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Fish oil produces an atherogenic lipid profile in hypertensive men

George S. Hughes, Thomas V. Ringer, Kathy C. Watts, Michael J. DeLoof, Steven F. Francom and Carol R. Spillers

The Upjohn Company, Upjohn Research Clinics, Kalamazoo, MI (U.S.A.)

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Summary

The effects of fish oil supplements on plasma and platelet membrane lipids, lipoproteins, sex steroid hormones, glucose, insulin, platelet aggregation, and blood pressure in normal subjects ($n = 13$) and patients with essential hypertension ($n = 13$) were studied in this randomized, double-blind, placebo-controlled, two-way crossover study. Treatments consisted of 30 days of 5 g of $n-3$ fatty acids (ten 1-g capsules of fish oil daily) or placebo capsules (ten wheat germ oil capsules daily) with a one-month washout in between each crossover. Serum lipids and lipoproteins were measured before dosing and every two weeks during the study. Sex steroid hormones, glucose, insulin, and fatty acid composition in platelet membrane phospholipids were measured before dosing and at the end of each crossover. During treatment with fish oil, only the hypertensive had increases in total cholesterol (8%, $p < 0.026$), LDL cholesterol (19%, $p < 0.006$) and apolipoprotein B (18%, $p < 0.026$). Serum androgens (total and free testosterone) were 30% lower in hypertensives than normotensives before any dosing, but were unchanged with placebo or fish oil capsules in either group. Plasma glucose, insulin, platelet aggregation, and the incorporation of $n-3$ fatty acids into platelet membrane phospholipid subfractions were similar in both normotensive and hypertensive men. Blood pressure was not affected by fish oil treatment in either group of men. These results provide evidence that fish oil may adversely affect serum lipids to yield an atherogenic lipid profile in hypertensive men.

Key words: Fish oil; Essential hypertension; LDL-cholesterol; Apolipoprotein B; Androgens

Introduction

Fish oil has received much attention for its potential benefits on a variety of factors which may be involved in the atherosclerotic process [1]. However, the administration of fish oil (or $n-3$ fatty acids) to patients with type II diabetes mellitus [2,3], or hyperlipidemias (types IIb and IV) [1,4–6] has been associated with adverse effects on glucose and lipid metabolism [2,4,6] but the reasons for these observations are not fully understood. Because there are interrelationships among glucose and lipid metabolism and blood pressure

Correspondence to: George S. Hughes, Jr., M.D., Upjohn Research Clinics-BCIU/Jasper, The Upjohn Company, 252 East Lovell Street, Kalamazoo, MI 49007, USA

[8,9] or endogenous sex steroid hormones [7] in patients with essential hypertension, fish oil may modulate plasma lipids by altering levels of endogenous sex steroid hormones [7], or insulin [2,3]. In order to test these concepts, we conducted a randomized, double-blind, two-way crossover study to evaluate the effects of fish oil on serum lipids, selected endogenous sex steroid hormones, glucose, insulin, and blood pressure in patients with essential hypertension and normotensive controls.

Methods

Subjects and protocol design

There were 13 subjects in each group of normotensive subjects or hypertensive patients. All subjects had normal values for complete blood count, serum chemistries, urinalysis, electrocardiogram, and endocrine tests including prolactin, free and total testosterone, luteinizing hormone, estradiol, thyroxine, T_3-resin uptake, and thyroid stimulating hormone. All participants were nonsmokers and did not use alcohol (or had any history of alcohol abuse). There was no evidence of hyperlipidemias or secondary hypertension by physical examination, history or laboratory tests. All hypertensive patients had a diastolic blood pressure of at least 90 mm Hg (taken in supine position) on at least three separate occasions before the start of the study. Hypertensive patients were tapered off all medications and were medication free for at least 2 weeks prior to the start of the study. Subjects were instructed in isocaloric diets by a registered dietitian to maintain weight throughout the study. The caloric intake was similar in normotensive and hypertensive subjects. The composition of the diets was 50% of calories from carbohydrates, 35–40% from fat (2:1 polyunsaturated/saturated fat ratio), and 15–20% from protein. The daily intake of sodium was controlled at approximately 150 mmol.

Subjects were randomized to receive 30 days of either 10 fish oil capsules per day (1-g, Promega®, Parke-Davis, equal to 350 mg of EPA and 150 mg DHA per capsule for a total of 5.0 g of *n*–3 fatty acids per day), or 10 placebo capsules of wheat germ oil per day (770 mg of oil per capsule, Jewel/Osco). The study medications were given over a 30-day period, followed by a 1-month washout, and then the subjects were crossed over to the other study drug for an additional 30 days. Subjects were seen weekly in the outpatient clinic to evaluate blood pressure, compliance with diet with a registered dietitian (with diet diaries which listed all foods consumed) and medication (by pill count assessment) and side effects. Subjects were instructed to have intakes as discussed above. Safety laboratory studies including complete blood count, lipids, liver function tests and body composition (using a bioanalytic impedance analysis) [10], were determined every 2 weeks throughout the study. In addition to the safety studies mentioned above, the following studies were drawn at baseline and at the end of each 30-day period after a 12-h fast: estradiol, free and total testosterone, free and weakly bound testosterone, sex hormone-binding globulin, total cholesterol, cholesterol in HDL, LDL, and VLDL, apoliprotein A_1, apolipoprotein B, glucose, insulin and platelet aggregation. A 24-h urine collection and simultaneous plasma renin activity were done during the last day of the crossover period to assess sodium and compliance with the prescribed diet. This technique was also used to classify hypertensive patients with regards to renin status and blood pressure (e.g., normal-renin hypertension) [11]. The protocol was approved by the Protocol Review Committee of The Upjohn Company and the Bronson Hospital Human Use Committee. The protocol was conducted according to the Declaration of Helsinki.

Procedures

Lipid (including cholesterol and triglycerides) and lipoprotein values were measured according to the techniques that were described elsewhere [12–14]. In brief, serum lipoproteins (VLDL, LDL, and HDL) were separated by ultracentrifugation in a density solution of 1.006. The buoyant lipoprotein fraction (VLDL) was recovered, and the high-density (HDL) was separated from the low-density lipoprotein (LDL) by selective precipitation using heparin and calcium chloride [12,13]. The HDL fraction was determined by a method of rapid precipitation on a separate serum sample using magnesium chloride and dextran sulfate to precipitate the VLDL and LDL leaving the clear HDL for cholesterol assay [13]. Apolipoprotein A_1

and B were measured by rate nephelometry on Array® using Beckman Instruments and apolipoprotein A_1 and B kits (APA and APB, respectively) from Beckman Instruments (Brea, CA) are described elsewhere [14].

Sex steroid hormone values were measured by radioimmunoassay at Smith-Kline Biosciences (Van Nuys, CA) [15].

Platelet aggregation was performed according to techniques described elsewhere [16]. Platelet aggregation was performed on Payton Model 1010 dual-channel aggregometers (Scarborough, Ontario, Canada). Output from the aggregometers was transmitted to an IBM-PC via an interface (Chronology Aggrolink) where the aggregometer output was plotted graphically and the maximum slope and amplitude of each curve determined. Each aggregation curve was monitored and recorded for a minimum of five minutes. ADP (5 and 10 μl of 2×10^{-4} mol/l; Sigma Diagnostics, St. Louis, MO) and epinephrine (5 and 10 μl of 1×10^{-4} mol/l; Chrono-Par, Havertown, PA) were used as agonists.

Lipid composition of platelet phospholipids was determined with separation of phospholipid classes with thin layer chromatography and gas chromatography, as described elsewhere [17].

Blood pressure was measured in the supine position with a Dinamap™ blood pressure monitor (Critikon, Inc., Tampa, FL) in the right arm of each volunteer during each patient visit.

Analysis

The analysis focused upon identifying treatment (placebo vs. fish oil) and group (normotensive vs. hypertensive) differences. It was assumed that there were no period effects and that the one-month washout period was adequate so that there were no residual treatment effects carried over from the first treatment period to the second. These assumptions were tested to the extent possible prior to analyzing the data and appear to be reasonable. The paired *t*-test was used to identify changes within treatment and group combinations over time (within subject comparisons). A repeated measures analysis of variance model was used for comparing treatment and group effects (between and within subject comparisons). The model incorporated factors for group, subjects nested within group, treatment, and the group by treatment interaction. The dependent variable used was the change from baseline scores within a study period. All statistical analyses were performed using PROC GLM of SAS (Cary, NC). Pearson correlation coefficients were used in selected sections. All units are mean ± SD and are expressed in SI units (except apolipoprotein B). The alpha level used was 0.05.

Results

Demographics and blood pressure

The hypertensive group was slightly older than normotensive men (normotensives, 31.7 ± 8.8 years; hypertensives, 42.1 ± 8.5, $p < 0.01$). However, total body weight (normotensives, 69.0 ± 7.2 kg; hypertensives, 69.0 ± 8.3 kg), body mass index (normotensives, 21.7 ± 2.3 kg/m^2; hypertensives, 21.6 ± 2.9 kg/m^2), body fat (normotensives, 20.5 ± 3.2%; hypertensives, 19.5 ± 3.3%), were not significantly different between groups at baseline

TABLE 1

EFFECT OF FISH OIL AND PLACEBO CAPSULES ON BLOOD PRESSURE, BODY WEIGHT AND BODY COMPOSITION

Mean ± SD

	Normotensive men ($n = 13$)			Hypertensive men ($n = 13$)		
	Baseline	Placebo	Fish oil	Baseline	Placebo	Fish oil
Blood pressure (mm Hg)						
systolic	128.4 ± 7.6	125.0 ± 9.9	127.4 ± 7.3	141.9 ± 11.7 *	140.3 ± 12.1 *	142.8 ± 11.2 *
diastolic	72.3 ± 7.6	71.2 ± 8.8	69.6 ± 6.8	89.0 ± 10.4 *	90.1 ± 11.6 *	90.3 ± 9.2 *
mean	91.0 ± 6.0	89.2 ± 7.0	88.7 ± 4.9	106.6 ± 10.2 *	106.8 ± 11.0 *	107.8 ± 10.0 *

* $P < 0.001$, blood pressure (systolic, diastolic and mean) normotensive subjects vs hypertensive patients; baseline refers to the last time that blood pressure was taken prior to administration of study drug and after patients were free of antihypertensive drugs for at least 2 weeks.

TABLE 2

EFFECT OF FISH OIL AND PLACEBO CAPSULES ON SERUM LIPIDS, APOLIPOPROTEINS A AND B, GLUCOSE AND INSULIN

Mean ± SD.

	Normotensive men ($n = 13$)			Hypertensive men ($n = 13$)		
	Baseline	Placebo	Fish oil	Baseline	Placebo	Fish oil
Total cholesterol (mmol/l)	4.87 ± 0.57	4.40 ± 0.58	4.36 ± 0.58	5.19 ± 0.58	4.98 ± 0.79	5.40 ± 0.77 *
HDL cholesterol (mmol/l)	1.13 ± 0.26	1.15 ± 0.42	1.03 ± 0.18	1.00 ± 0.26†	0.94 ± 0.19	1.01 ± 0.29
LDL cholesterol (mmol/l)	3.31 ± 0.74	2.98 ± 0.72	3.11 ± 0.51	3.47 ± 0.73	3.31 ± 0.77	3.94 ± 0.84‡
VLDL cholesterol (mmol/l)	0.43 ± 0.36	0.36 ± 0.15	0.23 ± 0.09	0.72 ± 0.50	0.73 ± 0.39	0.44 ± 0.15
Triglycerides (mmol/l)	1.06 ± 0.96	0.88 ± 0.38	0.58 ± 0.25	1.71 ± 1.17	1.85 ± 1.01	1.13 ± 0.81
Apolipoprotein A_1 (mmol/l)	125.5 ± 22.0	132.4 ± 25.8	118.5 ± 15.7	124.2 ± 17.3	127.2 ± 15.8	121.1 ± 18.7
Apolipoprotein B (mg/dl)	74.9 + 22.0	72.3 ± 18.5	77.5 ± 13.6	100.9 ± 26.3§	92.8 ± 23.5	109.0 ± 27.4 *
Glucose (mmol/l)	5.04 ± 0.37	5.01 ± 0.33	4.91 ± 0.48	5.12 ± 0.39	5.09 ± 0.30	5.08 ± 0.39
Insulin (pmol/l)	–	126.7 ± 59.5	130.0 ± 53.9	–	132.5 ± 33.8	122.0 ± 25.6

* $P < 0.025$, placebo vs. fish oil, hypertensive group only.
\+ $P < 0.025$, baseline, normotensive vs. hypertensive groups.
‡ $P < 0.006$, placebo vs. fish oil, hypertensive group only.
§ $P < 0.026$, baseline, normotensive vs. hypertensive groups.

and were unchanged during the study. The mean values for blood pressure (systolic, diastolic and mean taken in supine position), for normotensive subjects and hypertensive patients at baseline and following the end of each phase of the study are shown in Table 1. Baseline diastolic blood pressure measurements were slightly lower in hypertensive men than the 3 initial readings taken before any study medications were given. Blood pressure was higher in the hypertensive group during each phase of the study ($P < 0.001$), than normotensive men, but was unchanged during the study in either normotensive or hypertensive groups. All subjects had normal-renin hypertension [11].

Lipids and lipoproteins

The values for total cholesterol, cholesterol in HDL, LDL, and VLDL, triglycerides, apolipoprotein A_1, apolipoprotein B, glucose, and insulin are shown in Table 2. Baseline values for lipids and lipoproteins were not significantly different between normotensives and hypertensives, with the exception of apolipoprotein B ($P < 0.026$) and HDL cholesterol ($P < 0.025$). In the normotensive group, there were no statistically significant changes in mean values for lipids, lipoproteins, glucose, or insulin during the study. However, there were significant increases in total cholesterol, LDL cholesterol and apolipoprotein B for all ($n = 13$) of the hypertensive patients when given fish oil (Table 2). In contrast, 12 of 13 of the hypertensive patients had no changes in the above values when given placebo capsules. The remaining hypertensive patient had increases in LDL cholesterol, total cholesterol, and apolipoprotein B of approximately 15% each above baseline. In the normotensive subjects, two subjects (one during the fish oil period and one during the placebo period) raised LDL cholesterol, total cholesterol, and apolipoprotein B by about 15–20% each above baseline. Only 2 of the study participants (one normotensive subject and one hypertensive patient), who had higher baseline triglycerides (at least 1 SD above the mean) also had increases of LDL and total cholesterol, and apolipoprotein B. For these participants, serum triglycerides and VLDL cholesterol fell by 50–60% while LDL and total cholesterol and apolipoprotein B each increased by about 30% during both the placebo and fish oil periods. In both the normotensive and hypertensive groups there was a trend for mean values for VLDL cholesterol and triglycerides to decline, but the results were not statistically significant perhaps in part due to wide intersubject variability.

TABLE 3

EFFECT OF FISH OIL AND PLACEBO CAPSULES ON SELECTED SERUM SEX STEROID HORMONES

Mean ± SD

	Normotensive men ($n = 13$)			Hypertensive men ($n = 13$)		
	Baseline	Placebo	Fish oil	Baseline	Placebo	Fish oil
Estradiol (pmol/l)	120.7 ± 49.2	116.9 ± 56.7	124.5 ± 42.3	89.8 ± 31.9	92.3 ± 33.6	87.3 ± 31.3
Testosterone, total (mmol/l)	20.45 ± 6.57	22.4 ± 7.94	23.6 ± 4.72	14.3 ± 4.31 *	15.46 ± 7.71	17.4 ± 7.07
Testosterone, free (nmol/l)	0.668 ± 0.244	0.777 ± 0.304	0.833 ± 0.221	0.451 ± 0.067 *	0.526 ± 0.25	0.586 ± 0.23
Testosterone, free and weakly-bound (nmol/l)	12.04 ± 4.85	13.65 ± 5.62	14.45 ± 4.09	8.16 ± 1.52 +	9.34 ± 4.73	10.45 ± 4.39

* $P < 0.003$, hypertensive vs. normotensive groups at baseline.

\+ $P < 0.006$, hypertensive vs. normotensive groups at baseline.

Hormones

Mean levels of estradiol, total testosterone, free testosterone and free and weakly bound testosterone are shown in Table 3. Baseline mean levels for estradiol were not different between normotensive and hypertensive groups. However, values for all measured androgens were lower in the hypertensive subjects. The values for estradiol and androgens were unchanged during the study for either the normotensive or hypertensive groups.

Following placebo and fish oil periods, there were modest correlations of androgens with HDL-cholesterol, apolipoproteins A and B in the hypertensive group. Similar findings were not observed in the normotensive group. For hypertensives during the placebo period, HDL cholesterol was directly correlated with free testosterone (hypertensive $r = 0.63$, $P < 0.02$; normotensives $r = 0.31$, $P = 0.30$) (Fig. 1), total testosterone ($r = 0.64$, $P < 0.029$), and free and weakly bound testosterone ($r = 0.64$, $P < 0.018$), but VLDL cholesterol was inversely related to total testosterone ($r = -0.56$, $P < 0.046$). Similar relationships were generally true on fish oil but did not reach statistical significance except for HDL cholesterol and total testosterone ($r = 0.60$, $P < 0.02$) only in the hypertensive group. During fish oil supplementation, apolipoprotein B was directly correlated with free testosterone ($r = 0.59$, $P < 0.033$), free and weakly bound testosterone ($r = 0.59$, $P < 0.03$) and total

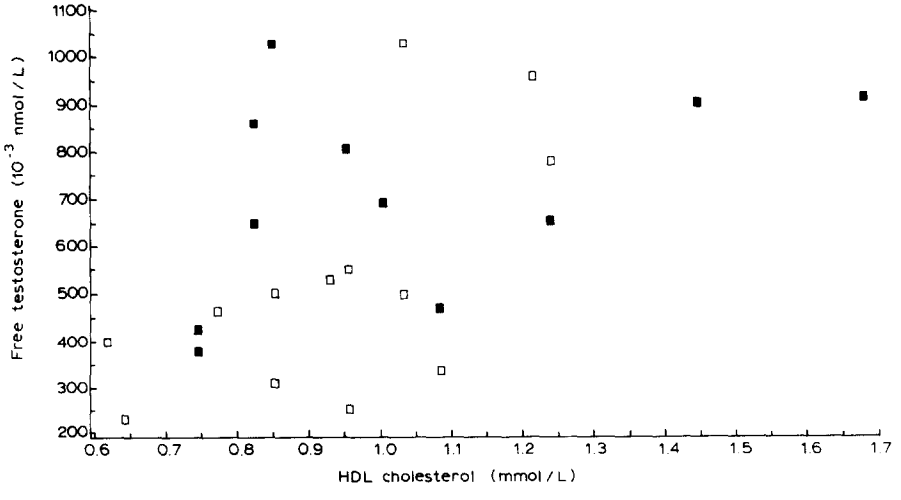

Fig. 1. HDL-cholesterol versus free testosterone in normotensive subjects (■) and hypertensive patients (□) during the placebo period.

TABLE 4

EFFECT OF FISH OIL AND PLACEBO CAPSULES ON LEVELS OF CHOLESTEROL AND SELECTED FATTY ACIDS IN PLATELET MEMBRANE PHOSPHOLIPIDS
Mean ± SD

Membrane components	Normotensive men ($n = 13$)		Hypertensive men ($n = 13$)	
	Placebo	Fish oil	Placebo	Fish oil
TC ($\mu g/10^9$ platelets)	77.7 ±21.7	78.0 ±19.9	73.3 ±10.6	71.0 ±14.8
CE ($\mu g/10^9$ platelets)	23.1 ±12.4	18.2 ± 9.4	19.5 ± 7.1	21.8 ±12.4
TGL ($\mu/10^9$ platelets)	15.0 ± 9.3	14.8 ±14.8	11.3 ± 6.6	14.7 ± 6.6
Phospholipids (%)				
Phosphatidylcholine				
EPA	0.06± 0.17	3.55± 2.67 *	0.21± 0.23	3.37± 0.74 *
DHA	1.30± 0.81	1.82± 0.74	1.31± 0.49	2.64± 1.00 *
AA	13.1 ± 2.7	11.2 ± 3.2	16.2 ± 2.6	11.8 ± 4.1†
Phosphatidylethanolamine				
EPA	0.24± 0.41	3.04± 1.28 *	0.20± 0.39	5.0 ± 1.96 *
DHA	2.74± 1.31	3.91± 1.35	3.26± 1.62	5.0 ± 2.09‡
AA	31.71± 0.0	30.0 ± 9.27	43.2 ± 7.4	35.4 ±11.2§
Phosphatidylserine				
EPA	0.0 ± 0.0	0.26± 0.52	0.37± 0.79	0.86± 1.03
DHA	0.72± 0.91	1.66± 1.56	0.53± 0.75	2.62± 1.92§
AA	14.0 ± 4.8	10.6 ± 4.7	18.3 ± 8.7	21.9 ±11.6
Phosphatidylinositol				
EPA	0.24± 0.74	0.42± 0.69	0.30± 0.84	1.03± 1.81
DHA	2.26± 4.6	0.60± 0.83	0.55± 0.99	0.70± 1.46
AA	15.64± 9.0	15.4 ± 9.1	21.5 ±13.7	23.8 ±12.1

TC = total cholesterol; CE = cholesterol esters; TGL = triglycerides; EPA = eicosapentaenoic acid; DHA = docosahexaenoic acid; AA = arachidonic acid.
* $P < 0.0001$, placebo vs. fish oil.
† $P < 0.001$, placebo vs. fish oil.
‡ $P < 0.011$, placebo vs. fish oil.
§ $P < 0.029$, placebo vs. fish oil.

testosterone ($r = 0.67$, $P < 0.032$) only in the hypertensive group.

Sex hormone binding globulin was normal and not significantly different in hypertensive and normotensive groups (data not shown). Subjects were in balance with respect to calcium and sodium intake throughout the study (data not shown).

Platelet membrane composition and function

Selected platelet membrane phospholipid levels for total cholesterol, cholesterol esters, triglycerides, and selected fatty acids such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) are shown in Table 4. There were no changes in total cholesterol, cholesterol esters, or triglycerides. However, there were several significant increases in EPA and DHA only in phosphatidylcholine, phosphatidylethanolamine, phosphatidylserine, but not phosphatidylinositol subfractions of platelet membranes in both normotensive and hypertensive groups during the administration of fish oil. Arachidonic acid generally decreased in all groups of phospholipids when fish oil was given in both normotensive and hypertensive groups, but was significant only in phosphatidylcholine and phosphatidylethanolamine subfractions in the hypertensive men (Table 4). Platelet aggregation was not significantly different among hypertensives or normotensives and was unaffected by the administration of fish oil in either group (data not shown).

Discussion

Our results indicate that fish oil induced a potentially atherogenic lipid profile including increased LDL cholesterol, apolipoprotein B and

total cholesterol only in the hypertensive patients. These findings have not been reported before in patients with essential hypertension. Increased levels of LDL cholesterol and apolipoprotein B have been observed with administration of fish oil (in similar doses as other studies) [2–5] to patients with type II diabetes mellitus [2] or hyperlipidemia, especially hypercholesterolemia and hypertriglyceridemia [4,5]. There may be several explanations for our findings which involve change in particle size or number of LDL or apo B, or perhaps alteration in other parameters such as sex steroids, glucose, or insulin metabolism which may affect lipoproteins.

There may be several reasons for the effects of fish oil on LDL. This could be due to increased production or decreased removal of LDL particles, or perhaps due to alteration in activity of lipoprotein lipase or hepatic extraction of VLDL [18,19]. Large triglyceride-enriched VLDL are directly removed from the circulation by the liver [18]. Smaller triglyceride-poor VLDL particles are converted to LDL [19]. As the triglyceride content of VLDL decreases more of the smaller triglyceride-poor VLDL particles are produced which are then converted to LDL. Although the serum LDL and total cholesterol increased, there were no significant changes in cholesterol, cholesterol esters, or triglycerides in platelet membranes. It is uncertain whether this finding is relevant to other membranes such as the vascular endothelium. However, just the increase in LDL cholesterol alone in the hypertensive men could be clinically relevant. For example, for every 0.026 mmol/l change in LDL cholesterol, there is a 1% increase in coronary risk [20], which means and increased risk of almost 20%.

Fish oil could indirectly affect serum lipids via alteration of sex steroid hormones [21,22], insulin [2,9], or hepatic and lipoprotein lipase activity [21,22]. Sex steroid hormones (endogenous or exogenous pharmacologic doses) are known to influence the activity of hepatic and lipoprotein lipases [21–24]. It is generally accepted that androgens (especially synthetic androgens) increase the activity of hepatic lipase and lead to reduction of HDL-cholesterol [23], whereas the opposite is true for estrogens [21,22]. More recent studies indicate that only the 17-alkyl substituted androgens produce these changes in HDL cholesterol and hepatic lipase, but nonaromatizable androgens do not [25]. Estrogens increase lipoprotein lipase activity [24]. However, studies have shown variable relationships of HDL cholesterol with androgens and lipoprotein lipase activity [26–28]. We confirmed that androgens are lower in hypertensive men [7]. We also found that there was a positive correlation between HDL cholesterol and testosterone, only in the hypertensive men. It is unclear whether the reduced levels of androgens that we observed in hypertensive men are analogous to lower levels of androgens that are seen in patients with diabetes mellitus [29], or in several [30–32], but not all studies of men with coronary artery disease [33]. For example, when hyperglycemia is controlled in type I and type II diabetics, triglycerides often decrease [3], lipoprotein lipase activity increases [34] and there is a simultaneous rise in endogenous androgens [29]. Whether there is any relationship between fish oil and perturbation of lipoprotein lipase activity and endogenous androgens merits further investigation. Additional potential hormonal and lipid interrelationships in men with essential hypertension [8] or coronary artery disease [9] have been observed. Correlations between low levels of testosterone and insulin have been shown in men with coronary artery disease [9]. However, we did not observe changes in insulin or glucose despite noting lower levels of androgens and elevation of LDL cholesterol in these hypertensive men.

We also addressed other issues about the effects of fish oil on blood pressure and the composition and function of platelets. We did not detect any changes in blood pressure which is in agreement with some studies, but not in others [1]. Generally the effects of fish oil are small (5–10 mm Hg) and dose-related (i.e., > 3 g EPA per day), but discrepancies among these studies could be due to the variety of marine sources for EPA, different quantities and/or types of fish, or differences in study design or the population used [1,35]. Diastolic blood pressure was attenuated during the initial three readings which were taken before any study medications were given. This phenomenon has been reported, but poorly understood in human hypertensive studies [36]. Platelet

membrane composition showed marked increase in EPA and DHA, as expected [1,37]. AA decreased, but only significantly in the hypertensive group for reasons unknown. Despite the change in platelet fatty acid composition, which confirmed similar alterations in other studies, there were no changes in platelet aggregation, which also has been reported [1,38]. In addition, there were no significant changes in body composition in both the normotensive and hypertensive groups. Because body composition, not body weight, can affect levels of sex steroid hormones [39], we felt that the lack of changes in body fat or lean body mass accompanied by lipid and lipoprotein changes with fish oil could probably be explained by the effects of fish oil on lipid metabolism.

In summary, this study demonstrates that administration of fish oil to patients with essential hypertension produced increases in total and LDL cholesterol, and apoliprotein B. It is possible that these changes in lipids may be mediated by sex steroid hormones which act in concert with insulin to modulate hepatic and lipoprotein lipases to produce an atherogenic lipid profile, but further studies are needed in this regard. It is suggested that the administration of fish oil supplements to patients with essential hypertension be used with caution and that careful attention should be paid to changes in lipids and lipoproteins. Perhaps the consumption of fish, rather than fish oil supplements, is the most appropriate long-term recommendation for the potential value of $n-3$ fatty acids in prevention of cardiovascular disease [39].

References

1 Von Schacky, C., Prophylaxis of atherosclerosis with marine omega-3 fatty acids, Ann. Intern. Med., 107 (1987) 890.

2 Glauber, H., Wallace, P., Griver, K. and Brechtel, G., Adverse metabolic effect of omega-3 fatty acids in noninsulin-dependent diabetes mellitus, Ann. Intern. Med., 108 (1988) 663.

3 Popp-Snijders, C., Schouten, J.A., Heine, R.J. and Van der Veen, E.A., Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in noninsulin dependent diabetes, Diabetes Res., 4 (1987) 141.

4 Sullivan, D.R., Sanders, T.A.B., Trayner, I.M. and Thompson, G.R., Paradoxical elevation of LDL and apoprotein B levels in hypertriglyceridaemic patients and normal subjects ingesting fish oil, Atherosclerosis, 61 (1986) 129.

5 Simons, L.A., Hickie, J.B. and Balasubramaniam, S., On the effects of dietary $n-3$ fatty acids (Maxepa) on plasma lipids and lipoproteins in patients with hyperlipidemia, Atherosclerosis, 54 (1985) 75.

6 Wilt, T.J., Lofgren, R.P., Nichol, K.L. et al., Fish oil supplementation does not lower plasma cholesterol in men with hypercholesterolemia, Ann. Intern. Med., 111 (1989) 900.

7 Hughes, G.S., Mathur, R.S. and Margolius, H.S., Sex steroid hormones are altered in essential hypertension, J. Hypertension, 7 (1989) 181.

8 Zavaroni, I., Bonora, E., Pagliara, M. et al., Risk factors for coronary artery disease in healthy persons with hyperinsulinemia and normal glucose tolerance, N. Engl. J. Med., 320 (1989) 702.

9 Lichtenstein, M.J., Yarnell, J.W.G., Elwood, P.C. et al., Sex hormones, insulin, lipids, and prevalent ischemic heart disease, Am. J. Epidemiol., 126(4) (1987) 647.

10 Gray, D.S., Bray, G.A., Gemayel, N. and Kaplan, K., Effect of obesity on bioelectrical impedance, Am. J. Clin. Nutr., 50 (1989) 255.

11 Brunner, H.R., Lavagh, J.L., Baer, L. et al., Essential hypertension: renin and aldosterone, heart attack and stroke, N. Engl. J. Med., 286 (1972) 441.

12 Hatch, F.T. and Lees, R.S., Practical methods for plasma lipoprotein analysis, Adv. Lipid Res., 6 (1968) 1.

13 Kostner, G.M., Enzymatic determination of cholesterol in high density lipoprotein fractions prepared by polyanion precipitation, Clin. Chem. 22 (1976) 695.

14 Maciejko, J.J., Levinson, S.S., Markyvich, L., Smith, M.P. and Blevins, R.D., New assay of apolipoproteins A-1 and B by rate nephelometry evaluated, Clin. Chem., 33(11) (1987) 2065.

15 The Smith-Kline Bio-Science Laboratories Handbook, 14th edition, Van Nuys, CA, 1987.

16 Kwaan, H.C., Colwell, J.A., Cruz, S., Suwanela, N. and Dobbie, J.G., Increased platelet aggregation in diabetes mellitus, J. Lab. Clin. Med., 80 (1972) 236.

17 Nagawa, Y., Orimo, H., Harasawa, M., Morita, I., Yashiro, K. and Murota, S., Effect of eicosapentaenoic acid on the platelet aggregation and composition of fatty acid in man, Atherosclerosis, 47 (1983) 71.

18 Packard, C.J., Munro, A., Lorimer, A.R., Gotto, A.M. and Shepherd, J., Metabolism of apolipoprotein B in large triglyceride-rich very low density lipoproteins of normal and hypertriglyceridemic subjects, J. Clin. Invest., 74 (1984) 2178.

19 Stalenhof, A.F., Malloy, M.J., Kane, J.P. and Havel, R.J., Metabolism of apolipoproteins of B-48 and B-100 of triglyceride-rich lipoprotein in normal and lipoprotein-lipase deficient humans, Proc. Natl. Acad. Sci. USA, 81 (1984) 1839.

20 Gordon, D.J., Probstfield, J.L., Garrison, R.J. et al., High-density lipoprotein cholesterol and cardiovascular disease: four prospective American studies, Circulation, 79 (1989) 8.

21 Sorva, R., Kuusi, T., Dunkel, L. and Taskinen, M.R., Effects of endogenous sex steroids on serum lipoproteins and post heparin plasma lipolytic enzymes, J. Clin. Endocrinol. Metab., 66 (1988) 408.

22 Appelbaum-Bowden, D., Haffner, S.M., Wahl, P.W., Hoover, J.J., Warnick, G.R., Albers, J.J. and Hazzard, W.R., Postheparin plasma triglyceride lipases. Relationships with very low density lipoprotein$_2$ cholesterol, Arteriosclerosis, 5 (1985) 273

23 Enholm, C., Huttunen, J.K., Kinnunen, P.J., Miettinen, T.A. and Nikkilaä, E.A., Effect of oxandrolone treatment on the activity of lipoprotein lipase, hepatic lipase and phospholipase A1 of human postheparin lipase, N. Engl. J. Med., 292 (1975) 1314.

24 Applebaum, D.M., Goldberg, A.P., Pykälistö, O.J., Brunzell, J.D. and Hazzard, W.R., Effect of estrogen on postheparin lipolytic activity, J. Clin. Invest., 59 (1977) 601.

25 Friedl, K.E., Hannan, C.J., Jones, R.E. and Plymate, S.R., High density lipoprotein cholesterol is not decreased if an aromatizable androgen is administered, Metabolism, 39 (1990) 69.

26 Nordøy, A., Aakvaag, A. and Thelle, D., Sex hormones and high density lipoproteins in healthy males, Atherosclerosis, 34 (1979) 431.

27 Heller, R.F., Miller, N.E., Lewis, B., Vermuelen, A., Fairney, A., James, V.H.T. and Swan, A.V., Associations between sex hormones, thyroid hormones and lipoproteins, Clin. Sci., 61 (1981) 649.

28 Brier, C., Drexel, H., Lisch, H.J., Mühlberger, V., Herold, M. and Knapp, E., Essential role of postheparin lipoprotein lipase activity and of plasma testosterone in coronary artery disease, Lancet, 1 (1985) 1241.

29 Gluud, C., Maddsbad, S., Krarup, T. and Bennett, P., Plasma testosterone and androstenedione in insulin dependent patients at time of diagnosis and during the first year of insulin treatment, Acta Endocrinol., 100 (1982) 406.

30 Gutai, J., LaPorte, R., Kuller, L., Dai, W., Falvo-Gerard, L. and Caggiula, A., Plasma testosterone, high density lipoprotein cholesterol and other lipoprotein fractions, Am. J. Cardiol., 48 (1981) 897.

31 Chute, C.G., Baron, J.A., Plymate, S.R. et al., Sex hormones and coronary artery disease, Am. J. Med., 83 (1987) 853.

32 Poggi, U.L., Argüelles, A.E., Rosner, J., De Laborde, N.P., Cassine, J.H. and Volmer, M.C., Plasma testosterone and serum lipids in male survivors of myocardial infarction, J. Steroid. Biochem., 7 (1976) 229.

33 Cauley, J.A., Gutai, J.P., Kuller, L.H. and Dai, W.S., Usefulness of sex steroid hormone levels in predicting coronary artery disease in men, Am. J. Cardiol., 60 (1987) 771.

34 Taskinen, M.R., Lipoprotein lipase in diabetes, Diabetes Metab. Rev., 3 (1987) 551.

35 Knapp, H.R. and FitzGerald, G.A., The antihypertensive effects of fish oil, N. Engl. J. Med., 320 (1989) 1037.

36 Kramer, M.S. and Shapiro, S.H., Scientific challenges in the application of randomized trials, JAMA, 252 (1984) 2739.

37 Boberg, M., Vessby, B. and Selinus, I., Effects of dietary supplementation with $n-6$ and $n-3$ long-chain polyunsaturated fatty acids on serum lipoproteins and platelet function in hypertriglyceridaemic patients, Acta Med. Scand., 220 (1986) 153.

38 Segal, K.R., Dunaif, A., Gutin, B., Albu, J., Nyman, A. and Pi-Sunyer, X., Body composition, not body weight, is related to cardiovascular disease risk factors and sex hormone levels in men, J. Clin. Invest., 80 (1987) 1050.

39 Kromhout, D., Bosschieter, E.B. and Cor De Lezenne Coulander, C. The inverse relation between fish consumption and 20-year mortality from coronary heart disease, N. Engl. J. Med., 312 (1985) 1205.