Adverse Metabolic Effect of Omega-3 Fatty Acids in Non-Insulin-Dependent Diabetes Mellitus

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Increased interest in using omega-3 fatty acids led us to examine their metabolic effects in six men with type II (non-insulin-dependent) diabetes mellitus. After 1 month of a diet supplemented with these fatty acids, the patients' fasting glucose rose from 13.1 ± 1.3 to 15.3 ± 1.3 mmol/L ($P = 0.03$) and glucose area during a mixed meal profile rose by 22% ($P = 0.04$). Basal hepatic glucose output rose from 97 ± 9 to 122 ± 8 mg/m² · min ($P = 0.004$) but glucose disposal rates measured by euglycemic glucose clamp were unchanged. Fasting insulin levels were similar; peak insulin levels stimulated by meals or intravenous glucagon fell by 30% and 39%, respectively. Plasma and erythrocyte content of omega-3 fatty acid rose significantly. After omega-3 fatty acid withdrawal, fasting glucose returned to baseline. Omega-3 fatty acid treatment in type II diabetes leads to rapid but reversible metabolic deterioration, with elevated basal hepatic glucose output and impaired insulin secretion but unchanged glucose disposal rates. Caution should be used when recommending omega-3 fatty acids in type II diabetic persons.

OMEGA-3 fatty acids are thought to affect a wide range of biologic processes. These highly polyunsaturated fatty acids, derived largely from marine animals, differ from the 18-carbon unsaturated fatty acids common in American diets (linoleic and oleic acids) in that their first double bond is located between the third and fourth carbon atoms from the methyl end (hence the designation N-3 or ω-3). The two major omega-3 fatty acids are eicosapentaenoic acid (EPA C20:5, ω3) with five double bonds and docosahexaenoic acid (DHA C22:6, ω3) with six double bonds. Major effects of these fatty acids include reduction of plasma triglyceride and lipoprotein levels (1-2), reduction of the thrombogenicity of platelets in the microcirculation (3) due to effects on the production of mediators derived from arachidonic acid (prostaglandins and leukotrienes [4]), altered inflammatory and immune cell function (5-7), and retarded development of atherosclerosis (8).

Epidemiologic studies have shown an association between fish consumption and reduced cardiac mortality (9), and between omega-3 fatty acid intake and decreased serum lipid levels and prolonged bleeding time. Studies of Canadian or Greenland Inuit (10-12) and native Indian tribes of Alaska (13) have shown a remarkably low incidence of type II (non-insulin-dependent) diabetes mellitus, in spite of a high-fat diet and obesity.

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Wide interest in using omega-3 fatty acids in diabetic patients is expected because type II diabetes is associated with hyperlipidemia (14) and accelerated atherogenesis (15). These fatty acids may influence metabolic status in a number of ways: There is a close and reciprocal relation between glucose and lipid oxidation (16-17); hypertriglyceridemia is associated with insulin resistance (18-19); the abnormal fluidity of cell membranes of diabetics can be reversed with omega-3 fatty acid supplementation (20), which may affect the function of membrane-associated proteins such as insulin receptors or glucose transporters (21); and the control of insulin secretion by pancreatic beta cells involves specific prostaglandin and leukotriene mediators (22-23) whose synthesis and function are influenced by omega-3 fatty acids.

For these reasons we studied the effects of dietary supplementation with a marine oil extract rich in omega-3 fatty acids in patients with type II diabetes. Insulin secretion, insulin's action to stimulate glucose disposal, and the endogenous production of glucose by the liver were investigated (24, 25). A rapid and significant deleterious effect of omega-3 fatty acids on carbohydrate metabolism in non-insulin-dependent diabetes mellitus patients was noted.

Materials and Methods

Six untreated men aged 59 ± 5 years (SE), with uncomplicated type II diabetes diagnosed a mean of 12 ± 2 years previously were studied. These men tended to be obese, with a mean weight of 88 ± 7 kg, height of 172 ± 3 cm, and body mass index of 29.6 ± 2.7 kg/m². Sulfonylurea treatment was stopped at least 3 weeks before the studies. No medication except for ferrous sulfate was prescribed. Studies were approved by the University of California, San Diego, Human Subject Committee, and patients gave written informed consent.

Materials used included glucagon and biosynthetic human regular insulin (Eli Lilly, Indianapolis, Indiana), 3-^{3}H-glucose (New England Nuclear, Boston, Massachusetts), and fish oil concentrate (MaxEpa, R.P. Scherer Corporation, Troy, Michigan).

Patients were admitted to the metabolic unit of the Veterans Administration Medical Center and given a weight maintenance diet (55% of calories from carbohydrate, 24% from protein, and 21% from fat) for at least 48 hours before the studies. An overall assessment of glucose tolerance with a 7-hour mixed meal profile and tests of beta cell function, assessed as insulin secretory responses to intravenous glucose and glucagon were done. Fasting hepatic glucose output was measured and the stimulation by insulin of glucose utilization using the euglycemic glucose clamp was assessed. Dietary supplementation with fish oil concentrate (MaxEpa, 18 g/d), providing 5.5 g of omega-3 fatty acids (eicosapentaenoic acid, 3.3 g and docosahexanoic acid, 2.2 g) and 108 mg of cholesterol, daily, was begun.

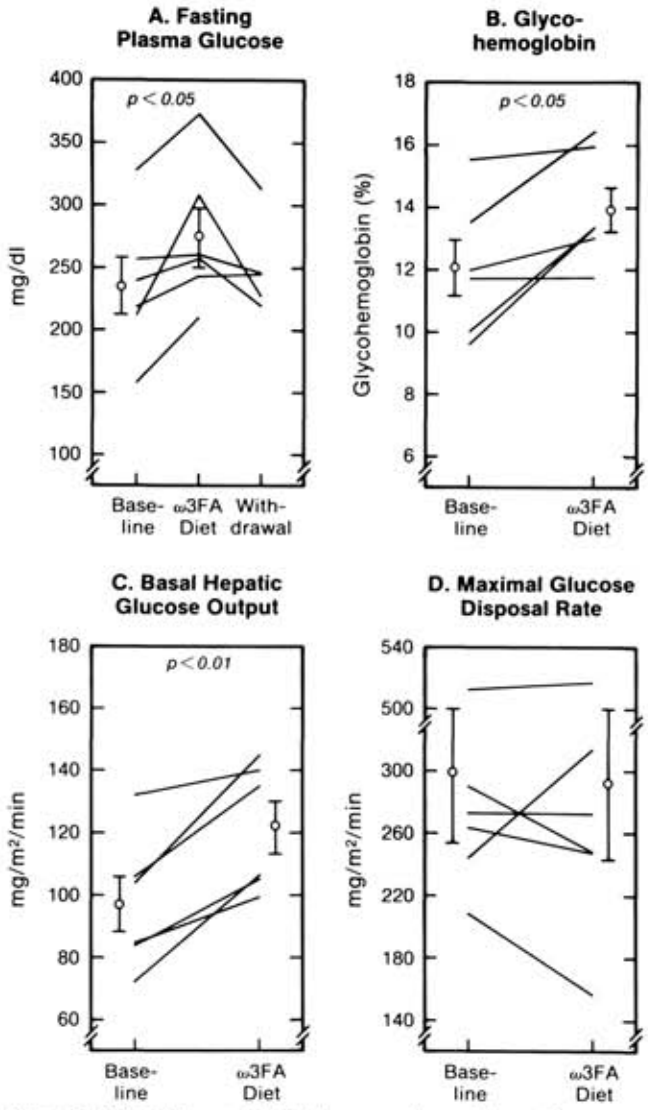

Figure 1. Effect of 1 month of dietary supplementation with omega-3 fatty acids (ω3FA) on fasting plasma glucose (*A*), glycohemoglobin measured by affinity chromatography (*B*), basal hepatic glucose output, measured by 3-^{3}H-glucose infusion (*C*), and glucose disposal rate measured at euglycemia with an insulin infusion of 300 mU/m^2 · min. (To convert plasma glucose values to mmol/L, multiply by 0.0555.)

Intensive dietary counseling ensured constancy of baseline diet and activity level. After 4 weeks the patients were readmitted and the baseline evaluations were repeated and the fatty acid supplementation continued.

After a 14-h overnight fast, the glucose, insulin, and free fatty acid responses to breakfast and lunch were measured hourly for 7 h. The meals consisted of a liquid formula (Sustacal; Mead Johnson, Evansville, Indiana) in which 55% of calories are derived from carbohydrates, 24% from protein, and 21% from fat. One fifth of daily caloric requirement was given at breakfast and two fifths at lunch. The insulin responses to intravenous bolus injections of glucose (300 mg/kg body weight) and glucagon (1 mg) while the patient was fasting were measured (26).

The basal rate of hepatic glucose output after overnight fasting was measured using 3-^{3}H-glucose infusion (27). A 60-μCi bolus of 3-^{3}H-glucose at 0700 h was followed by a constant infusion of 0.6 μCi/min for 150 min. Glucose-specific activity of arterialized venous blood was measured at 20-min intervals from 90 to 150 min, to determine rates of glucose turnover using Steele's equations modified to account for non-steady-state conditions (28). The principle of this technique (29) is that the steady-state specific activity of a continuously infused tracer (3-^{3}H-glucose) is inversely related to the turnover rate of the substance being traced (glucose). In the postabsorptive state hepatic glucose output equals the rate of glucose appearance. After the basal period, measurement of glucose turnover was continued during the subsequent clamp study.

After measurement of basal hepatic glucose output, an intravenous insulin infusion was begun with a bolus of 6 U/m^2 body surface area, delivered in a logarithmically decreasing pattern over 10 min, followed by a continuous insulin infusion of 300 mU/m^2 · min for up to 300 min to raise serum insulin levels acutely to approximately 6000 pmol/L (1000 μU/mL). Glucose was allowed to fall gradually for approximately 120 min from fasting levels to approximately 5 mmol/L, and was then clamped at this level by infusing a 20% glucose solution, at a rate determined in a feedback fashion by measurement of plasma glucose at 5-min intervals. Hourly rates of glucose turnover and exogenous glucose infusion were calculated as the mean of three measurements over 20-min intervals. Residual hepatic glucose output was calculated as the difference between the isotopically determined rate of glucose appearance and the glucose infusion rate. Glucose disposal rate was the sum of the glucose infusion rate and any residual hepatic glucose output. If the glucose infusion rate was more than the isotopically determined rate of appearance, hepatic glucose output was assumed to be 100% suppressed. Because the clamp was conducted at euglycemia, glycosuria did not contribute to glucose disposal.

Arterialized venous blood was taken from a warmed dorsal hand vein. Plasma glucose was measured by an automated glucose oxidase method (YSI 23A; Yellow Spring Instruments, Yellow Spring, Ohio). Glucose-specific activity, serum insulin, and glucagon were measured (30). (To convert reported values from Système International (SI) to older units, multiply by 18 for glucose to mg/dL, and by 0.161 for insulin to μU/mL. Serum lipid levels were determined using Lipid Research Clinic procedures. Free fatty acids were measured colorimetrically (31). Fatty acid composition of plasma and erythrocyte membrane lipids (32) was determined on a 10% Silar 5CP gas liquid chromatography column after methylation of fatty acids with boron fluoride-methanol (33). Glycosylated hemoglobin was measured by affinity chromatography (Isolab, Akron, Ohio).

Calculation of glucose turnover rates, data analysis, and statistical calculations were done with the CLINFO computer system of the University of California, San Diego, General Clinical Research Center. Data are shown as mean ± SE. Major changes from baseline are reported as mean change, with 95% confidence intervals. Statistical significance was tested with the two-tailed Student *t*-test for paired data or the Wilcoxon signed rank test for data not normally distributed, and analysis of variance adjusted for repeated measures (BMDP 2V software; Regents of the University of California, Berkeley, California, 1983). Correlation coefficients were calculated with the least-squares linear regression method.

Results

Capsule counts showed more than 90% compliance with the fish oil supplementation. No side effects were reported. Results of screening tests for hepatic, renal and hematologic values were unchanged. Weight fell slightly from 87.6 ± 7.4 to 86.2 ± 7.2 kg ($P = 0.01$). Bleeding times were unchanged (4.5 ± 0.5 compared to 4.9 ± 0.6 min).

Fasting glucose (calculated from the average of measurements on three mornings for each patient) rose significantly by 19% (95% confidence interval [CI], 1.1 to 36.3) from 13.1 ± 1.3 mmol/L to 15.3 ± 1.3 mmol/L ($P = 0.03$) after 4 weeks (Figure 1A). Glucose tolerance during the mixed meal profile (Figure 2B) also de-

teriorated significantly ($P = 0.04$ by analysis of variance). Mean glucose rose 24% from 16.2 ± 1.3 mmol/L to 19.7 ± 1.1 mmol/L ($P = 0.04$), and total area under the curve of plasma glucose rose 25% ($P = 0.04$, Figure 2B). Glycosylated hemoglobin rose 1.88% (95% CI, 0.20 to 3.57) from 12.1% ± 0.9% to 13.9% ± 0.7% ($P = 0.03$) during the 4 weeks (Figure 1B).

The fasting insulin level fell slightly from 110 ± 25 pmol/L to 90 ± 35 pmol/L ($P = 0.22$) after 1 month of fish oil supplementation. The mean insulin level over the course of the meal profile (Figure 2A) fell by 30% (95% CI, 17 to 42, $P = 0.03$). Both first- and second-phase insulin responses to intravenous glucose were poor as is typical in type II diabetes, and the overall insulin response was further reduced by fish oil supplementation ($P = 0.04$ by analysis of variance, data not shown). The insulin response to intravenous glucagon was brisk (Figure 3A) with a mean peak of 720 ± 230 pmol/L within 4 min. This response was markedly impaired by 39% (95% CI, 26 to 51) by the fish oil treatment (peak, 414 ± 105 pmol/L, $P = 0.03$). Overall insulin response to intravenous glucagon was reduced (Figure 3A, $P = 0.006$ by analysis of variance), although glucose levels were elevated (Figure 3B, $P = 0.04$ by analysis of variance). Fasting glucagon concentrations were unchanged (Table 1).

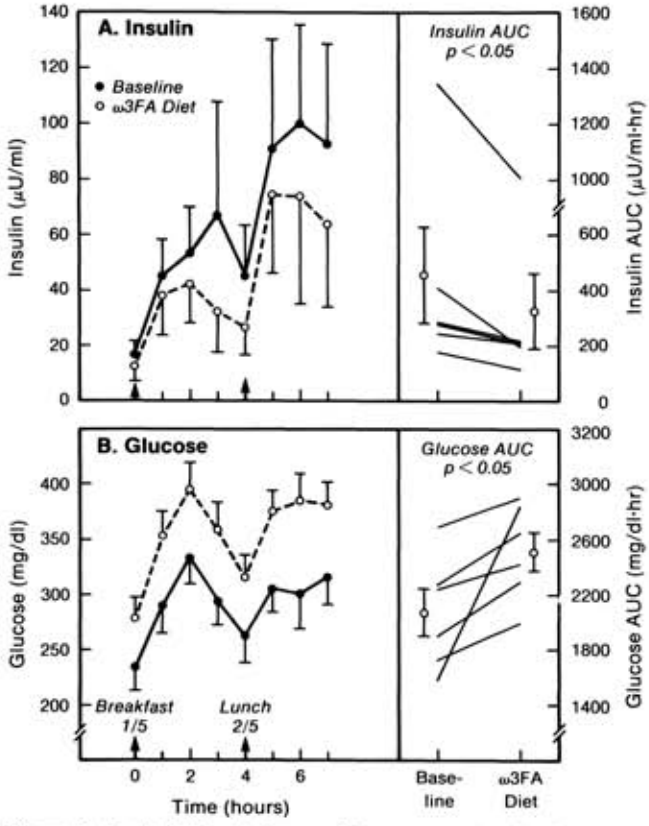

Figure 2. Insulin (*A*) and glucose (*B*) responses to mixed meals at breakfast (one fifth of daily calories) and lunch (two fifths of daily calories) at baseline and after 1 month of dietary supplementation with omega-3 fatty acids (ω3FA). (To convert plasma insulin values to pmol/L, multiply by 6.23.)

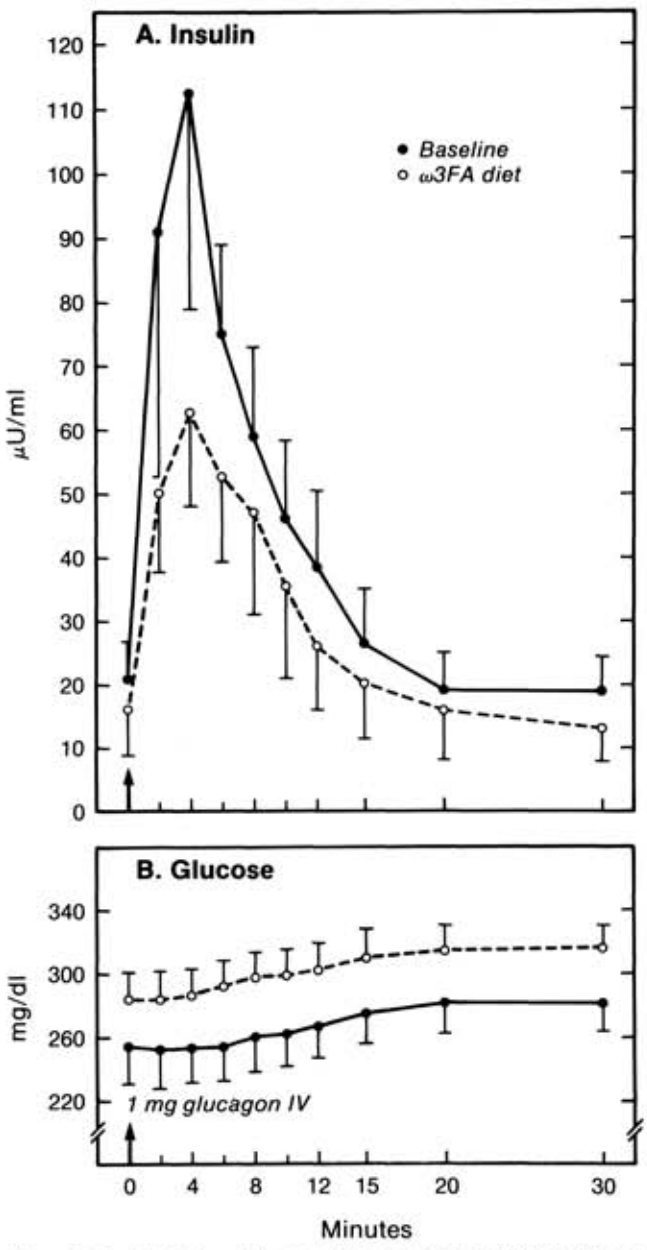

Figure 3. Insulin (*A*) and glucose (*B*) responses to intravenous glucagon at baseline and after 1 month of dietary supplementation with omega-3 fatty acids.

As in previous studies (27), the mean basal hepatic glucose output was elevated in these patients (97 ± 9 mg/m² · min) compared to rates of approximately 75 mg/m² · min in nondiabetic subjects (27), and rose by 25 mg/m² · min (95% CI, 12 to 37 mg/m² · min, $P = 0.004$) (Figure 1C). The level of fasting glucose was significantly related to the basal rate of hepatic glucose output before and after the fish oil treatment period ($r = 0.77$, $P = 0.03$). This concurs with suggestions that the level of hepatic glucose production in the postabsorptive state is the principal determinant of the degree of fasting hyperglycemia in diabetes mellitus (24), and that the deterioration in fasting glycemia occurring with fish oil treatment is due to a rise in the basal level of endogenous glucose production.

Table 1. Effects of One Month of Dietary Omega-3 Fatty Acid Supplementation on Fasting Levels of Plasma Lipids, Free Fatty Acid, and Glucagon in Six Patients with Type II Diabetes Mellitus

Value*	Baseline	Omega-3 Fatty Acid Diet	Change from Baseline†
Total triglyceride, *mmol/L*	3.52	2.11‡	−1.41 (−2.98 to 0.16)
Total cholesterol, *mmol/L*	5.20	5.30§	0.10 (−0.56 to 0.77)
HDL cholesterol, *mmol/L*	0.90	1.05§	0.10 (−0.09 to 0.30)
LDL cholesterol, *mmol/L*	2.80	3.30§	0.46 (−0.17 to 1.09)
Free fatty acid, *mmol/L*	0.33	0.44§	0.11 (−0.10 to 0.31)
Glucagon, *ng/L*	173	172§	−1 (−44 to 43)

* To convert cholesterol and triglyceride values to mg/dL, multiply by 38.67 and 88.57, respectively. HDL = high-density lipoprotein; LDL = low-density lipoprotein.
† Mean change from baseline with 95% confidence intervals.
‡ $P = 0.07$ compared with baseline.
§ $P > 0.20$ compared with baseline.

The effect of supraphysiologic levels of insulin on near maximal rates of glucose disposal was assessed before and after 1 month of the omega-3 fatty acid diet, using the hyperinsulinemic euglycemic glucose clamp technique. The steady-state plasma concentrations of glucose during the final hour of study were the same in the two clamp studies (4.7 ± 0.1 mmol/L, mean coefficient of variation, 3.2% ± 0.4%, before, compared with 4.8 ± 0.1 mmol/L, mean coefficient of variation, 5% ± 1%, after). The mean insulin levels achieved were unchanged (7480 ± 540, before, compared to 7655 ± 1250 pmol/L, after). During hyperinsulinemia and euglycemia there were no consistent changes in steady-state rates of glucose disposal (299 ± 44 mg/m^2 · min, before, compared with 292 ± 50 mg/m^2 · min, after, $P > 0.20$, Figure 1D). Suppression of endogenous glucose production by the liver was almost complete before and after the period of fish oil supplementation (86% ± 7% compared with 98% ± 2%, $P = 0.20$).

Five patients were reexamined 2 to 10 weeks after the end of the fish oil supplementation, on an unchanged diet and before institution of hypoglycemic therapy. Fasting glucose had returned to baseline values, suggesting that the metabolic disturbance induced by fish oil is rapidly reversible upon withdrawal (Figure 1A).

With treatment, fasting serum triglyceride levels fell by 1.41 mmol/L (95% CI, 0.16 to 2.98) from 3.52 to 2.11 mmol/L ($P = 0.07$), but total, low-density lipoprotein and high-density lipoprotein cholesterol levels were unchanged (Table 1). The plasma content of eicosapentaenoic acid rose from 1.4% ± 0.2% to 6.2% ± 1.0% ($P = 0.004$) and docosahexaenoic acid rose from 4.0% ± 0.4% to 7.7% ± 0.9% ($P = 0.01$) of total plasma fatty acids (Figure 4). Incorporation of the fatty acids into structural lipids was confirmed by the rise in eicosapentaenoic acid content of erythrocyte membrane lipids (Figure 4) from 2.5% ± 0.2% to 3.7% ± 0.3% ($P = 0.03$). Fasting plasma free fatty acid concentration was unchanged (Table 1). Free fatty acid suppression in response to the mixed meals was unchanged ($P = 0.38$ by analysis of variance).

Discussion

The effects of 1 month of dietary supplementation with a marine oil extract rich in the omega-3 fatty acids (eicosapentaenoic and docosahexaenoic acids) on carbohydrate metabolism in patients with severe type II (non-insulin-dependent) diabetes mellitus were studied because of recent interest in the clinical use of these fatty acids for problems frequently seen in diabetes, and because epidemiologic studies show a low prevalence of type II diabetes in populations consuming large quantities of marine fats (10-13). Consistent with previous observations (1, 2), serum triglyceride levels in our patients fell 40%, but total cholesterol levels were unchanged, with a tendency for low-density lipoprotein cholesterol levels to rise (Table 1).

A significant deterioration of these patients' diabetic state (a 19% rise in the fasting glucose level and a 24% rise in mean glucose levels during a mixed meal profile) occurred with 1 month of omega-3 fatty acid supplementation. The deterioration reversed when the fish oil supplements were stopped. The degree of fasting hyperglycemia before and after the omega-3 fatty acid supplementation was closely correlated to the basal rate of hepatic glucose production. Other studies have shown a significant relation between the fasting glucose level of diabetics and their rate of hepatic glucose output (34-36), and the level of hepatic glucose output may determine the severity of the fasting hyperglycemia of these patients (24). The 26% rise in basal hepatic glucose output observed probably accounts for the rise in fasting glucose level with omega-3 fatty acid ingestion. Because

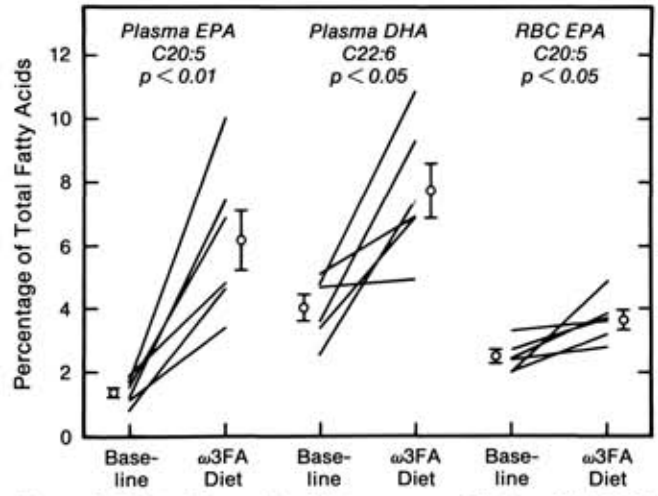

Figure 4. Effect of 1 month of dietary omega-3 fatty acid (ω3FA) supplementation on total plasma fatty acid content of eicosapentaenoic acid (*EPA*) and docosahexaenoic acid (*DHA*), and erythrocyte membrane content of eicosapentaenoic acid (*RBC EPA*).

fasting levels of insulin and glucagon did not change, the rise in hepatic glucose output may be due to an increased availability of gluconeogenic precursors or increased hepatic resistance to fasting levels of insulin. Almost complete suppression of hepatic glucose output during hyperinsulinemia was not altered by omega-3 fatty acid intake. Rates of insulin stimulated glucose disposal, measured with the euglycemic clamp technique at supraphysiologic insulin concentrations were unchanged. An effect of omega-3 fatty acids on submaximal rates of glucose disposal, manifested as a shift to the right or left in the dose response curve for insulin's effect to stimulate glucose disposal (24) was not excluded because we did not examine glucose disposal at lower, physiologic insulin levels.

Basal and stimulated insulin levels before and after omega-3 fatty acid supplementation show a major change in insulin release, which would contribute to the aggravated hyperglycemia, particularly after meals. Fasting insulin levels were not significantly altered, but mean and peak insulin levels after mixed meals were reduced 30%. The insulin response to intravenous glucose was poor (37), and showed further deterioration. This finding is characteristic of type II diabetes. Insulin response to the non-glucose secretagogue, glucagon, was markedly impaired by omega-3 fatty acids, reducing peak insulin levels 39% after an intravenous glucagon bolus. The mechanism whereby pancreatic beta cell function is altered by omega-3 fatty acids was not identified. However, eicosapentaenoic acid competitively inhibits arachidonic acid metabolism to eicosanoid mediators, producing mediators with altered biologic actions (4-6). Evidence suggests a major role for these eicosanoid mediators (prostaglandins and leukotrienes), and other products of phospholipase A2 action on membrane phospholipids, in the control of insulin secretion (22, 23, 38). Thus, there is a hypothetical mechanism whereby omega-3 fatty acid incorporation into plasma and membrane lipids might impair the regulation of insulin secretion.

We examined only a few patients in an unblinded study. However, because of the consistent and marked deterioration of glucose tolerance observed, it was unreasonable to continue these studies in more patients. Our patients consumed one fixed dose of a single preparation of omega-3 fatty acid enriched marine oil extract, in the dosage range having biologic effects (5, 39-42), yet smaller than the large doses used in some studies showing favorable effects on lipid metabolism (1, 2). Similar deleterious effects have recently been reported in diabetic patients consuming 8 g/d of omega-3 fatty acids for 8 weeks, using a different fish oil concentrate (43). Many in-vitro and in-vivo studies using chemically purified omega-3 fatty acids (41, 42, 44-46) have shown biologic effects similar to those of the omega-3 fatty acid enriched marine oil extracts, suggesting that the observed effects are due to the omega-3 fatty acids.

Our studies were limited to patients with type II diabetes, in whom endogenous insulin secretion is a major factor in metabolic regulation. The effect of omega-3 fatty acids on carbohydrate metabolism in type I insulin-dependent diabetics, in whom there is no residual beta cell function, has not been studied. The effects of fish oil supplementation on milder type II diabetics, patients treated with sulfonylurea drugs, and persons predisposed to develop diabetes because of obesity, age, or familial predisposition should be studied.

In non-diabetic persons omega-3 fatty acid reduction of atherogenesis may occur through modulation of platelet function, reflected clinically as a prolongation of bleeding time (4, 47, 48). We did not observe such an effect. However, abnormal platelet function is well documented in diabetes (49), and may be associated with an altered influence of omega-3 fatty acids on platelet eicosanoid metabolism and platelet function (3, 4).

Dietary supplementation with 5.4 g/d of omega-3 fatty acids for 1 month results in a rapid but reversible deterioration of glucose homeostasis, associated with an elevation of basal rates of endogenous glucose production by the liver, which can account for the rise in fasting glucose levels. In spite of the elevated plasma glucose levels, there is a significant impairment in insulin release, which can contribute to worsened meal tolerance. There is no change in the effect of hyperinsulinemia to stimulate whole-body glucose disposal. Because hypertriglyceridemia and accelerated atherogenesis frequently accompany type II diabetes and omega-3 fatty acids may be useful in treating hypertriglyceridemia and preventing atherosclerosis, interest in using these fatty acids is strong. However, use of omega-3 fatty acids may have major adverse metabolic consequences. Until these issues can be studied further, caution should be used when recommending their use in patients with type II diabetes. There is no evidence that the usual dietary intake of fish has any adverse metabolic effects. Omega-3 fatty acids may be a useful tool to probe the role of prostaglandins and leukotrienes in normal beta cell function and in the abnormal regulation of insulin release characteristic of non-insulin-dependent diabetes mellitus.

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