

Comparison of the effects of fish and fish-oil capsules on the n-3 fatty acid content of blood cells and plasma phospholipids¹⁻³

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ABSTRACT

Background: n-3 Fatty acids (FAs) have been shown to be beneficial for cardiovascular health. Whether n-3 FAs from oily fish consumed weekly or from fish-oil capsules taken daily are equally bioavailable is not clear.

Objective: The purpose of this study was to compare the rate and extent of enrichment of blood cell membranes [ie, red blood cells (RBCs)] and plasma phospholipids with n-3 FAs from these 2 sources.

Design: Healthy premenopausal female volunteers were randomly assigned to consume a daily average of 485 mg eicosapentaenoic (EPA) and docosahexaenoic (DHA) acids either from 2 servings of oily fish (ie, salmon and albacore tuna) per week or from 1-2 capsules/d.

Results: After 16 wk, EPA+DHA in RBCs in the fish group ($n = 11$) increased from $4.0 \pm 0.6\%$ of total FAs to $6.2 \pm 1.4\%$, whereas it rose from $4.3 \pm 1.0\%$ to $6.2 \pm 1.4\%$ in the capsule group ($P < 0.0001$ for both; NS for group effect). Similar results were observed in plasma phospholipids. EPA+DHA stabilized in the latter after 4 wk but continued to rise through week 16 in RBCs. EPA in RBCs increased significantly ($P = 0.01$) more rapidly in the fish group than in the capsule group during the first 4 wk, but rates did not differ significantly between groups thereafter. Total FA variances were less in RBCs than in plasma phospholipids ($P = 0.04$).

Conclusion: These findings suggest that the consumption of equal amounts of EPA and DHA from oily fish on a weekly basis or from fish-oil capsules on a daily basis is equally effective at enriching blood lipids with n-3 FAs. *Am J Clin Nutr* 2007;86:1621-5.

KEY WORDS n-3 Fatty acids, eicosapentaenoic acid, docosahexaenoic acid, fish, fish oil, erythrocytes, phospholipids

INTRODUCTION

A greater intake of the long-chain n-3 fatty acids (FAs) eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) has been recommended by a variety of scientific and regulatory bodies to reduce population risk for coronary artery disease (CAD) (1). The American Heart Association has divided its recommendations into 3 categories: persons without known CAD, those with CAD, and those with elevated serum triacylglycerol concentrations (2). The intakes suggested for persons in those categories are, respectively, ≥ 2 fish meals/wk (preferably oily fish), ≈ 1 g EPA+DHA/d (from oily fish or from capsules), and 2-4 g EPA+DHA/d from capsules. A presumption of an equivalence between oily fish and fish-oil capsules is inherent in these recommendations, and yet few studies have examined whether n-3

FAs are equally bioavailable from these 2 very different matrices. In a pilot study including 4-8 volunteers who had consumed either salmon or fish-oil supplements, Visioli et al (3) found similar increases in serum phospholipid EPA (per mg EPA consumed) from either source, but a 3 times greater increase in serum DHA concentrations when the DHA came from salmon than when it came from fish-oil capsules. This study was small and retrospective; moreover, the EPA and DHA intakes from these 2 sources were not matched, and the study was not randomized. A larger study compared the effects of eating salmon and taking cod liver oil on serum n-3 FAs; it found that the former was a more efficient vehicle (4). However, in neither of these studies were EPA and DHA intakes prospectively matched. In the present study, we sought to compare the effects of equivalent, nutritionally relevant intakes of marine n-3 FAs from oily fish given 2 times/wk and of daily fish-oil capsule supplementation on the EPA and DHA content of blood cell membranes [ie, red blood cells, RBCs, or the omega-3 index, a proposed risk marker for cardiovascular mortality (5)] and of the plasma phospholipid (PPL) fraction. We also compared the tolerability of each approach.

SUBJECTS AND METHODS

Subjects

Women between 21 and 49 y old who were premenopausal and not pregnant or nursing and who had a body mass index (in kg/m^2) < 30 were recruited. Exclusions were gastrointestinal disorders that could interfere with fat absorption, an intention to lose weight, consumption of > 2 alcoholic drinks/d, and regular (> 2 times/mo) consumption of tuna or salmon supplemented with fish-oil or flaxseed oil capsules.

Written informed consent was obtained from all participants. The protocol was approved by the St Luke's Hospital Institutional Review Board.

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Study design

After qualifying for the trial, women were randomly assigned to either the fish ($n = 11$) or capsule ($n = 12$) group. Those in the former group were asked to consume every 2 wk three 171-g (6-ounce) cans of albacore tuna (StarKist; Del Monte Foods, San Francisco, CA) and one 171-g fillet of Norwegian Atlantic-farmed salmon (American Seafood International, New Bedford, MA). The cans of tuna and frozen salmon fillets were provided (along with recipes) for consumption at home. The fish could be eaten for more than one meal, but all servings had to be consumed within 24 h. The tuna and salmon could not be consumed on the same day. The importance of complete consumption was stressed but not directly monitored.

Those women randomly assigned to the capsule group were asked to take 17 n-3 FA capsules (Omega-3; CardioTabs, Kansas City, MO) at a rate of 1-2/d according to a provided schedule. This particular n-3 FA supplement was chosen because its FA composition is more reflective of that of salmon and tuna (ie, it is DHA rich) than is that of most supplements, which typically are EPA rich.

To ascertain the number of capsules to prescribe, we analyzed 3 capsules, 3 fillets of salmon, and 3 cans of albacore tuna—each in triplicate. For the capsules, an oil aliquot was removed and weighed. The internal standard (17:0) was added, the sample was methylated and analyzed by gas chromatography (GC) as described below. For the fish, the complete cooked salmon fillet and the contents of the entire can of albacore tuna were weighed and homogenized, and 3 aliquots were extracted according to a method of Bligh and Dyer (6). The albacore tuna averaged 185 ± 29 mg EPA and 1010 ± 150 mg DHA (1195 mg EPA+DHA) per can. The salmon averaged 777 ± 222 mg EPA and 2429 ± 797 mg DHA per fillet. Accordingly, 3 cans of albacore tuna and one salmon fillet provided 1333 mg EPA and 5460 mg DHA over 2 wk, for a total daily average of 485 mg EPA+DHA (95 mg + 390 mg, respectively). Each capsule contained 86 ± 2 mg EPA and 311 ± 12 mg DHA. Seventeen capsules, taken over a 2-wk span, provided an average total of 482 mg EPA+DHA/d (104 mg + 378 mg, respectively). The average amount of linoleic acid and arachidonic acid (AA) provided by the fish and the capsules was 22 and 44 mg/d and 8 and 8 mg/d, respectively. The duration of the study was 16 wk, and clinic visits were scheduled every 2 wk.

Tolerability of the fish and the fish-oil capsules was compared by using a questionnaire. Subjects were asked 3 questions at the end of the study: 1) Did you experience any fishy aftertaste (ie, “burps”) during the study? 2) If so, how frequent were the “burps”? 3) If so, how unpleasant were they?

Analysis of lipids and lipoproteins

For measurement of fasting plasma lipids and lipoproteins, blood was drawn after a fast of ≥ 10 h into tubes containing 1 mg EDTA/mL. Whole plasma triacylglycerol and cholesterol concentrations were measured enzymatically (Cholesterol/HP; Roche Diagnostics, Indianapolis, IN) and by using a triacylglycerol reagent (GPO-Trinder; Bayer Diagnostics, Tarrytown, NY) on a Cobas Fara analyzer (Roche Analytic Instruments Inc, Nutley, NJ) according to the manufacturer’s instructions. Plasma HDL cholesterol was measured after precipitation of the apolipoprotein B-containing lipoproteins (7). LDL-cholesterol concentrations were calculated by using the Friedewald equation (8). If the triacylglycerol concentration was >400 mg/dL (as was seen in

$<5\%$ of the blood samples), no value for LDL cholesterol was reported. CVs for all of these assays are $<3\%$.

Analysis of n-3 fatty acids

Blood cell membranes

Frozen whole blood was thawed, hemolyzed in water (1:14), and spun for 5 min at 4°C at $2800 \times g$ in an ultracentrifuge (TL100 equipped with a TLA-100.3 rotor; Beckman Instruments, Fullerton, CA). The supernatant fluid (containing hemoglobin and serum lipids) was discarded, and the pellet (almost entirely composed of RBC membranes) was suspended in 1 mL boron-trifluoride methanol (BF_3 ; Sigma, St Louis, MO) and transferred to a screw-cap test tube. The tubes were heated for 10 min at 100°C to hydrolyze and methylate the membrane glycerophospholipid FAs (9). After the tubes were cooled, water and hexane (1:1) were added, and the tube was briefly shaken and then centrifuged for 3 min at $1500 \times g$ and at room temperature to separate the layers. The upper (hexane) layer was removed, the solvent was evaporated under nitrogen, and the blood sample was resuspended in decane and transferred to a vial for analysis by flame ionization GC.

Plasma phospholipids

Plasma lipids were extracted according to the method of Carlson (10) with the use of methanol, methylene chloride, and saline, and the phospholipid fraction was isolated by using thin-layer chromatography on silica gel G (Analtech Inc, Newark, DE) with heptane:diethyl ether:formic acid (80:20:2). The phospholipid band was collected and heated for 10 min at 100°C in BF_3 to produce FA methyl esters, which were recovered and prepared for GC analysis as described below.

Gas chromatography

Fused silica capillary columns (100-m length, 0.25-mm internal diameter, 0.25- μm film thickness; SP-2560; Supelco, Bellefonte, PA) were used to determine FA composition. The methyl esters were analyzed in gas chromatographs (GC14A1; Shimadzu Scientific Instruments, Columbia, MD for those derived from PPL; GC9A; Shimadzu Scientific Instruments for those derived from RBC membranes). The inclusion of a weighed external standard FA mixture (GLC673b; NuCheck Prep, Elysian, MN) allowed for control of the differences in response factors between the instruments (the response factor for palmitic acid was assumed to be 1.0).

Statistical analysis

Data not normally distributed (ie, EPA, AA, total cholesterol, triacylglycerol) were log transformed for analysis. The mean response profile was examined across time by treatment group with the use of lowess smoothing, which suggested (*see Results*) that a piece-wise general linear model would fit well for both the RBC and PPL sample types. Akaike’s Information Criterion was used to compare models with different timepoints, and a knot (ie, inflection point) at 4 wk produced the best fit. After we examined all residual pair-wise correlations from an ordinary least-squares model, we implemented a Toeplitz correlation structure for the repeated measures. Estimated total variances between RBC and PPL FAs were compared by using the $F(21, 21)$ distribution. A post hoc power analysis based on the observed variances found



that we would not have been able to detect a between-group difference in RBC EPA+DHA of ≤ 1.5 . Data are presented as means \pm SDs, and a P value < 0.05 was considered statistically significant. Analyses were performed by using SAS software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

Subjects

All women were premenopausal. The 2 groups (fish group, $n = 11$; capsules group, $n = 12$) did not differ with respect to body mass index (26.1 ± 2.1 and 25.5 ± 2.1 , respectively) or racial backgrounds ($n = 9, 2$, and 0 and $9, 2$ and 1 for whites, blacks, and Asians, respectively, in the fish and capsules groups, respectively). They did, however, differ significantly ($P = 0.01$) in age (35 ± 8.7 and 43 ± 3.8 y, respectively), but age was not a significant response predictor in any of the longitudinal analyses. There was no significant weight change during the study in either group (a gain of 0.1 kg and 0.7 kg, respectively). Compliance with the fish-oil capsule protocol was $97 \pm 8\%$, and the participants uniformly reported complete consumption of the provided fish.

Baseline red blood cells and plasma phospholipid fatty acid content

The baseline EPA content of RBC membranes was 20% lower in the fish group than in the capsule group ($P = 0.03$), but the EPA content of the PPL did not differ significantly between the groups (Table 1). There were no baseline differences between groups with either the RBC or PPL sample type.

Rate of fatty acid increase in plasma phospholipid and red blood cells: capsules compared with fish

Rates (ie, slopes) were compared between the PPL and RBC sample types and between groups in 2 phases: the first 4 wk and the last 12 wk (Table 2). The only significant group \times time interaction for any FA of interest in either sample type in either period was that for EPA in RBCs during the first 4 wk: the rate of increase of EPA in RBCs was $\approx 7\%$ faster in the fish group than in the capsule group ($P = 0.01$). Because there were no other significant group interactions, data from all 23 women (both the fish and capsule groups) were combined, and the responses over time between the PPL and RBC sample types were evaluated.

PPL concentrations of EPA rose by 19%/wk over the first month, which was significantly greater than the slope in RBC EPA in the capsule group ($P = 0.0003$) but not significantly different from that in the fish group (Table 2). EPA did not rise further over the next 3 mo in either sample type. For DHA, during the first month, concentrations rose in PPL more than twice as quickly as in RBCs (Table 2), but RBC DHA continued to rise over the next 3 mo, whereas PPL DHA did not. The summed metric EPA+DHA had the same response pattern as did DHA alone. AA concentrations decreased significantly ($P = 0.004$) in PPL (but not in RBCs) during the first phase, and neither slope was different from zero in the second phase.

Fatty acid variances in plasma phospholipids and red blood cells

Estimated total variances for all 4 FA variables (EPA, DHA, EPA+DHA, and AA) in PPL and RBCs were analyzed to determine whether one marker was more biologically stable than

TABLE 1

Effects of fish feeding versus capsule supplementation on the proportion of total fatty acids present as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and arachidonic acid (AA) in blood cell membranes and plasma phospholipids¹

	RBC membranes		Plasma phospholipids	
	Fish	Capsules	Fish	Capsules
EPA				
Week				
0	0.80 \pm 0.12	0.99 \pm 0.17 ²	0.53 \pm 0.25	0.57 \pm 0.11
2	1.04 \pm 0.27	1.22 \pm 0.14	0.98 \pm 0.49	1.00 \pm 0.25
4	1.43 \pm 0.35	1.27 \pm 0.21	1.83 \pm 1.09	1.00 \pm 0.17
6	1.21 \pm 0.17	1.26 \pm 0.30	1.25 \pm 1.10	1.09 \pm 0.32
8	1.39 \pm 0.34	1.20 \pm 0.25	1.30 \pm 0.81	1.10 \pm 0.38
10	1.26 \pm 0.44	1.32 \pm 0.31	1.10 \pm 0.83	1.12 \pm 0.38
12	1.15 \pm 0.36	1.21 \pm 0.18	1.09 \pm 0.67	1.04 \pm 0.39
14	1.39 \pm 0.41	1.29 \pm 0.26	1.93 \pm 1.05	0.90 \pm 0.29
16	1.34 \pm 0.35	1.30 \pm 0.40	1.52 \pm 0.88	1.02 \pm 0.35
DHA				
Week				
0	3.22 \pm 0.58	3.34 \pm 0.79	3.22 \pm 0.55	2.84 \pm 0.80
2	3.72 \pm 0.52	3.86 \pm 0.73	4.54 \pm 0.91	4.03 \pm 0.78
4	4.13 \pm 0.84	4.02 \pm 0.78	5.18 \pm 1.36	4.31 \pm 0.86
6	4.13 \pm 0.67	4.20 \pm 0.86	5.33 \pm 1.23	5.31 \pm 1.76
8	4.52 \pm 0.61	4.33 \pm 0.94	5.79 \pm 1.88	4.92 \pm 1.74
10	4.50 \pm 0.83	4.54 \pm 0.95	4.65 \pm 1.12	4.73 \pm 1.20
12	4.61 \pm 1.06	4.60 \pm 0.99	5.12 \pm 1.06	4.52 \pm 1.15
14	4.81 \pm 1.17	4.66 \pm 1.00	5.17 \pm 0.94	4.70 \pm 1.81
16	4.83 \pm 1.16	4.86 \pm 1.10	5.28 \pm 1.04	4.53 \pm 1.35
AA				
Week				
0	15.5 \pm 1.9	16.0 \pm 1.4	13.0 \pm 2.5	12.2 \pm 2.6
2	15.3 \pm 1.6	16.2 \pm 1.5	11.9 \pm 1.4	11.5 \pm 2.0
4	15.1 \pm 2.1	16.1 \pm 2.1	12.2 \pm 2.3	11.3 \pm 2.4
6	15.0 \pm 1.9	15.8 \pm 1.9	11.3 \pm 2.2	11.3 \pm 2.6
8	15.7 \pm 1.1	16.0 \pm 2.5	11.6 \pm 1.7	11.0 \pm 2.3
10	15.5 \pm 1.4	15.4 \pm 2.5	11.1 \pm 1.9	11.4 \pm 1.9
12	15.4 \pm 1.7	15.8 \pm 3.0	11.6 \pm 1.9	11.5 \pm 2.2
14	14.7 \pm 1.9	15.6 \pm 1.7	11.8 \pm 1.6	11.1 \pm 2.0
16	14.8 \pm 1.5	15.7 \pm 1.3	11.7 \pm 1.6	11.1 \pm 2.1

¹ All values are $\bar{x} \pm$ SD. Baseline differences between groups were evaluated by t test. The group \times time interaction was significant ($P = 0.01$) only for red blood cell EPA: the fish group increased more during the first 4 wk than did the capsule group. For time trends by sample type, see Table 2.

² $P < 0.01$.

the other. Variances (% of total FAs) were as follows: 0.24 versus 0.6 ($P = 0.001$) for EPA, 1.66 versus 0.9 ($P = 0.09$) for DHA; 2.62 versus 1.31 ($P = 0.06$) for EPA+DHA; and 0.03 versus 0.01 ($P = 0.04$) for AA. Hence, variances for RBC FAs were 25–50% of those for PPL FAs.

Serum lipid and lipoproteins

Effects of capsules and fish on serum lipids were first evaluated for group \times time interactions (Figure 1). There were no interactions for total, LDL, or HDL cholesterol; consequently, the groups were pooled and the time effects on each lipid were evaluated. There were time effects for total and LDL cholesterol (Table 2). Mean LDL cholesterol increased from 106 to 115 mg/dL ($P = 0.01$). There were no effects on HDL cholesterol. There was a significant group \times time interaction for triacylglycerol ($P = 0.01$). Mean plasma triacylglycerols increased from 68

TABLE 2

Predicted change in fatty acids of interest over time¹

	EPA ²		DHA		EPA + DHA		AA ²	
	0–4 wk	4–16 wk	0–4 wk	4–16 wk	0–4 wk	4–16 wk	0–4 wk	4–16 wk
	%		%		%		%	
Red blood cells	Interaction ³	NS	6.3 ^{4,5}	2 ^{4,5}	7.6 ^{4,5}	1.6 ^{4,5}	NS ⁵	NS
Plasma phospholipids	19 ⁴	NS	15.3 ⁴	NS	15.1 ⁴	NS	-2.2 ⁴	NS

¹ EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; AA, arachidonic acid. Change was measured as the percentage change per week from baseline.² Lognormal distribution; otherwise normal.³ The fish group increased 13.6%/wk, and the capsule group increased 6.3%/wk, for a 7%/wk difference between groups, $P = 0.01$.⁴ Slope significantly different from 0, $P < 0.0004$.⁵ Slope significantly different from plasma phospholipid, $P < 0.02$.

to 85 mg/dL ($P = 0.03$) in the capsule group but decreased from 104 to 94 mg/dL ($P = 0.22$) in the fish group over 16 wk.

Side effects

The frequency of fishy aftertaste was significantly ($P < 0.001$) higher in the capsule group than in the fish group (10/12 and 1/11, respectively). For the 7 subjects in the capsule group, it occurred ≥ 1 time/wk, and it was most often considered “mildly unpleasant.”

DISCUSSION

This study showed that, regardless of whether n-3 FAs are consumed from oil-rich fish or fish-oil capsules, there was, after 16 wk of treatment, no difference in the effect on the major long-chain n-6 or n-3 FAs, whether measured in RBCs or in PPL. Over that period, the consumption of ≈ 485 mg EPA+DHA/d from fish or capsules produced a 40–50% rise in RBC EPA+DHA and a 60–80% rise in PPL EPA+DHA. We found that EPA+DHA concentrations rose more quickly in PPL than in RBCs; the former stabilized by 4 wk and the latter continued to rise over the span of the 4-mo test period. This finding confirms previous studies indicating that the turnover of EPA and DHA in plasma is faster than that in RBCs (11). The EPA content

of RBCs over weeks 0–4 was the only FA compartment (and the only time frame) in which a difference between fish and capsules was detectable; EPA concentrations rose 7% faster in the former than the latter, but only during the first month, after which time the concentrations did not differ significantly between groups. This suggests that, at least in the short-term, EPA may be more bioavailable from fish than from capsules. AA concentrations decreased by $\approx 2\%/wk$ in PPL during the first month, but they did not change significantly thereafter or in RBCs at any time. Finally, the biological variability of FAs in RBCs was $\approx 50\%$ of that observed in PPL. Such a difference in variances is not unexpected, because the latter (transported as it is in plasma lipoproteins) is more likely to be subject to day-to-day variation in composition than is the RBC membrane.

Essential FAs are known to transfer directly from plasma to RBC membranes (12), and, for linoleic acid at least, to reach a new steady state within ≈ 2 wk (13). DHA, at 1 g/d, was reported to reach a steady state in PPL within 4 wk and in RBCs in 4–6 mo (14). Studies with labeled DHA showed that albumin-bound, nonesterified DHA was poorly transferred to RBCs, whereas DHA esterified in lysophosphatidylcholine was incorporated into RBC (and platelet) membranes within hours of ingestion (15). The factors that influence the rate of incorporation of EPA and DHA into both plasma and tissues deserve further investigation.

The AHA has recommended the intake of ≈ 2 fish meals (preferably oily fish)/wk for primary prevention of CAD. In the present study, that intake provided ≈ 485 mg EPA+DHA/d, which is approximately the intake currently recommended by government health agencies in the United Kingdom Britain (16) and Australia and New Zealand (17). The AHA also recommends ≈ 1 g EPA+DHA/d for patients with known cardiovascular disease (2). That amount is about twice the dose provided here and thus would be expected to produce twice the increase in RBC EPA+DHA (ie, an increase to 8% instead of to 6%). Such an effect was previously observed (5). The former concentration has been proposed as a “cardioprotective target value” (5).

Minimal effects of this intake of EPA+DHA on plasma lipids and lipoproteins were anticipated. We found, however, that the capsules produced a small increase in triacylglycerols (which remained within the normal range), but the fish did not. Total and LDL cholesterol rose slightly in the combined groups. Nevertheless, LDL-cholesterol and triacylglycerol concentrations remained in the normal range in both groups. Past studies of fish feeding have rarely fed this small amount of n-3 FAs, but, when

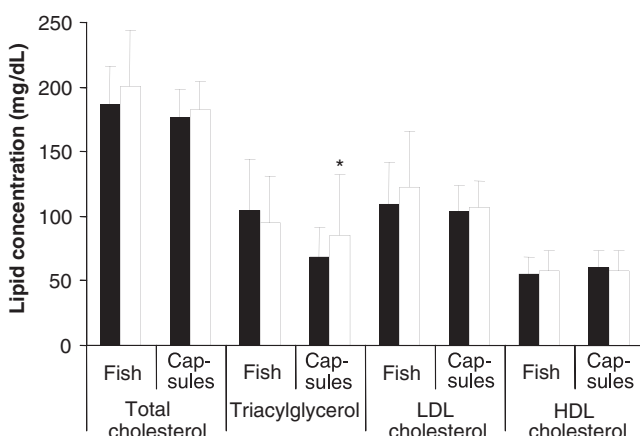


FIGURE 1. Mean (\pm SD) effects of twice-weekly fish consumption ($n = 11$) and daily fish-oil capsule supplementation ($n = 12$) on serum lipids and lipoproteins at baseline (■) and week 16 (□). Significant ($P = 0.01$) week \times group interactions were seen only for triacylglycerols. Week effects were significant for total and LDL cholesterol. For analysis of effects on total, LDL, and HDL cholesterol, groups were pooled. In the aggregate, total and LDL cholesterol increased significantly over time ($P = 0.01$). * $P = 0.025$ versus baseline.



examined, neither triacylglycerol nor LDL cholesterol was affected (18). Higher doses of n-3 FAs do lower triacylglycerol and, in some subjects, raise LDL cholesterol (19).

Fish consumption was associated with fewer episodes of a fishy aftertaste than was capsule consumption, which suggests increased tolerability of the former. Fish also provides high-quality protein and trace minerals (especially selenium and iodine) that are not provided by supplements. In contrast, capsules are more convenient to consume, and they provide none of the mercury or chemical contaminants (20) that can be found in fish (21). However, a recent risk-benefit analysis indicated that the cardiovascular benefits of consuming fish (ie, salmon) far outweigh ($\approx 400:1$) any risks due to the potential presence of these contaminants (21).

The present study differed in several ways from previous studies exploring the question of bioavailability (3, 22–24). It examined nutritionally achievable intakes of n-3 FAs (ie, ≈ 500 mg/d) that are currently recommended by several health organizations and agencies. It compared daily capsules with twice-weekly fish consumption, and 2 forms of n-3 FA were used (ie, ethyl esters in capsules and FAs carried in triacylglycerols and phospholipids in fish). The study was randomized and prospectively designed to compare the effects of these 2 sources of n-3 FAs on 2 commonly used measures of n-3 status: RBCs and PPLs. It is important that both EPA and DHA intakes (not just total n-3 FAs) were matched in the 2 groups. Finally, blood samples were taken at a frequency that would allow tracking of the rate of rise, and (given that the RBC lifespan is ≈ 16 wk) the study was planned to be long enough to achieve a new steady state in both n-3 markers. This steady state, however, was not achieved: the EPA+DHA content was still increasing at 16 wk.

This was a small study, and we would not have been able to detect relatively small response differences between the groups. Fish and capsule consumption was not directly supervised, so we cannot be certain of daily intakes. Future studies should include a larger sample size, both men and women, a wider variety of ages, and various doses of n-3 FAs; they should last for >4 mo; and they could also include a washout phase to track the rate of clearance of these FAs from plasma and RBC membranes.

In conclusion, the EPA+DHA content of RBCs or PPLs did not differ significantly when equivalent doses of n-3 FAs were provided twice a week from fish or daily from capsules for 4 mo. Accordingly, either source could be used to bolster tissue n-3 concentrations, and evidence from past randomized trials suggests that both would be expected to result in a lower risk of CAD events.

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The authors' responsibilities were as follows: WSH: conceived of the project, wrote the protocol, obtained the funding and institutional review board approval, and contributed significantly to the manuscript; SAS: conducted laboratory analyses and wrote the first draft of the manuscript; and JVP and PJG: performed the statistical analyses. WSH is a scientific advisor to Monsanto and Reliant Pharmaceuticals, and SAS is employed by OmegaMetrix, LLC (a company that offered n-3 FA blood testing and that is now defunct). The other authors had no personal or financial conflict of interest.

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