

# Effect of Fish Oil Supplementation on the Excretion of the Major Metabolite of Prostaglandin E in Healthy Male Subjects

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We investigated the effect of fish oil supplementation on the synthesis of prostaglandin E (PGE) *in vivo* by measuring the excretion of its catabolite, PGE-M, in 24-hr urine by gas chromatography/mass spectrometry. Forty healthy male volunteers (24–57 years of age) consumed a controlled basal diet providing 40% of energy from fat (P/S ratio about 0.8:1), 130 mg/1000 kcal cholesterol, and a minimum of 22 mg/day of  $\alpha$ -tocopherol ( $\alpha$ -T), for three experimental periods lasting a total of 28 weeks. During period 1 (10 weeks) the diet was supplemented with placebo (PO) capsules (15 × 1 g/day) consisting of a blend of fats approaching the fatty acid profile of the basal diet. This was followed by a second 10-week period during which the subjects received 15 × 1 g/day capsules of fish oil concentrate (FOC). During period 3 (8 weeks) they continued the 15 g/day intake of FOC but received an additional 200 mg/day of  $\alpha$ -T. PO and FOC capsules contained 1 mg  $\alpha$ -T/g fat as antioxidant. A 14% reduction of PGE-M excretion was observed after 10 weeks of FOC supplementation (period 2), compared to an identical period of placebo supplementation (period 1),  $P=0.009$ . PGE-M excretion during the last week of period 3 was not significantly different from that at the end of period 2. The reduction in PGE synthesis in response to the relatively high marine oil supplementation was large in many subjects participating in this study. *Lipids* 26, 500–503 (1991).

A protective effect of  $\omega$ 3 polyunsaturated fatty acids (PUFA) against atherothrombotic disorders has been established reasonably well from studies with humans and animal models (1–5). The underlying biochemical mechanisms of this protective action are not entirely understood, but a major role has been attributed to effects on  $\omega$ 6 fatty acid metabolism with resultant changes in the profile of products of arachidonate cyclooxygenation (5,6). Considerable work has been done to evaluate the effects of  $\omega$ 3 PUFA on thromboxane (TXA<sub>2</sub>) and prostacyclin (PGI<sub>2</sub>) synthesis (4,6–10). This is justified in view of the preeminent roles of these eicosanoids in vascular biology. It is a reasonable assumption, however, that in addition to thromboxane and prostacyclin, other eicosanoids may also respond to dietary manipulations of adequate magnitude.

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Abbreviations:  $\alpha$ -T,  $\alpha$ -tocopherol; EPA, eicosapentaenoate; FOC, fish oil concentrate; GC/MS, gas chromatography/mass spectrometry; PGE, prostaglandin E; PGE-M, 11 $\alpha$ -hydroxy-9,15-dioxo-2,3,4,5,20-pentanoic-19-carboxyprostanic acid; PGI<sub>2</sub>, prostacyclin; PO, placebo oil; P/S, ratio dietary linoleate to saturated fatty acids; PUFA, polyunsaturated fatty acids; TXA<sub>2</sub>, thromboxane A<sub>2</sub>.

Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) has been characterized as the most common and most potent of mammalian prostaglandins. It is clearly involved in mechanisms of blood pressure regulation (11,12), tumorigenesis (13–15), and immune response modulation (16–18). Notwithstanding these critical roles, surprisingly little is known about the capacity of dietary fish oil to modulate PGE<sub>2</sub> synthesis in humans *in vivo* and attendant physiologic consequences (4).

The present study was designed to determine if some changes in physiological variables attributed to fish oil consumption might be explained by altered PGE biosynthesis. Based on the ubiquity and potency of PGE, we expected this work to help identify other, yet uncovered, effects of fish oil consumption. We quantified the effect of a relatively high supplementation of a marine oil concentrate on prostaglandin E biosynthesis, by measuring the urinary excretion rate ( $\mu$ g/24 hr) of 11 $\alpha$ -hydroxy-9,15-dioxo-2,3,4,5,20-pentanoic-19-carboxyprostanic acid (PGE-M). This compound is commonly regarded (19,20) as an index of systemic production of E-series prostaglandins (E<sub>2</sub>+E<sub>1</sub>).

## MATERIALS AND METHODS

**Subjects.** Forty non-smoking male subjects, 24–57 years of age (mean 37.6 ± 8.8, SD), were selected among volunteers from the area surrounding the Beltsville Agricultural Research Center (Beltsville, MD). They were screened by a preliminary medical questionnaire to eliminate those with complicating health problems and unusual dietary habits. Regular users of dietary supplements (especially vitamin E) and of excessive quantities of alcohol were also excluded. Potential subjects were examined by a physician, and by hematological and chemical screening of blood and urine. Those with plasma  $\alpha$ -tocopherol ( $\alpha$ -T) levels outside of the normal range were excluded. Body weights were between 90 and 120% of the desirable weights as given in the 1983 Metropolitan Life Insurance tables. Aspirin, aspirin-containing drugs and other anti-inflammatory drugs were not allowed during the study. Occasional use of tylenol was the only permitted analgesic. Antibiotics and other medications taken during the study under a physician's direction were evaluated for possible effects on study parameters. All procedures were approved by the Human Studies Committees of the National Institutes of Health and the Georgetown University School of Medicine.

**Controlled diets.** The basal diet for the controlled dietary periods was designed to reflect the typical dietary pattern of Beltsville area volunteers as determined in earlier studies, except that the fat level of the diet was reduced to allow isoenergetic supplementation with 15 g/day placebo oil (PO) or fish oil concentrate (FOC) without permitting energy from fat to exceed 40% of total. Cholesterol intake was about 130 mg/1000 kcal. All nutrients

for which food data are available were provided by the diets in amounts to meet the Recommended Dietary Allowances (21). Caloric intake was adjusted in increments of 400 kcal to maintain constant body weights throughout the study. The contents of long-chain ( $C_{20}$ ,  $C_{22}$ , and  $C_{24}$ )  $\omega$ 3 fatty acids were minimized in the basal diet by excluding fish from the menus, while vitamin E content was minimized by excluding highly fortified foods from the diet.

A fourteen-day menu cycle provided variety and helped maintain acceptability of the diets. During the controlled diet periods, breakfast and supper were consumed in the Beltsville Human Nutrition Research Center, Human Studies Facility (HSF), Monday through Friday. A box lunch was provided at breakfast time. Weekend and holiday meals were pre-packaged in the HSF for home consumption and used the same menus as other days of the menu cycle. No foods other than those provided by the study were permitted, and alcohol consumption was not allowed during the controlled diet periods.

**Lipid supplementation/placebo oil (PO).** The placebo consisted of a blend of commonly available fats (corn oil, beef tallow, lard) approaching the fatty acid profile of the basal diet, and was encapsulated in one-gram amounts with one mg  $\alpha$ -T per capsule as antioxidant. PO was prepared and encapsulated by Hoffmann-La Roche, Inc. (Nutley, NJ), and was indistinguishable in external appearance from the fish oil concentrate.

**Fish oil concentrate (FOC).** The  $\omega$ 3 fatty acid supplement (ROPUGA®) was an anchovy oil derivative prepared in one batch sufficient for the duration of the study. FOC was prepared by Hoffmann-La Roche by a distillation/deodorization process which increases the  $\omega$ 3 fatty acid content to about 50%, compared to about 30% for most commercial fish oil supplements. FOC was also provided as hard gelatin capsules containing one gram of fat and one mg  $\alpha$ -T. Table 1 shows the main fatty acid constituents of the placebo and fish oil supplements. Both supplements were administered to participants at the rate of 15 g/day, 7 capsules at breakfast and 8 capsules at supper.

**Experimental protocol.** Prior to supplementation, the subjects were on a self-selected diet for two weeks while baseline measurements were taken. This was followed by the controlled diets described above for a total of 28 weeks divided into three periods according to the supplement given: Period 1 (ten weeks) 15 g/day PO; Period 2 (ten weeks) 15 g/day FOC; Period 3 (eight weeks) 15 g/day FOC plus 200 mg/day  $\alpha$ -tocopherol in two equal doses. Dietitians observed the subjects as they consumed the oil capsules and the vitamin E supplements. No attempt was made to provide a placebo for the vitamin E supplement. The estimated daily intake of nutrients for the three periods was (in percent of energy): fat, 40%; carbohydrate, 45%; and protein, 15%.  $\alpha$ -Tocopherol intake from natural foods was at least 22 mg. Table 2 shows the estimated daily fatty acid intakes during the controlled-diet periods.

**Urine collection.** Three consecutive 24-hr urines were collected during the last week of each period. Samples were collected in silanized glass bottles and kept on ice during the collection period. After the 24-hr collections were completed, the volumes were measured, 2%-portions of each 24-hr collection were pooled and either analyzed immediately or stored at  $-22^{\circ}\text{C}$ .

**Measurement of PGE-M.** Analyses of 11 $\alpha$ -hydroxy-9,15-dioxo-2,3,4,5,20-pentanor-19-carboxyprostanic acid

TABLE 1

Principal Fatty Acid Constituents of Placebo and Fish Oil Supplements

Fatty acids	g/100 g Supplement	
	Placebo	Fish oil
14:0	2.1	4.9
16:0	21.8	9.3
16:1 $\omega$ 7	2.4	6.5
18:0	13.3	1.4
18:1 $\omega$ 9	36.4	5.4
18:2 $\omega$ 6	13.7	1.9
18:3 $\omega$ 3	0.4	1.0
18:4 $\omega$ 3	ND <sup>a</sup>	4.6
20:1 $\omega$ 9	0.4	0.4
20:4 $\omega$ 6	0.2	1.4
20:4 $\omega$ 3	ND	1.1
20:5 $\omega$ 3	ND	30.2
22:5 $\omega$ 3	ND	2.5
22:6 $\omega$ 3	ND	13.1
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Saturated <sup>b</sup>	38.4	16.5
Monounsaturated <sup>b</sup>	42.8	15.7
Polyunsaturated <sup>b</sup>	14.4	63.6
$\omega$ 6 Fatty acids	13.9	3.7
$\omega$ 3 Fatty acids	0.4	52.5
Ratio $\omega$ 3/ $\omega$ 6 Fatty acids	$\sim$ 0.0	14.2

<sup>a</sup>None detected.<sup>b</sup>Including minor constituents.

TABLE 2

Estimated Daily Fatty Acid Intake on Controlled Diets<sup>a</sup> (g/day at 2800 kcal)

Fatty acids	Supplement	
	Placebo	Fish oil
Total saturated (S)	33	29
Palmitic (16:0)	20	18
Stearic (18:0)	9	7
Total monounsaturated (M)	46	42
Oleic (18:1 $\omega$ 9)	44	39
Total polyunsaturated (P)	27	33
Total $\omega$ 3 polyunsaturated	2	10
$\alpha$ -Linolenic (18:3 $\omega$ 3)	2	2
Eicosapentaenoic (20:5 $\omega$ 3)	0	5
Docosahexaenoic (22:6 $\omega$ 3)	0	2
Total $\omega$ 6 polyunsaturated	25	23
Linoleic (18:2 $\omega$ 6)	25	23

<sup>a</sup>Including contributions from indicated supplement.

(PGE-M) were done on 20-mL aliquots of the 72-hr pools prepared as described above. This enabled us to assess the mean daily excretion of PGE-M during the 72-hr period. Procedures and instruments were described previously by Ferretti *et al.* (22). When prolonged urine storage was unavoidable, the PGE-M values were adjusted to compensate for decay according to a first-order rate constant determined in our laboratory (23). PGE-M excretion rates are expressed as  $\mu\text{g}/24$  hr.

**Statistical analysis.** Twenty-four-hr PGE-M excretion rates and lipid intakes were evaluated by paired *t*-tests with the computer methodology of the Statistical Analysis System (SAS Institute, Inc., Cary, NC). All *P* values less than 0.05 were considered statistically significant.

## RESULTS

Four subjects were withdrawn entirely from the study because they developed health conditions that required administration of interfering prescription drugs. This left 36 subjects for analysis. Period 3 PGE-M excretion data from one subject (No. 35) were disregarded because of a health problem that required prescription drugs during period 3, and period 3 PGE-M data from another subject (No. 36) were disregarded because of non-adherence to study protocol. The data were analyzed by analysis of variance. There were no significant carryover effects. A paired *t*-test was therefore utilized for comparison between diets as planned in the study design.

TABLE 3

PGE-M Urinary Excretion Rates ( $\mu\text{g}/24$  hr) During the last Week of the Indicated Diet Periods

Subject	Diet period			% Reduction <sup>a</sup>
	1	2	3	
1	3.79	3.44	3.36	9.2
2	30.83	13.11	26.05	57.5
3	13.15	11.67	6.40	11.3
4	11.48	21.91	7.92	-90.8
5	9.44	15.64	21.39	-65.7
6	14.71	13.09	7.63	11.0
7	8.05	6.09	8.64	24.3
8	19.62	12.49	17.13	36.3
9	12.71	9.07	8.53	28.6
10	11.06	11.03	9.35	0.3
11	5.93	4.85	4.23	18.2
12	23.18	9.85	5.68	57.5
13	52.28	38.54	40.96	26.3
14	14.48	12.58	14.75	13.1
15	11.12	2.78	16.47	75.0
16	6.09	5.66	6.35	7.1
17	18.61	13.65	12.64	26.7
18	5.04	4.45	4.33	11.7
19	12.76	10.04	12.95	21.3
20	10.84	5.53	3.83	49.0
21	8.00	7.78	7.43	2.7
22	8.24	8.24	9.03	0.0
23	4.52	4.01	3.85	11.3
24	60.92	58.98	48.64	3.2
25	4.61	4.84	4.35	-5.0
26	17.49	13.96	14.22	20.2
27	41.14	29.31	38.56	28.8
28	16.89	16.00	12.16	5.3
29	11.93	8.21	8.17	31.2
30	12.33	9.79	8.07	20.6
31	10.78	10.57	8.69	1.9
32	10.16	11.29	12.03	-11.1
33	7.76	6.06	8.23	21.9
34	13.44	13.05	12.28	2.9
35	6.55	6.92	UD <sup>b</sup>	-5.6
36	24.93	15.94	UD <sup>b</sup>	36.1

<sup>a</sup>Reduction calculated as period 1 minus period 2.

<sup>b</sup>Data not recorded (see Results).

The mean PGE-M urinary excretions ( $\mu\text{g}/24$  hr) during the last week of periods 1, 2 and 3 were  $15.41 \pm 2.12$  (SEM) (N=36),  $12.51 \pm 1.78$  (N=36) and  $12.77 \pm 1.85$  (N=34), respectively. Paired *t*-tests indicated a significant reduction of PGE-M excretion during period 2, compared to that of period 1 [difference =  $2.90 \pm 0.89$  (SEM)  $\mu\text{g}/24$  hr, *P*=0.002]. The reduction based on individual contributions was 14% (*P*=0.009). Excretion rates of each subject for the three feeding periods are shown in Table 3. PGE-M excretion during the last week of period 3 was not significantly different from that at the end of period 2.

## DISCUSSION

PGE-M excretion rates during periods 1 and 2 provide clear evidence that fish oil supplementation inhibits *in vivo* production of E-series prostaglandins in most individuals. PGE synthesized in the kidneys and seminal vesicles are excreted virtually unmetabolized, thus they escape measurement with our methodology. The rationale for disregarding their contribution to total synthesis has been discussed (24). PGE-M excretion reflects PGE production at sites easily accessible to systemic clearance. In a study of much shorter duration (four weeks), Knapp and FitzGerald (4) reported a non-significant trend toward lower PGE-M values in a group of eight volunteers receiving 50 mL/day of fish oil. In a rat study, Hornstra and Stegen (25) demonstrated a diet-induced shift in the ratio monoic to dioic prostaglandin metabolites. Although our work is concerned with the synthesis and metabolism of PGE alone—and not of the aggregate PGE + PGF, as is the paper by Hornstra and Stegen (25)—it is still possible that our results were similarly influenced by the dietary manipulation, if indeed the metabolic shift observed in rats also occurs in humans.

Research by other investigators on the effect of  $\alpha$ -tocopherol on arachidonate cyclooxygenation has produced conflicting results. In our study, a large vitamin E supplement was provided during period 3. Vitamin E was given to counteract the effects of oxidative stress (26) from prolonged intake of several grams of  $\omega$ 3 PUFA and to determine if a large daily dose of vitamin E has any measurable effect on PGE synthesis when other dietary parameters were held constant. Two-hundred mg/day of  $\alpha$ -T had no significant effect on PGE-M excretion.

In view of the high simultaneous intake of linoleate (25 g/day), the magnitude of PGE-M excretion rate reduction (14%) during FOC supplementation is, in our opinion, remarkable. The relevant issue we have to address is: What is the biological impact of changes in PGE production of the magnitude measured in this study? The synthesis of PGE is not localized in a specific tissue as is the case with thromboxane A<sub>2</sub> (platelets) and most of prostacyclin (vascular endothelium). The biological functions of PGE are manifold depending on the tissue where the synthesis takes place; hence the physiologic consequences of reduced PGE production are not as obvious or predictable as those of a reduced synthesis of TXA<sub>2</sub> and PGI<sub>2</sub>.

In a recent pilot study on long-term fish oil supplementation Ferretti *et al.* (27) demonstrated that, in addition to a reduction of renal PGE<sub>2</sub> synthesis in absolute terms, the pre-supplementation (renal) synthetic ratio PGE<sub>2</sub>/PGE<sub>2</sub>=O changed to PGE<sub>3</sub>/PGE<sub>2</sub>>O following fish oil administration. Thus, in this specific case, to assess the

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effect of marine oil on renal physiology as modulated by arachidonate metabolism we must consider not only the effects of reduced PGE<sub>2</sub> synthesis but also the different biological activity of PGE<sub>3</sub> as compared to that of PGE<sub>2</sub>. In view of the central role of PGE<sub>2</sub> in renal physiology (28), we wondered whether a shift in the PGE<sub>3</sub>/PGE<sub>2</sub> ratio might have a detrimental effect on renal function (27). This is an issue of obvious concern which has been expressed by other investigators, especially in reference to subjects with impaired renal function (4). Presumably, similar shifts in the PGE<sub>3</sub>/PGE<sub>2</sub> synthetic ratio take place concurrently in other tissues.

Present knowledge of PGE biology strongly suggests that, in addition to renal function, the impact of PGE modulation is most likely to be manifested in the cardiovascular (11,12,29-32) and immune (16,17,33-38) systems, and possibly in tumorigenesis (13,15,39-41). Therefore, it is desirable to assess the long-term effects of a diet-induced reduction of PGE biosynthesis. Perhaps the most critical question that must be answered is: What is the extent of dietary lipid manipulation necessary to influence the eicosanoid system to a clinically significant degree? We also need to know more about the biological activity of PGE<sub>3</sub> vis-à-vis that of PGE<sub>2</sub>.

In conclusion, the results of this study, if considered in conjunction with the regulatory roles attributed to prostaglandin E in critical areas of human physiology, suggest that prolonged use of fish oil supplements should not be incorporated into dietary recommendations until the pharmacology of marine lipids is better understood.

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