. 1). The increase was 14% during fish oil and 11% during safflower oil supplementation. The absolute increase in FBG during oil supplementation periods correlated with the baseline FBG for each subject (fish oil, $r = .83$, $P < .005$; safflower oil, $r = .75$, $P = .012$). Fasting serum insulin and C-peptide levels did not change.

Data from the clamp studies were available from only nine subjects. Basal HGO was slightly, but not significantly, elevated during both supplementation periods and was correlated with FBG levels ($r = .71$, $P < .001$). Insulin-stimulated glucose disposal, measured during the euglycemic clamp, was similar during each dietary period, as was the degree of suppression of HGO (baseline, 89%; safflower oil, 92%; fish oil, 91%; Table 3). The steady-state insulin levels achieved during the euglycemic clamp studies were not significantly different (baseline, 637 ± 78 pM; safflower oil, 603 ± 62 pM; fish oil, 617 ± 56 pM).

TABLE 2
Dietary composition data

	Baseline	Safflower oil	Fish oil
Energy intake (kcal/day)	2000 ± 208	1994 ± 292	1939 ± 211
Carbohydrate (g/day)	227 ± 25	228 ± 30	218 ± 26
Saturated fat (g/day)	32 ± 5	29 ± 6	29 ± 6
Monounsaturated fat (g/day)	28 ± 5	27 ± 6	29 ± 5
Polyunsaturated fat (g/day)	14 ± 2	15 ± 3	12 ± 2
Cholesterol (mg/day)	296 ± 50	291 ± 57	276 ± 40

Details of dietary composition obtained from analysis of 4-day food records during each dietary period. Nutrients provided by oil capsules during the supplementation periods are not included. Differences between dietary periods were not significant. Values are means ± SE. $n = 8$ for each dietary period; 2 subjects failed to supply complete dietary records.

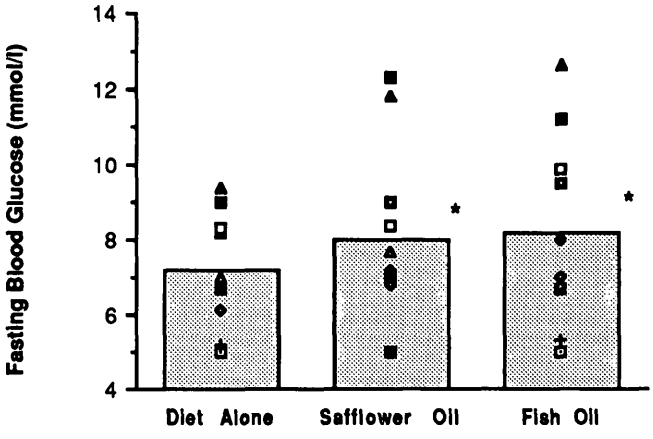

FIG. 1. Individual and mean fasting blood glucose levels at end of baseline (diet alone), safflower oil, and fish oil supplementation. Individual subjects indicated by *symbols*. Mean for each dietary period indicated by *bars*. *$P < .05$ vs. diet alone.

Plasma lipids. The plasma levels of EPA and DHA (expressed as a percentage of total plasma fatty acids) increased in all subjects during fish oil supplementation (EPA: baseline, 0.1%; safflower oil, 0.3%; fish oil, 3.8%; $P < .001$; DHA: baseline, 2.1%; safflower oil, 2.6%; fish oil, 4.3%; $P < .01$). Total serum nonesterified fatty acid levels did not change significantly. Plasma triglyceride and cholesterol levels fell significantly between entry into the study and completion of the baseline diet period (triglyceride: entry vs. baseline, 2.41 ± 0.46 vs. 1.80 ± 0.30 mM, $P = .024$; cholesterol: entry vs. baseline, 6.03 ± 0.38 vs. 5.50 ± 0.32 mM, $P = .01$).

As shown in Table 4, triglyceride levels did not change significantly during either period of oil supplementation compared with the baseline. During fish oil supplementation, triglyceride levels decreased in the 4 subjects with baseline hypertriglyceridemia (>2 mM), whereas the response varied in the remaining subjects, 1 of whom developed an elevated triglyceride level (Fig. 2). This subject, who failed to submit a complete dietary record, had a greater weight gain than the others (+3.2 kg vs. baseline), implying some degree of dietary noncompliance. However, even if this subject's results are excluded, the change in triglyceride levels is not significant ($P = .16$). Similarly, there was no significant effect of either period of oil supplementation on plasma total cholesterol, HDL-chol, or LDL-chol levels compared with baseline (Table 4). Because of technical difficulties, baseline HDL-chol data for 3 subjects were not adequate. Consequently, the HDL- and LDL-chol levels reported in Table 4 refer to only the 7 subjects with complete data. However, data from all 10 subjects were available for both oil supplementation periods (HDL-chol: safflower oil vs. fish oil, 0.91 ± 0.07 vs. 0.94 ± 0.06 mM, NS; LDL-chol: safflower oil vs. fish oil, 3.54 ± 0.21 vs. 3.71 ± 0.23 mM, NS).

Washout. Data were also analyzed to assess the adequacy of the washout. There was a clear tendency for parameters to return toward baseline levels at the end of the washout between the first and second oil treatments (defined temporally). This tendency was seen in the levels of FBG (base-

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TABLE 3
Parameters of glucose metabolism

	Fasting blood glucose (mM)	Fasting serum insulin (pM)	HGO (μmol · kg^{-1} · min^{-1})		Clamp glucose disposal (μmol · kg^{-1} · min^{-1})
			Basal	Clamp	
Baseline	7.2 ± 0.5	90 ± 14	15.9 ± 1.3	1.7 ± 0.7	22.3 ± 3.2
Safflower oil	8.0 ± 0.8*	98 ± 17	17.2 ± 1.6	1.4 ± 0.5	21.2 ± 3.8
Fish oil	8.2 ± 0.8*	96 ± 19	16.9 ± 1.3	1.5 ± 0.8	21.5 ± 3.5

Parameters of glucose metabolism obtained basally and during the euglycemic clamp at the end of each dietary period. Values are means ± SE. n = 10 for fasting blood glucose and serum insulin levels; n = 9 for basal and clamp hepatic glucose output (HGO) and clamp glucose disposal.
*$P < .05$ vs. baseline.

line, 7.2 ± 0.5; 1st oil, 7.9 ± 0.7; washout, 7.1 ± 0.5; 2nd oil, 8.3 ± 0.8 mM; $P < .05$ baseline and washout vs. each oil period), plasma triglyceride (baseline, 1.80 ± 0.30; 1st oil, 1.67 ± 0.31; washout, 2.26 ± 0.50; 2nd oil, 1.79 ± 0.22 mM; $P < .05$ washout vs. 1st oil period), and plasma cholesterol (baseline, 5.50 ± 0.32; 1st oil, 5.36 ± 0.29; washout, 5.90 ± 0.45; 2nd oil, 5.33 ± 0.25 mM; $P < .05$ washout vs. each oil period).

DISCUSSION

We found that supplementing a standard diabetic diet with 10 g of fish oil concentrate daily, providing 3 g ω3FAs, caused a small to moderate deterioration of glycemic control in 10 subjects with relatively mild NIDDM without affecting insulin sensitivity. Basal HGO correlated with FBG levels. This relationship, which has been reported previously (30,31), suggests that increased HGO contributed to the worsening of glycemic control during oil supplementation. Compliance with fish oil ingestion was indicated by the consistent rise in plasma EPA and DHA levels.

The similar hyperglycemic response to safflower oil ingestion suggests that the extra dietary energy (~5% of total intake) or fat intake, rather than ω3FAs specifically, caused the adverse response to fish oil supplementation. In obese NIDDM subjects, energy intake appears to be an important determinant of glycemia. Substantial restriction of energy intake produces rapid metabolic improvements, even before the occurrence of major weight loss (32,33), with partial reversal when a weight-maintenance diet is subsequently introduced (33). In a previous study in nondiabetic subjects, short-term hypercaloric diets led to an increase in FBG (34); although the extra energy intake considerably exceeded that in this study, diabetic subjects with poor glycemic control may be sensitive to the hyperglycemic effect of even mildly hypercaloric diets.

Because both oil periods followed the baseline period, an alternate explanation for the rise in FBG is a progressive failure of dietary compliance over the course of the study. However, this possibility is not supported by the analysis of food records. Moreover, the return of FBG to baseline levels during the washout period further suggests that oil ingestion was responsible for the hyperglycemia.

Other studies of fish oil supplementation in NIDDM subjects have demonstrated variable adverse effects on glycemic control (35–38). Glauber et al. (35) gave 5.5 g/day of ω3FAs for 1 mo to subjects withdrawn from hypoglycemic therapy and noted an increase in FBG and basal HGO. Insulin sensitivity, assessed by euglycemic clamp, was not altered. Friday et al. (36) also reported an increase in FBG after ingestion of 8 g/day ω3FAs for 8 wk. In both of these studies, food-stimulated insulin secretion did not increase despite increased postprandial plasma glucose levels, implying a defect in insulin secretion. Unlike this study, there was no control for the extra fat or energy intake in either of those studies. Schectman et al. (37) used a safflower oil control period; however, glucose turnover and insulin sensitivity were not assessed. They observed an increase in glycohemoglobin, but FBG was unchanged after ingestion of 4 g/day ω3FAs for 1 mo; a similar nonsignificant increase in glycohemoglobin occurred during safflower oil adminis-

TABLE 4
Fasting plasma lipids

	Triglyceride (mM)	Cholesterol (mM)		
		HDL	LDL	Total
Baseline	1.80 ± 0.30	0.83 ± 0.02	3.52 ± 0.23	5.50 ± 0.32
Safflower oil	1.80 ± 0.31	0.82 ± 0.03	3.28 ± 0.24	5.28 ± 0.28
Fish oil	1.65 ± 0.23	0.86 ± 0.05	3.44 ± 0.19	5.40 ± 0.26

Fasting plasma triglyceride and total, high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol levels measured at the end of each dietary period. Values are means ± SE. n = 10 for triglyceride and total cholesterol data; n = 7 for HDL- and LDL-cholesterol (see RESEARCH DESIGN AND METHODS for details).

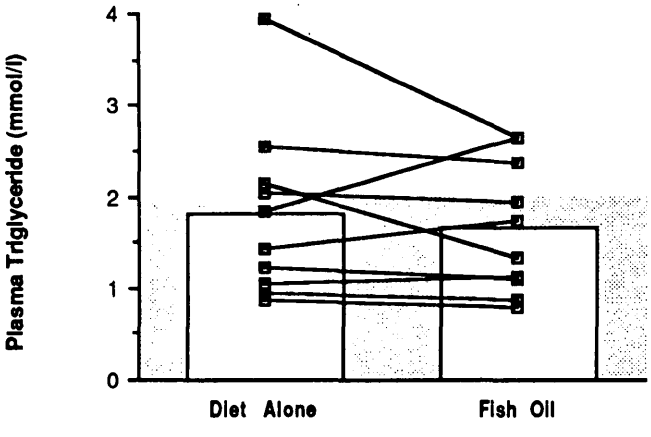

FIG. 2. Individual and mean fasting plasma triglyceride levels at end of baseline (diet alone) and fish oil supplementation. □, individual subjects; *open bars*, mean for each dietary period; *shaded area*, normal range (<2 mM). Note decrease during fish oil supplementation in 4 subjects with baseline hypertriglyceridemia.

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tration. Both FBG and glycohemoglobin increased significantly after a subsequent 4-wk ingestion of 7.5 g/day ω3FAs. When lesser amounts were given (2.7 g/day) by another group, glycohemoglobin rose after 4 wk and returned to baseline after 8 wk, without any change in FBG (38). Only one study has reported an increase in insulin sensitivity (determined by the steady-state plasma glucose level during a constant insulin/glucose infusion), with no change in FBG after ingestion of 3 g/day ω3FAs for 8 wk (39). These studies and our study suggest that a hyperglycemic response to fish oil is more likely with higher doses of ω3FAs and in subjects with poor glycemic control; there may also be a tendency for such an effect to wane with more prolonged use. If, as this study suggests, the hyperglycemic response is related to the extra calorie load, then appropriate reduction of other dietary energy sources should prevent this deleterious effect.

The failure of fish oil supplementation to improve insulin sensitivity contrasts with our studies in animals. Nondiabetic rats developed insulin resistance when fed a safflower oil–rich diet (21), and this was prevented by substituting a small amount of fish oil isocalorically (22). In contrast with the human study, however, the rat study assessed the preventive effect of fish oil, and the confounding effect of extra energy intake was avoided with dietary substitution, not supplementation. Furthermore, the rat diets did not contain saturated fat; our more recent animal studies indicate that interactions between saturated and unsaturated dietary fats may modify the individual effects of fats on insulin action (40). In addition, the incorporation of ω3FAs into cell membrane phosphatidylinositol, which does not occur in humans (41,42), could theoretically influence the release of the postulated insulin mediator linked to phosphatidylinositol (43) and thus alter insulin action in rats but not humans.

In this study, there was no significant change in plasma lipids during fish oil supplementation. In most studies, fish oil administration lowered plasma triglyceride levels in healthy (5,6) and hyperlipidemic (7,8) subjects. Although we found no significant effect overall, triglyceride levels decreased in all four subjects with hypertriglyceridemia. Recent studies specifically examining the effect of fish oils in NIDDM have shown variable responses, with triglyceride levels decreasing significantly in some (36,37,39) but not in others (35,38). In one of the latter studies, a significant hypotriglyceridemic effect was obtained only when the subjects with the highest baseline levels were analyzed separately (38). The only other study that used a safflower oil control period in NIDDM subjects demonstrated oil-induced changes in plasma lipids; however, diet was not modified (37). In this study, plasma triglyceride and cholesterol levels fell significantly during the baseline period, after initial dietary counseling to achieve a conventional diabetic diet; this may have limited further improvements during oil supplementation. The lack of effect of fish oil on total cholesterol, LDL-chol, and HDL-chol in this study is consistent with most other studies in NIDDM subjects (35,37–39). However, note that in two of these reports, there were surprising increases in plasma apolipoprotein B levels, related to the LDL fraction (37,38). This is of concern because of the reported correlation between LDL apolipoprotein B levels and the presence of CAD (44).

The return of measured parameters to baseline levels during the washout period suggests that 3 wk was sufficient to allow a clear differentiation between the effects of each oil-supplementation period. Despite a nonsignificant reduction in plasma lipids during oil-supplementation periods compared with baseline, levels tended to be higher during the washout period. This may reflect a temporary easing of dietary compliance during a nontreatment period in which diet was not monitored; alternatively, it may represent a rebound phenomenon after oil ingestion was stopped.

Dietary fish oil supplementation caused a hyperglycemic response in our NIDDM subjects, probably related to the extra calorie load, without producing a significant improvement in plasma lipids or insulin sensitivity. In deciding whether fish oils may have a therapeutic role in NIDDM, several points need to be considered. First, as discussed previously, variable changes in plasma lipids have been reported in other studies. Second, fish oils have been reported to improve other factors related to the development of CAD, such as blood pressure (38), blood viscosity (13), leukotriene metabolism (12), and platelet aggregability (9–11), which were not assessed in this study. Thus, there are potential advantages and disadvantages of fish oil ingestion in terms of metabolic control and CAD risk in NIDDM. Several of the abnormalities related to NIDDM are largely reversible if optimal glycemic control is achieved through a combination of dietary modification, weight loss (where appropriate), and exercise. However, the frequent failure of such a strategy indicates the need for additional therapies. Until further studies clarify the longer-term effects, fish oil supplementation should be used with caution in patients with NIDDM. A corresponding reduction of other dietary energy sources may lessen any adverse effect.

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REFERENCES

1. Kromhout D, Bosscheiter EB, de Lezenne Coulander C: The inverse relation between fish consumption and 20-year mortality from coronary heart disease. *N Engl J Med* 312:1205–209, 1985
2. Hirai A, Terano T, Saito H: Eicosapentaenoic acid and platelet function in Japanese. In *Nutritional Prevention of Cardiovascular Disease*. Lovenburg W, Yamori Y, Eds. New York, Academic, 1984, p. 231–39
3. Shekelle RB, Missell LV, Paul O, Shryock AM, Stamler J: Fish consumption and mortality from coronary heart disease (Letter). *N Engl J Med* 313:820, 1985
4. Norell SE, Ahlbom A, Feychting M, Pederson NL: Fish consumption and mortality from coronary heart disease. *Br Med J* 293:426, 1986
5. Harris WS, Connor WE, McMurray MP: The comparative reductions of the plasma lipids and lipoproteins by dietary unsaturated fats—salmon oil versus vegetable oils. *Metabolism* 32:179–84, 1983
6. Harris WS, Connor WE, Inkeles SB, Illingworth DR: Dietary omega-3 fatty acids prevent carbohydrate-induced hypertriglyceridemia. *Metabolism* 33:1016–19, 1984
7. Phillipson BE, Rothrock DW, Connor WE, Harris WS, Illingworth DR: Re-

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duction of plasma lipids, lipoproteins, and apoproteins by dietary fish oils in patients with hypertriglyceridemia. *N Engl J Med* 312:1210–16, 1985
8. Simons LA, Hickie JB, Balasubramaniam S: On the effects of dietary n-3 fatty acids (MaxEPA) on plasma lipids and lipoproteins in patients with hyperlipidaemia. *Atherosclerosis* 54:75–88, 1985
9. Dyerberg J, Bang HO, Stoffersen E, Moncada S, Vane JR: Eicosapentaenoic acid and prevention of thrombosis and atherosclerosis? *Lancet* 2:117–19, 1978
10. Knapp HR, Reilly IA, Alessandrini P, Fitzgerald GA: In vivo indexes of platelet and vascular function during fish-oil administration in patients with atherosclerosis. *N Engl J Med* 314:937–42, 1986
11. Von Schacky C, Fischer S, Weber PC: Long-term effects of dietary marine omega-3 fatty acids upon plasma and cellular lipids, platelet function, and eicosanoid formation in humans. *J Clin Invest* 76:1626–31, 1985
12. Lee TH, Hoover RL, Williams JD, Sperling RI, Ravalese J, Spur BW, Robinson DR, Corey EJ, Lewis RA, Austen KF: Effects of dietary enrichment with eicosapentaenoic and docosahexaenoic acids on in vitro neutrophil and monocyte leukotriene generation and neutrophil function. *N Engl J Med* 312:1217–24, 1985
13. Terano T, Hirai A, Hamazaki T, Kobayashi S, Fujita T, Tamura Y, Kumagai A: Effect of oral administration of highly purified eicosapentaenoic acid on platelet function, blood viscosity and red cell deformability in healthy human subjects. *Atherosclerosis* 46:321–31, 1983
14. Leaf A, Weber PC: Cardiovascular effects of n-3 fatty acids (Review). *N Engl J Med* 318:549–57, 1988
15. von Schacky C: Prophylaxis of atherosclerosis with marine omega-3 fatty acids: a comprehensive strategy: *Ann Intern Med* 107:890–99, 1987
16. Panzram G: Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 30:123–31, 1987
17. Bang HO, Dyerberg J, Sinclair HM: The composition of the Eskimo food in northwestern Greenland. *Am J Clin Nutr* 33:2657–61, 1980
18. Kromann N, Green A: Epidemiological studies in the Upernavik district, Greenland: incidence of some chronic diseases 1950–1974. *Acta Med Scand* 208:401–406, 1980
19. Mouratoff GJ, Carroll NV, Scott EM: Diabetes mellitus in Eskimos. *JAMA* 199:107–12, 1967
20. Kahn CR: Insulin resistance: a common feature of diabetes mellitus. *N Engl J Med* 315:252–53, 1986
21. Storlien LH, James DE, Burleigh KM, Chisholm DJ, Kraegen EW: Fat feeding causes widespread in vivo insulin resistance, decreased energy expenditure and obesity in the rat. *Am J Physiol* 251:E576–83, 1986
22. Storlien LH, Kraegen EW, Chisholm DJ, Ford GL, Bruce DG, Pascoe WS: Fish oil prevents insulin resistance induced by high fat feeding. *Science* 237:885–88, 1987
23. Paul AA, Southgate, DAT: *McCance and Widdowson's the Composition of Foods*. London, Her Majesty's Stationery Office, 1978 (Med. Res. Counc. Spec. Rep., no. 297)
24. DeFronzo RA, Tobin JD, Andres R: Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 237:E214–23, 1979
25. Jenkins AB, Chisholm DJ, James DE, Ho KY, Kraegen EW: Exercise induced hepatic glucose output is precisely sensitive to the rate of systemic glucose supply. *Metabolism* 34:431–34, 1985
26. Allaine GC, Poon LC, Chan CSG: Enzymatic determination of total serum cholesterol. *Clin Chem* 20:470–75, 1974
27. Bucolo G, David H: Quantitative determination of serum triglycerides by the use of enzymes. *Clin Chem* 19:476–82, 1973
28. Burstein M, Scholnik HR, Morfin R: Rapid method for the isolation of lipoproteins from human serum by precipitation with polyanions. *J Lipid Res* 11:583–95, 1970
29. Steele R: Influence of glucose loading and of injected insulin on hepatic glucose output. *Ann NY Acad Sci* 82:420–30, 1959
30. DeFronzo RA, Ferrannini E, Koivisto V: New concepts in the pathogenesis and treatment of non-insulin-dependent diabetes mellitus. *Am J Med* 75:52–81, 1983
31. Revers RR, Fink R, Griffin J, Olefsky JM, Kolterman OG: Influence of hyperglycaemia on insulin's in vivo effects in type 2 diabetes. *J Clin Invest* 73:664–72, 1984
32. Hughes TA, Gwynne JT, Switzer BR, Herbst C, White G: Effects of caloric restriction and weight loss on glycemic control, insulin release and resistance, and atherosclerotic risk in obese patients with type 2 diabetes mellitus. *Am J Med* 77:7–17, 1984
33. Henry RR, Schaeffer L, Olefsky JM: Glycemic effects of intensive caloric restriction and isocaloric refeeding in non-insulin-dependent diabetes mellitus. *J Clin Endocrinol Metab* 61:917–25, 1985
34. Olefsky J, Crapo PA, Ginsberg H, Reaven GM: Metabolic effects of increased caloric intake in man. *Metabolism* 24:495–503, 1975
35. Glauber HS, Wallace P, Griver K, Brechtel G: Adverse metabolic effects of omega-3 fatty acids in non-insulin-dependent diabetes mellitus. *Ann Intern Med* 108:663–68, 1988
36. Friday KE, Childs MT, Tsunehara CH, Fujimoto WY, Bierman EL, Ensinck JW: Elevated plasma glucose and lowered triglyceride levels from omega-3 fatty acid supplementation in type II diabetes. *Diabetes Care* 12: 276–81, 1989
37. Schectman G, Kaul S, Kissebah AH: Effect of fish oil concentrate on lipoprotein composition in NIDDM. *Diabetes* 37:1567–73, 1987
38. Kasim SE, Stern B, Khilnani S, McLin P, Baciorowski S, Jen KLC: Effects of omega-3 fish oils on lipid metabolism, glycemic control, and blood pressure in type 2 diabetic patients. *J Clin Endocrinol Metab* 67:1–5, 1988
39. Popp-Snijders C, Schouten JA, Heine RJ, van der Meer J, van der Veen EA: Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in non-insulin-dependent diabetes. *Diabetes Res* 4:141–47, 1987
40. Storlien LH, Jenkins AB, Chisholm DJ, Kraegen EW: Role of specific nutrients in determining hepatic and peripheral insulin sensitivity: effect of subtypes of fats and simple sugars. In *Diabetes 88*. Larkins RG, Zimmet PZ, Chisholm DJ, Eds. Amsterdam, Excerpta Med., Elsevier, 1989, p. 593–96
41. Von Schacky C, Siess W, Weber PC: A comparative study of eicosapentaenoic metabolism by human platelets in vivo and vitro. *J Lipid Res* 26:457–64, 1985
42. Von Schacky C, Weber PC: Metabolism and effects on platelet function of the purified eicosapentaenoic and docosahexaenoic acids in humans. *J Clin Invest* 76:2446–50, 1985
43. Larner J: Insulin-signaling mechanisms: lessons from the Old Testament of glycogen metabolism and the New Testament of molecular biology. *Diabetes* 37:262–75, 1988
44. Avogaro P, Bon GB, Cassolato G, Wuinci GB: Are apolipoproteins better discriminators than lipid for atherosclerosis? *Lancet* 1:901–903, 1979

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