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The Independent and Combined Effects of Aerobic Exercise and Dietary Fish Intake on Serum Lipids and Glycemic Control in NIDDM

A randomized controlled study

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OBJECTIVE — The triglyceride-lowering effects of ω-3 fats and HDL cholesterol–raising effects of exercise may be appropriate management for dyslipidemia in NIDDM. However, fish oil may impair glycemic control in NIDDM. The present study examined the effects of moderate aerobic exercise and the incorporation of fish into a low-fat (30% total energy) diet on serum lipids and glycemic control in dyslipidemic NIDDM patients.

RESEARCH DESIGN AND METHODS — In a controlled, 8-week intervention, 55 sedentary NIDDM subjects with serum triglycerides >1.8 mmol/l and/or HDL cholesterol <1.0 mmol/l were randomly assigned to a low-fat diet (30% daily energy intake) with or without one fish meal daily (3.6 g ω-3/day) and further randomized to a moderate (55–65% Vo_{2max}) or light (heart rate <100 bpm) exercise program. An oral glucose tolerance test (75 g), fasting serum glucose, insulin, lipids, and GHb were measured before and after intervention. Self-monitoring of blood glucose was performed throughout.

RESULTS — In the 49 subjects who completed the study, moderate exercise improved aerobic fitness (Vo_{2max}) by 12% (from 1.87 to 2.07 l/min, $P = 0.0001$). Fish consumption reduced triglycerides (0.80 mmol/l, $P = 0.03$) and HDL_3 cholesterol (0.05 mmol/l, $P = 0.02$) and increased HDL_2 cholesterol (0.06 mmol/l, $P = 0.01$). After adjustment for age, sex, and changes in body weight, fish diets were associated with increases in GHb (0.50%, $P = 0.05$) and self-monitored glucose (0.57 mmol/l, $P = 0.0002$), which were prevented by moderate exercise.

CONCLUSIONS — A reduced fat diet incorporating one daily fish meal reduces serum triglycerides and increases HDL_2 cholesterol in dyslipidemic NIDDM patients. Associated deterioration in glycemic control can be prevented by a concomitant program of moderate exercise.

Cardiovascular disease is the leading cause of mortality and morbidity in patients with NIDDM (1). Incidence of coronary heart disease (CHD) in NIDDM is at least twice that of nondiabetic subjects (2), possibly related to the increased prevalence of dyslipidemia, manifested by elevated serum triglycerides and low HDL cholesterol levels, particularly the HDL_2 cholesterol subfraction. Low HDL, HDL_2, and VLDL cholesterol and high total and VLDL triglycerides are powerful predictors of CHD in NIDDM (3). A recent American Diabetes Association consensus statement emphasized the treatment of these lipoprotein abnormalities as specific targets for intervention strategies in NIDDM patients (4).

Dietary ω-3 fatty acids have led to consistent reductions in plasma triglycerides and small increases in HDL cholesterol in both normolipidemic (5) and hypertriglyceridemic subjects (6). Dietary ω-3 fatty acids consistently lower triglycerides in NIDDM (7,8) and potentially benefit platelet and monocyte function, eicosanoid formation, and blood pressure (9). HDL cholesterol concentrations, however, have usually remained unaltered. Despite these potentially beneficial effects, enthusiasm for the widespread use of ω-3 fatty acids in NIDDM patients has been tempered by reports of increased plasma glucose and glycated hemoglobin (10,11), plasma total cholesterol (11), LDL cholesterol (12), and apolipoprotein B (11). These effects have generally been associated with large doses of ω-3 fatty acids administered as fish oil capsules.

To date, however, little consideration has been given to the effects of dietary fish supplementation in NIDDM patients, particularly in the setting of a recommended low-fat diabetic diet. Furthermore, no one has examined whether the modest increases in fasting glucose and glycated hemoglobin seen with ω-3 fatty acids could possibly be counterbalanced by the addition of other treatment modalities. Regular exercise, for example, could potentially improve both glucose homeostasis and the dyslipidemic profile seen in NIDDM (13).

We hypothesized that the combination of dietary fish supplementation with an aerobic exercise program could result in beneficial effects of ω-3 fatty acids on serum lipids and prevent any deterioration in glycemic control. We now report a randomized, controlled intervention trial of the independent and combined effects of

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C, no fish and light exercise (control subjects); CHD, coronary heart disease; F, fish and light exercise; F/ME, fish and moderate exercise; ME, no fish and moderate exercise.

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dietary fish supplementation and aerobic exercise training on serum lipids and glycemic control in dyslipidemic NIDDM patients consuming a low-fat (30% total energy intake) diet.

RESEARCH DESIGN AND METHODS

Subjects and study design

Nonsmoking subjects, aged 30–65 years, with treated (diet and/or medication) NIDDM were recruited through local media publicity and entered a screening program. Subjects were not taking fish oil supplements or eating more than one fish meal per week and had been sedentary (nonparticipation in regular vigorous exercise [>60 min/week]) for at least the previous 6 months. Subjects were excluded if they were taking insulin or medication for lipid disorders, drinking >30 ml ethanol (3 standard drinks) per day, had a previous history or evidence of heart, liver, or renal disease, neuropathy, or retinopathy, or had asthma or any orthopedic disorder that precluded exercise participation. Of 127 subjects attending for screening, 55 (40 men, 15 women) met the entry criteria, which also included a fasting serum triglyceride >1.8 mmol/l and/or HDL cholesterol <1.0 mmol/l and BMI <36 kg/m^2. All subjects underwent a comprehensive medical examination, including medical history, physical examination, and a resting 12-lead electrocardiogram. Antidiabetic and antihypertensive medication were continued during the study. Subjects gave their written consent, and all methods and procedures were approved by the Human Rights Committee of the University of Western Australia.

Following a 4-week baseline period, subjects entered a two-way factorial intervention of parallel design for 8 weeks. Block randomization was used to allocate subjects to one of four treatment groups, a low-fat diet (≤30% of daily energy intake) alone or with the inclusion of one fish meal daily (3.6 g ω-3/day), and within each of these arms, either a moderate (55–65% of Vo_{2max}) or light (heart rate <100 bpm) (control) exercise training group. Usual physical activity levels and dietary habits were encouraged during the baseline period and were assessed by questionnaires and 24-h diet records, respectively.

Dietary intervention

All four treatment groups, fish and moderate exercise (F/ME); fish and light exercise (F), no fish and moderate exercise (ME), and no fish and light exercise (control subjects, or C), were placed on diets supplying 30% or less of total energy intake from fat (<10% saturated fat),with the remainder distributed between carbohydrates and protein. Diets were individually designed for each subject using the estimated energy intake obtained from the two weighed 3-day food records performed during baseline. All groups were advised to reduce their sodium intake to <100 mmol/day by avoiding added salt and known salty foods and by eating low-salt food products. Compliance with the low-fat diet was assessed by weekly interviews with the dietitian and completion of a food checklist.

Subjects in the F/ME and F groups were instructed to include one fish meal per day in their low-fat diet for every day of the week. A selection of previously analyzed fish (14) was provided free of cost, including Greenland turbot fillets (~200 g/day), canned sardines (~106 g/day), tuna (~102 g/day), and salmon (~54 g/day). This quantity of fish provided approximately 3.6 g/day of ω-3 fatty acids.

Subjects were provided with food scales for use during the study. The dietitian provided individual instruction on the keeping of food records at the beginning of the study. The food recording procedure was also documented in an information folder given to each subject. Nutritional data obtained from food records were analyzed by a dietitian using the Diet/1 (version 3) Nutrient Analysis software program (Xyris Software, Brisbane, Queensland, Australia) using the 1991–1992 Australian Nutrient Database. This package consists of >2,000 food items containing total kilojoule (1 kcal = 4.18 kJ), fat (total, saturated, polyunsaturated, monounsaturated), protein, total carbohydrate, starch, sugars, alcohol, cholesterol, fiber, vitamin (A,B,C), thiamin, riboflavin, niacin, minerals, sodium, potassium, magnesium, calcium, phosphorous, iron, and zinc content. While no nutrient modifications were made to existing food items, foods were added if sufficient nutrient information was available, either from the food label or the manufacturer. Where information could not be obtained, an alternative food of similar nutrient profile was coded. Subjects were requested to provide recipes for all meals prepared at home and were asked to record the weight of individual ingredients and the cooked weight of their serving of the dish. These dishes were coded by individual ingredients and added as recipes to the database. One weighed 3-day food record was obtained at the end of the intervention and was used to assess changes in nutrient intake from the second set of 3-day food records obtained at baseline. For both of these, food recording was performed on 2 weekdays and 1 non-weekday.

Exercise testing and training

Maximal exercise testing provided assessment of cardiovascular fitness levels before and after intervention and was used to prescribe individual training workloads. Cardiovascular fitness (Vo_{2max}) was determined by a maximal continuous multistage exercise test on an electronically braked bicycle ergometer (Siemans-Elema AB, Medicinsk Teknik, Solna, Sweden) (15).

Exercise training was performed on 3 nonconsecutive days of the week in a supervised laboratory setting for 8 weeks.
Moderate exercise. Each session consisted of a 5-min warm-up and 5-min cool-down period of stationary cycling on a bicycle ergometer with no workload and 30 min stationary cycling at an individually prescribed workload determined from the baseline exercise testing. Subjects were required to pedal at a constant rate of 60 rpm throughout each session. During the first week, workloads were individually adjusted to a level corresponding to 50–55% of the baseline Vo_{2max}. For the remaining weeks, the workload was set and maintained at 55–65% of the baseline Vo_{2max}. Heart rate was monitored throughout to assess the intensity of each session.
Light exercise. The light exercise protocol served as a control exercise program and was designed to provide participative involvement but not elicit changes in cardiovascular fitness. Each session involved stationary cycling with no workload for 10 min followed by a series of stretching/flexibility exercises for 30 min. Heart rate was monitored throughout each session to ensure that an upper limit of 100 bpm was not exceeded.

Clinical and laboratory measurements

Fasting blood samples for the analysis of serum lipids, glucose, and insulin were taken in duplicate (separated by 7 days) and once for GHb and platelet phospholipids during baseline and at the end of intervention. A standard oral glucose tolerance test was performed on one of these visits, and the total area under curve for serum glucose

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Table 1—*Baseline characteristics of the groups*

	Fish and moderate exercise	Fish and light exercise	No fish and moderate exercise	Control (light exercise)
n	14	12	11	12
Age (years)	52.6 ± 7.2	54.1 ± 8.2	52.3 ± 8.3	53.0 ± 7.0
Sex (M/F)	10/4	10/2	8/3	9/3
Duration of diabetes (years)	6.8 ± 5.1	3.7 ± 3.0	3.8 ± 3.2	4.4 ± 4.1
Treatment regimen				
Diet only	3	4	3	4
Oral hypoglycemic medication	11	8	8	8
Weight (kg)	85.7 ± 15.0	89.4 ± 13.6	85.6 ± 10.6	88.4 ± 16.2
BMI (kg/m^2)	29.9 ± 3.0	29.8 ± 4.4	29.1 ± 2.4	29.7 ± 4.3
Umbilicus circumference (cm)	105.1 ± 7.2	105.8 ± 10.8	103.6 ± 6.4	107.3 ± 11.9
Waist-to-hip ratio	1.0 ± 0.04	1.01 ± 0.04	1.01 ± 0.04	1.02 ± 0.07
Blood pressure (mmHg)				
Systolic*	133 ± 17.4	131 ± 15.3	124 ± 11.9	114 ± 13.9
Diastolic	74 ± 10.5	74 ± 7.1	72 ± 6.4	68 ± 9.8
Aerobic capacity				
$V_{O_{2max}}$ (l/min)	1.9 ± 0.5	2.2 ± 0.7	1.9 ± 0.3	2.0 ± 0.6
$V_{O_{2max}}$ (ml · kg^{-1} · min^{-1})	21.5 ± 3.9	25.4 ± 7.9	22.3 ± 3.1	22.6 ± 4.7
Serum lipids (mmol/l)				
Triglycerides	2.0 (3.7)	1.7 (9.9)	2.3 (2.7)	2.1 (5.0)
Total cholesterol	4.9 ± 0.9	5.0 ± 0.9	4.7 ± 0.7	5.4 ± 1.1
HDL cholesterol	0.83 ± 0.15	0.89 ± 0.14	0.84 ± 0.16	0.85 ± 0.14
LDL cholesterol†	3.2 ± 0.8	3.3 ± 0.9	2.8 ± 0.5	3.8 ± 1.1
Serum glucose and insulin				
Fasting glucose (mmol/l)	10.0 ± 3.5	8.9 ± 2.6	9.6 ± 3.3	8.8 ± 2.1
Glucose AUC (mmol · l^{-1} · 120 min^{-1})	2,004 ± 500	1,787 ± 465	1,916 ± 480	1,810 ± 340
Fasting insulin (pmol/l)	78.3 ± 33.7	78.2 ± 47.2	89.5 ± 97.2	100.3 ± 53.2
Insulin AUC (pmol · l^{-1} · 120 min^{-1})	22,671 ± 7,834	28,158 ± 19,949	39,310 ± 53,798	30,264 ± 18,008
GHb (%)	8.3 ± 1.5	8.0 ± 1.5	8.8 ± 2.7	8.1 ± 1.4

Data are expressed as means ± SD, except for triglycerides: given the non-normal distribution of triglycerides, values reported are median (range). AUC, area under the curve. *P = 0.01 for between-group difference (ANOVA). †The sample size for LDL cholesterol was 44.

and insulin was calculated using the trapezoidal method with fasting concentrations (incremental area) and zero as the baseline. All blood samples were taken at least 48 h after the last exercise session.

Baseline and postintervention serum lipid, glucose, and insulin levels and body weight were calculated as the mean from the final 2 weeks of each respective testing period. Subjects were weighed without shoes using a calibrated beam balance scale.

Serum cholesterol and triglycerides were determined enzymatically. HDL cholesterol was assayed on a heparin-manganese chloride supernate, and HDL_2 and HDL_3 cholesterol by a single precipitation procedure (16). LDL cholesterol was calculated from the Friedewald formula (17). LDL cholesterol was not calculated if the triglyceride level was >3.4 mmol/l. Glycated hemoglobin was measured by high-performance liquid chromatography, serum glucose by autoanalyzer, and serum insulin by EIA (enzyme immunoassay). Platelet phospholid composition was determined using methods previously described (14). Serum was snap frozen and stored at −80°C, and samples obtained at baseline and end of the intervention were measured in a single assay to minimize interassay variation.

Self-monitoring of blood glucose

A nurse experienced in diabetes management trained subjects to perform self-monitoring of blood glucose using portable home monitors at four separate time points on 2 exercise and 2 nonexercise days of each week. The measurements required included fasting, 2 h after lunch, immediately after an exercise session (exercise day) or 24-h postexercise (nonexercise day), and 2 h after the evening meal.

Statistical analysis

Two-way analysis of variance (ANOVA) was used to assess between-group comparisons, the main effects of fish and exercise for baseline and postintervention measurements, and the difference between the these two measurements. Multiple regression analyses, adjusted for age, sex, and changes in body weight, were used to assess treatment group effects relative to the Control group (no fish and light exercise).

To evaluate changes in self-monitored blood glucose readings during the intervention period, a pooled time series regression analysis using a random effects model was performed according to procedures previously described (18). Results are expressed as means ± SD or the regression coefficient (B) and SE.

Power calculations showed that there was a power of at least 80% to detect main effects of 1 mmol/l in fasting glucose, 0.5% change in GHb, 1 mmol/l change in triglycerides, 0.1 mmol/l change in HDL cholesterol, and 0.5 mmol/l change in LDL cholesterol.

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Table 2—*Total energy intake and macronutrients at baseline and change during the intervention*

Group	Total energy (kJ/day)	Total carbohydrates (% of energy)	Carbohydrate: Complex (% of energy)	Carbohydrate: Sugars (% of energy)	Total protein (% of energy)
Fish and moderate exercise					
Baseline	8,561 ± 1,741*	44.6 ± 6.2	29.4 ± 3.7	14.7 ± 5.6	20.6 ± 3.8
Change	−1,576 ± 1,741	3.0 ± 6.6	1.0 ± 6.6	2.1 ± 5.8	3.9 ± 3.7
Fish and light exercise					
Baseline	9,202 ± 2,294*	45.9 ± 10.3	27.3 ± 6.9	17.0 ± 4.7	20.3 ± 4.6
Change	−994 ± 2,025	3.4 ± 6.7	2.3 ± 7.0	−0.5 ± 4.4	4.0 ± 4.8
No fish and moderate exercise					
Baseline	8,030 ± 3,141*	42.4 ± 9.0	29.0 ± 6.9	12.8 ± 5.0	22.8 ± 3.7
Change	−1,803 ± 1,997	6.2 ± 7.9	4.3 ± 7.4	1.7 ± 4.7	0.9 ± 5.4
Control subjects (light exercise)					
Baseline	6,427 ± 2,107*	46.4 ± 8.3	31.9 ± 4.8	14.0 ± 6.2	21.9 ± 4.5
Change	−188 ± 2,091	−1.6 ± 9.9	−1.6 ± 7.6	0.2 ± 5.0	1.8 ± 5.5

Group	Total fat (% of energy)	Fatty acids: Polyunsaturated (% of energy)	Fatty acids: Monounsaturated (% of energy)	Fatty acids: Saturated (% of energy)	Fiber (g/day)	Alcohol (% of energy)
Fish and moderate exercise						
Baseline	31.5 ± 6.7	4.9 ± 1.8	10.7 ± 2.6	12.5 ± 4.0	25.4 ± 9.6	1.3 ± 3.2
Change	−3.9 ± 6.2	2.0 ± 2.8†	−1.5 ± 3.1	−4.1 ± 4.0	6.8 ± 8.9	0.4 ± 2.4
Fish and light exercise						
Baseline	28.9 ± 8.4	4.6 ± 1.6	10.4 ± 3.8	10.9 ± 4.2	33.9 ± 13.8	2.9 ± 3.8
Change	−3.2 ± 5.6	2.1 ± 2.1†	−1.6 ± 2.7	−3.7 ± 3.6	3.2 ± 7.8	−1.9 ± 2.9
No fish and moderate exercise						
Baseline	30.7 ± 12.0	5.9 ± 2.4	11.6 ± 6.7	10.5 ± 3.5	26.4 ± 7.9	2.3 ± 3.3
Change	−6.3 ± 9.7	−0.2 ± 2.5	−2.9 ± 6.4	−3.1 ± 2.8	1.5 ± 5.6	−0.9 ± 1.8
Control subjects (light exercise)						
Baseline	28.8 ± 6.3	5.3 ± 4.0	9.8 ± 2.4	10.6 ± 3.0	24.4 ± 11.1	1.0 ± 2.1
Change	0.2 ± 10.3	−0.4 ± 3.8	−0.5 ± 3.8	−0.2 ± 4.5	3.0 ± 12.3	−0.6 ± 1.8

Data are means ± SD. Change refers to differences between postintervention and baseline measurements. *P = 0.06 between groups at baseline (ANOVA); †P = 0.01 main fish effect (ANOVA).

RESULTS — Forty-nine of the 55 subjects who commenced the study completed the 8-week intervention and were included in the analysis. Six subjects withdrew due to either changes in medication or other commitments. Medication levels were unchanged during the study in the remaining subjects, as assessed by a fortnightly medication frequency questionnaire. There were 14, 12, 11, and 12 subjects from the F/ME, F, ME, and C groups, respectively, included in the final analysis (Table 1). In total, 11 subjects were recruited solely on the basis that serum triglyceride levels were >1.8 mmol/l, while 20 subjects had HDL cholesterol <1.0 mmol/l. A total of 18 subjects had triglycerides >1.8 mmol/l and HDL cholesterol <1.0 mmol/l. The four groups were well matched for baseline characteristics (Table 1). No significant differences (ANOVA) were observed between the groups at baseline other than for systolic blood pressure. All subjects completed at least 21 of a possible 24 exercise sessions in the 8-week period, and there were no major complications reported from either exercise regimen. Weekly food checklists and weighed diet food records performed mid-intervention provided an indication of the compliance with the low-fat diet. During the intervention, there were no significant changes in alcohol consumption, medication levels, or physical activity other than the prescribed exercise.

Table 2 presents the results of baseline total energy intake and macronutrients and the change from baseline to the end of intervention for the four groups. Total energy intake for all four groups was lower than would be anticipated for weight maintenance in obese subjects and may reflect the underreporting of energy intake. A nonsignificant decrease in energy intake was observed for all four groups (1,156 ± 1,993 kJ, P = 0.22), with the greatest decrease associated with moderate exercise when compared with the light exercise groups (1,071 ± 1,939 kJ, P = 0.06). The addition of fish to the diet contributed to a significant increase in the percentage daily intake of dietary polyunsaturated fat (2.4 ± 2.8%, P = 0.006).

Mean body weight for all the groups combined fell 1.7 ± 1.8 kg (P = 0.04). Weight reductions by group were 2.4 ± 2.3 kg (F/ME), 1.4 ± 1.9 kg (F), 2.1 ± 1.7 kg (ME), and 0.6 ± 1.6 kg (C). Significantly greater weight reduction was observed in the moderate exercise groups combined (1.3 ± 0.1 kg, P < 0.05) compared with the light exer-

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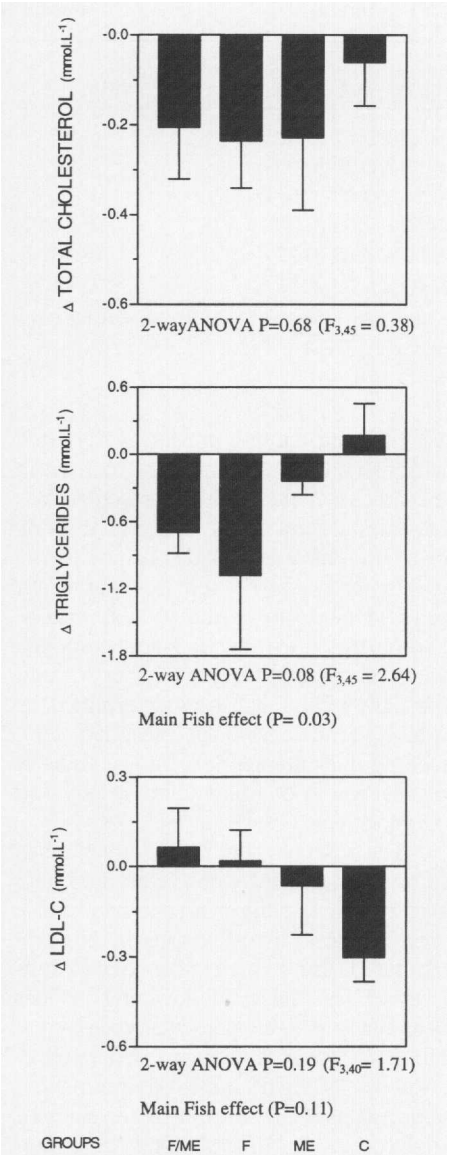

Figure 1—*Changes in serum total cholesterol, triglycerides, and LDL cholesterol from baseline to end of intervention, by group. F/ME, fish and moderate exercise; F, fish and light exercise; ME, no fish and moderate exercise; C (control), no fish and light exercise. Group, main fish (F/ME and F vs. ME and C), and exercise (F/ME and ME vs. F and C) effects (two-way ANOVA) are indicated.*

cise groups. The percentage changes in cardiovascular fitness (VO_{2max}, l/min) were 11 ± 10.5% (F/ME), −2.0 ± 4.2% (F), 11 ± 8.1% (ME), and 0.2 ± 7.1% (C). A significant (P = 0.001) 12% increase in cardiovascular fitness occurred in the moderate exercise groups compared with the light exercise groups.

Serum lipids

In ANOVA, the addition of fish to the low-fat diet resulted in a reduction in triglycerides (0.80 ± 1.3 mmol/l , P = 0.03) (Fig. 1), a reduction in HDL_3 cholesterol (0.05 ± 0.07 mmol/l, P = 0.02), and a rise in HDL_2 cholesterol (0.06 ± 0.07 mmol/l, P = 0.01) (Fig. 2). An increase in LDL cholesterol (0.22 ± 0.42 mmol/l) observed with fish was not significant (P = 0.1). In regression analysis, after adjustment was made for age, sex, and change in body weight, the magnitude of these changes (main effects) for triglycerides (−0.87 ± 0.2 mmol/l, P = 0.0001), HDL_3 cholesterol (−0.04 ± 0.02, P = 0.02) and HDL_2 cholesterol (−0.06 ± 0.02, P = 0.007) was largely unaffected (data not shown). However, the change in LDL cholesterol (0.24 ± 0.1 mmol/l) associated with fish was significant (P = 0.03). Relative to control subjects, moderate exercise alone (ME) decreased triglycerides by 0.68 ± 0.3 mmol/l (P = 0.03; Table 3). The combination of fish with moderate (F/ME) or light exercise (F) reduced triglycerides by 1.21 ± 0.3 and 1.22 ± 0.3 mmol/l, respectively (P = 0.0001), and both contributed to a rise in HDL_2 cholesterol by 0.08 ± 0.3 mmol/l (P = 0.02). Increases in HDL cholesterol seen in the fish and moderate exercise (F/ME; 0.05 ± 0.03 mmol/l, P = 0.08) and no-fish and moderate exercise (ME) groups (0.06 ± 0.03 mmol/l, P = 0.06) were not significant. There were no significant group effects observed for total serum cholesterol or LDL cholesterol.

Serum glucose and insulin

In ANOVA, moderate exercise led to significant reductions in fasting glucose (1.2 ± 1.5 mmol/l, P = 0.01), the glucose area under the curve (160.0 ± 244.3 mmol · l^{-1} · 120 min^{-1}, P = 0.03), and GHb (0.34 ± 0.66%, P = 0.07) compared with the light exercise groups (Fig. 3).

After adjustment for age, sex, and change in body weight in regression analysis, changes in fasting glucose (−0.47 ± 0.43 mmol/l, P = 0.3), glucose area under the curve (−81.7 ± 733, P = 0.3), and GHb (−0.15 ± 0.18%, P = 0.4) associated with moderate exercise no longer remained significant. However, a nonsignificant increase in GHb (0.33 ± 0.17%, P = 0.06) was associated with eating fish. No significant main effects of either moderate exercise or fish were observed for fasting serum insulin and insulin area under the curve (data not shown). Of the two fish-eating groups, the fish and light exercise (F) group demonstrated a significant (0.50 ± 0.24%, P = 0.05) rise in glycated hemoglobin, which was attenuated in the F/ME group (0.19 ± 0.25%, P = 0.44; Table 4). Fasting serum insulin levels were decreased in the fish and light exercise (F) group (21.71 ± 10.7 pmol/l, P = 0.05) compared with control subjects.

Blood glucose measured by self-monitoring throughout the intervention showed a significant increase of 0.57 ± 0.15 mmol/l (P = 0.0002) in the fish and light exercise group (F) compared with control subjects after adjustment for age, sex, changes in body weight, and initial baseline values (week 1; Table 4). In contrast, significant

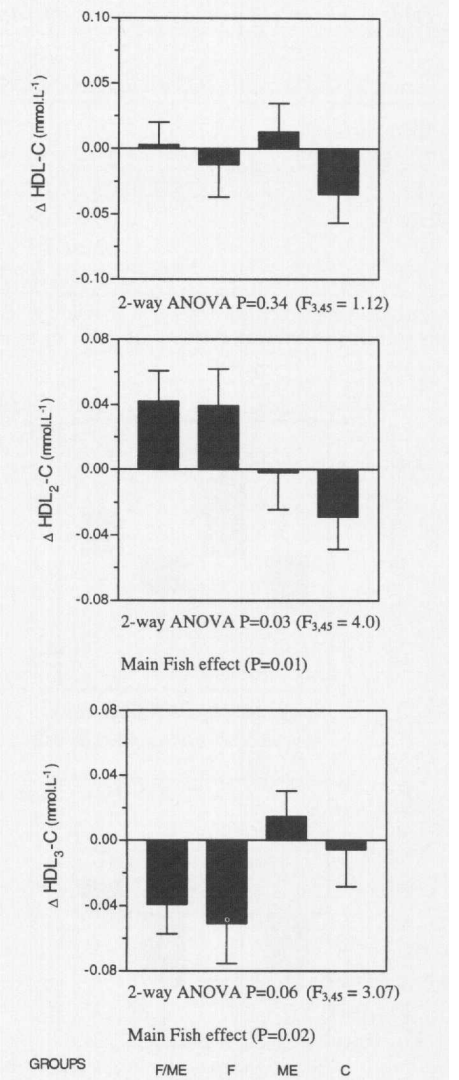

Figure 2—*Changes in serum total HDL, HDL_2, and HDL_3 cholesterol from baseline to end of intervention by group. F/ME, fish and moderate exercise; F, fish and light exercise; ME, no fish and moderate exercise; C (control), no fish and light exercise. Group, main fish (F/ME and F vs. ME and C), and exercise (F/ME and ME vs. F and C) effects (two-way ANOVA) are indicated.*

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Table 3—*Regression analysis for the interactive effects of fish and exercise on serum lipids*

Serum lipids (mmol/l)	Fish and moderate exercise	Fish and light exercise	No fish and moderate exercise	Adjusted r^2
Total cholesterol	−0.16 ± 0.17 (0.34)	−0.19 ± 0.16 (0.24)	−0.23 ± 0.17 (0.20)	0.80
Triglycerides	−1.21 ± 0.28 (0.0001)	−1.22 ± 0.28 (0.0001)	−0.68 ± 0.29 (0.03)	0.54
HDL	0.05 ± 0.03 (0.08)	0.04 ± 0.03 (0.17)	0.06 ± 0.03 (0.06)	0.76
HDL_2	0.08 ± 0.03 (0.02)	0.08 ± 0.03 (0.02)	0.03 ± 0.03 (0.38)	0.62
HDL_3	−0.02 ± 0.03 (0.46)	−0.03 ± 0.03 (0.26)	0.03 ± 0.03 (0.22)	0.50
LDL	0.27 ± 0.18 (0.13)	0.25 ± 0.17 (0.15)	0.04 ± 0.19 (0.85)	0.75

Data are regression coefficients ± SE (*P* value). Interactive effects are determined relative to control subjects (no fish/light exercise). The dependent variable is the post-measurement with adjustments made for baseline measurements, age, sex, and change in body weight.

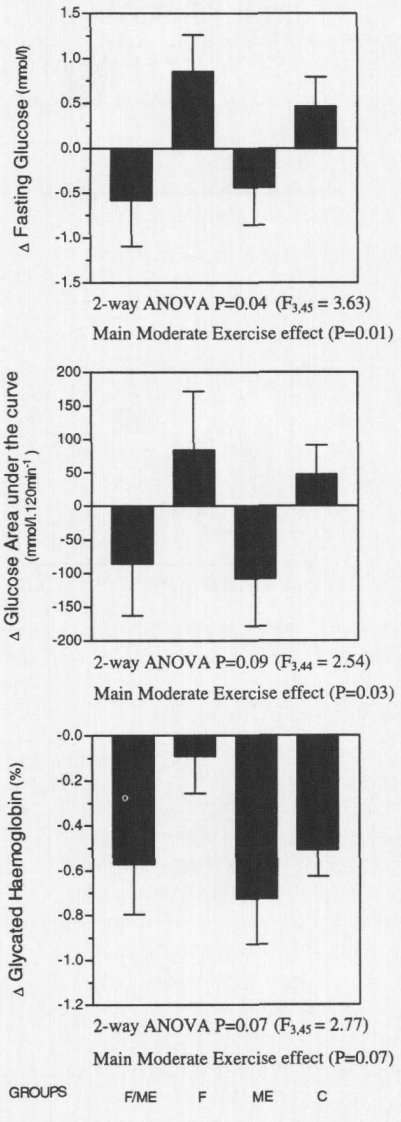

Figure 3—*Changes in fasting serum glucose, glucose area under the curve, and GHb from baseline to end of intervention, by group. F/ME, fish and moderate exercise; F, fish and light exercise; ME, no fish and moderate exercise; C (control), no fish and light exercise. Group, main fish (F/ME and F vs. ME and C), and exercise (F/ME and ME vs. F and C) effects (two-way ANOVA) are indicated.*

decreases were observed for both the fish and moderate exercise group (F/ME) (0.72 ± 0.15 mmol/l, $P = 0.001$) and the no-fish and moderate exercise group (ME) (0.52 ± 0.16 mmol/l, $P = 0.001$).

Platelet phospholipid fatty acids

The fatty acid composition of platelet phospholipids at baseline was similar in all groups. The changes in ω-6 (18:2, 20:3, 20:4, 22:4) and ω-3 (20:5, 22:5, 22:6) polyunsaturated fatty acids from baseline to end of intervention in Fig. 4 indicate compliance with the regular fish intake in the fish-eating groups. The addition of fish to the diet significantly increased the percentage composition of ω-3 fatty acids (4.8 ± 1.8%, $P = 0.001$) and led to a decrease in ω-6 fatty acids (5.8 ± 2.5%, $P = 0.001$).

Relationship between changes in platelet phospholipid fatty acids and glycemic control

After adjustment for age, sex, and change in weight, the increase in platelet phospholipid ω-3 (20:5, 22:5, 22:6) fatty acid composition was independently associated in regression analysis with a rise in fasting serum glucose (0.2 ± 0.09 mmol/l , $P = 0.03$; adjusted $r^2 = 0.76$), glucose area under the curve (27.83 ± 12.9 mmol · l^{-1} · 120 min^{-1}, $P = 0.04$; adjusted $r^2 = 0.79$) and GHb (0.1 ± 0.04%, $P = 0.01$; adjusted $r^2 = 0.83$) (data not shown). The ω-3 fatty acids did not correlate with fasting serum insulin or insulin area under the curve.

CONCLUSIONS — This randomized, controlled study in dyslipidemic non-insulin-dependent diabetics has demonstrated that ω-3 fatty acids supplied by fish meals added to a diet providing 30% energy as fat (4) results in a substantially improved serum lipid profile, as evidenced by reduced triglycerides and increased HDL_2 cholesterol. The deleterious effects on glycemic control previously reported with fish oils accompanied the increase in dietary fish intake but were prevented by a concomitant moderate exercise training program. This was well tolerated by participants and contributed to significant improvements in cardiovascular fitness. Participants also tolerated and complied with the reduced-fat diet with or without the daily intake of fish as determined by weekly food checklists, weighed food records mid-intervention, and analysis of platelet/red blood cell membrane fatty acid compositions.

The observed significant reductions in serum triglycerides with dietary ω-3 fatty acid supplementation are in accordance with previous investigations in NIDDM (8,11,12) and hypertriglyceridemic subjects (6). The triglyceride-lowering qualities of ω-3 fatty acids are particularly relevant to NIDDM patients, since hypertriglyceridemia is their most common lipid abnormality (19). Furthermore, elevated triglycerides in NIDDM significantly predict CHD (3,20) with at least a twofold increase in NIDDM patients with serum triglycerides >2.3 mmol/l (3).

In healthy subjects (21) and NIDDM patients (7,8,11), plasma concentrations of HDL cholesterol have either been increased or unaltered by dietary ω-3 fatty acid supplementation. Previous studies in NIDDM, however, have not reported changes in HDL subfractions. In IDDM patients, dietary ω-3 fats increase HDL cholesterol, primarily due to increased HDL_2 cholesterol, with little change in HDL_3 cholesterol (22). We have previously shown increases following supplementation of a low-fat diet with dietary fish in total HDL and HDL_2 cholesterol in men at risk of heart disease (14). Similar effects were seen in the present study, with a fall in HDL_3 and a rise in HDL_2 cholesterol, which is of potential clinical importance given that HDL_2 cho-

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Table 4—*Regression analysis for interactive effects of fish and exercise on indexes of glycemic control*

	Fish and moderate exercise	Fish and light exercise	No fish and moderate exercise	Adjusted r^2
Fasting glucose (mmol/l)	−0.06 ± 0.59 (0.92)	0.74 ± 0.56 (0.19)	−0.09 ± 0.60 (0.88)	0.81
Glucose AUC (mmol · l^{-1} · 120min^{-1})	−6.3 ± 99.6 (0.95)	106.4 ± 97.8 (0.28)	−48.7 ± 101.4 (0.63)	0.79
Fasting serum insulin (pmol/l)	−19.59 ± 10.8 (0.08)	−21.71 ± 10.7 (0.05)	−14.4 ± 11.0 (0.20)	0.69
Insulin AUC (pmol · l^{-1} · 120 min^{-1})	1357 ± 2786 (0.63)	−2986 ± 2754 (0.28)	1469 ± 2842 (0.61)	0.97
Glycated hemoglobin (%)	0.19 ± 0.25 (0.44)	0.49 ± 0.24 (0.05)	0.03 ± 0.26 (0.92)	0.90
Self-monitored glucose (mmol/l)	−0.72 ± 0.15 (0.00001)	0.57 ± 0.15 (0.0002)	−0.52 ± 0.16 (0.001)	0.64

Data are regression coefficients ± SE (*P* value). Interactive effects are determined relative to control subjects (no fish/light exercise). The dependent variable is the post-measurement with adjustments made for baseline measurements, age, sex, and change in body weight.

lesterol concentrations (the subfraction suggested to be most protective against coronary heart disease [3]) are significantly reduced in NIDDM compared with nondiabetic subjects (23). Furthermore, low HDL cholesterol (<0.9 mmol/l) was recently shown to be the single most important predictor of future CHD events in NIDDM, with the risk of CHD death increased fourfold among these patients (3). This inverse relationship with CHD was predominately due to HDL_2 cholesterol, consistent with previous studies in nondiabetic subjects (24).

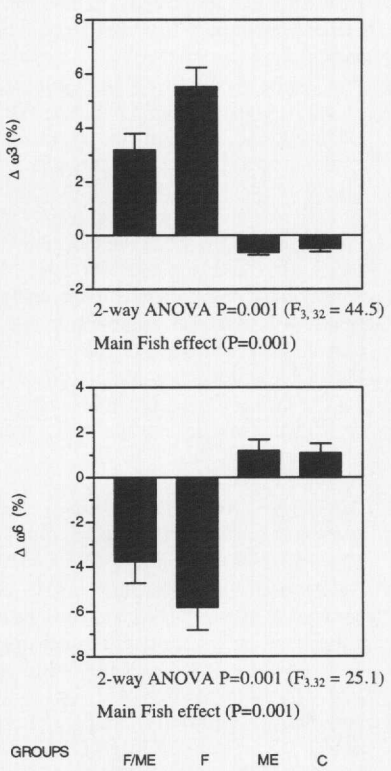

Figure 4—*Changes in ω-6 (18:2, 20:3, 20:4, 22:4) and ω-3 (20:5, 22:5, 22:6) fatty acids in platelet phospholipids from baseline to end of intervention, by group. F/ME, fish and moderate exercise; F, fish and light exercise; ME, no fish and moderate exercise; C (control), no fish and light exercise. Group, main fish (F/ME and F vs. ME and C), and exercise (F/ME and ME vs. F and C) effects (two-way ANOVA) are indicated.*

Dietary ω-3 fatty acid supplementation in patients with NIDDM has been reported to impair glycemic control (9). Increases in fasting glucose, increased plasma glucose response to oral or intravenous glucose or a mixed-meal challenge, and increases in GHb have been demonstrated in some (10–12, 25–27) but not all studies (28). Consequently, despite the potential anti-atherogenic benefits of ω-3 fatty acids, Vessby (29) has suggested the need for caution in their widespread use in NIDDM. Generally, these adverse effects have been associated with large doses of ω-3 fatty acids (4–10 g/day) (10,11,26,27), although blood glucose has also increased after 3 g daily (12,25). In contrast, lower doses of ω-3 fatty acids (2.5–4 g/day) have generally had transient or no effect on glycemic control (8,11,28,30). These findings suggest that potential deterioration in glycemic control is dose dependent. In the present study, the low-fat fish diet in conjunction with light exercise led to a small increase in glycated hemoglobin and a significant increase in glucose levels as assessed by self-monitoring, compared with control subjects. These results indicate that, at least in the short term, mild deterioration in glycemic control can occur even when relatively low doses of ω-3 fatty acids (3.6 g/day) are incorporated as fish into a reduced-fat diet. The significant correlations seen between the increased incorporation of ω-3 fatty acids into platelet phospholipids and elevations in fasting glucose, GHb, and the glucose area under the curve support this notion.

The prevention of fish-induced deterioration in glycemic control by moderate exercise training demonstrated in the present study is a unique finding and could provide useful practical advice for the management of lipid disorders in NIDDM. The combination of moderate exercise with fish not only blunted the rise in GHb but also ameliorated the increase in self-monitored glucose levels seen with the fish and light exercise. One possible explanation for the prevention of a deterioration in glycemic control with ω-3 fats combined with moderate exercise training, compared with ω-3 fats alone, could be the improved peripheral insulin sensitivity (31,32) and insulin secretion (31) associated with exercise training in NIDDM patients. It is possible that the increases in hepatic glucose production and diminished insulin secretion commonly associated with ω-3 fatty acids (9) could be counterbalanced by the improvements in insulin sensitivity and insulin secretion associated with aerobic exercise.

There was greater weight loss with moderate exercise compared with the light exercise program. Analysis of food records showed a tendency toward a decrease in total energy intake in the groups assigned to moderate exercise, which, combined with the increased energy expenditure, explains the differences in weight loss. Adjustment for the changes in body weight showed that the moderate exercise effects on fasting glucose and glucose area under the curve were not independent of weight loss. These findings are in accordance with previous investigations in NIDDM subjects showing that improved glycemic control is generally (32–34), but not always (35), accompanied by a fall in body weight. The small weight reduction in these obese subjects as a consequence of this short-term exercise training program is clinically relevant, since the combination of regular exercise training and diet has been demonstrated to be more effective in improving glycemic control than diet or exercise alone in previous studies (33).

Few studies have assessed the impact of exercise training on lipoprotein metabo-

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lism in patients with NIDDM. While some have observed improved lipid profiles (33,36), others have failed to demonstrate any changes (31,37). Warner et al. (38) reported significant triglyceride reductions and HDL cholesterol elevations in hyperlipidemic subjects when fish oil supplementation was combined with an exercise training program for 12 weeks. In our study, moderate exercise appeared to contribute further to the highly significant increase in HDL_2 cholesterol seen with dietary fish supplementation. However, despite observing triglyceride-lowering effects of dietary fish, the changes seen in triglycerides with moderate versus light exercise control were of similar magnitude.

Lifestyle modifications such as diet and regular exercise are pertinent to the ongoing management of NIDDM; hence, the long-term adoption of a combined exercise and dietary fish approach requires further investigation. In addition, epidemiological data suggests that the anti-atherogenic benefits of ω-3 fatty acids in fish may be derived from quantities of fish less than that consumed in the present study (39).

This study has shown that in NIDDM patients with dyslipidemia, dietary fish as part of a low-fat diet leads to significant reductions in serum triglycerides and elevations in HDL_2 cholesterol. These beneficial changes coincided with modest deterioration in glycemic control and a small rise in LDL cholesterol, which in the case of the former was prevented by the addition of a moderate exercise training program. Therefore, ω-3 fatty acids from dietary fish when combined with moderate exercise, at least in the short term, could have a significant impact on the treatment of lipid disorders in patients with NIDDM without adverse effects on glycemic control. Additional benefits in preventing cardiovascular disease are likely from the effects of fish oils on platelet function (9) and from exercise effects on endothelial function and the coagulation system (40).

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