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EFFECTS OF HIGH-DOSE FISH OIL ON RHEUMATOID ARTHRITIS AFTER STOPPING NONSTEROIDAL ANTIINFLAMMATORY DRUGS

Clinical and Immune Correlates

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Objective. **To determine the following: 1) whether dietary supplementation with fish oil will allow the discontinuation of nonsteroidal antiinflammatory drugs (NSAIDs) in patients with rheumatoid arthritis (RA); 2) the clinical efficacy of high-dose dietary $\omega 3$ fatty acid fish oil supplementation in RA patients; and 3) the effect of fish oil supplements on the production of multiple cytokines in this population.**

Methods. **Sixty-six RA patients entered a double-blind, placebo-controlled, prospective study of fish oil supplementation while taking diclofenac (75 mg twice a day). Patients took either 130 mg/kg/day of $\omega 3$ fatty acids or 9 capsules/day of corn oil. Placebo diclofenac was substituted at week 18 or 22, and fish oil supplements were continued for 8 weeks (to week 26 or 30). Serum levels of interleukin-1β (IL-1β), IL-2, IL-6, and IL-8 and tumor necrosis factor α were measured by enzyme-linked immunosorbent assay at baseline and during the study.**

Results. **In the group taking fish oil, there were significant decreases from baseline in the mean (±SEM) number of tender joints (5.3 ± 0.835; $P < 0.0001$), duration of morning stiffness (−67.7 ± 23.3 minutes; $P = 0.008$), physician's and patient's evaluation of global arthritis activity (−0.33 ± 0.13; $P = 0.017$ and −0.38 ± 0.17; $P = 0.036$, respectively), and physician's evaluation of pain (−0.38 ± 0.12; $P = 0.004$). In patients taking corn oil, no clinical parameters improved from baseline. The decrease in the number of tender joints remained significant 8 weeks after discontinuing diclofenac in patients taking fish oil (−7.8 ± 2.6; $P = 0.011$) and the decrease in the number of tender joints at this time was significant compared with that in patients receiving corn oil ($P = 0.043$). IL-1β decreased significantly from baseline through weeks 18 and 22 in patients consuming fish oil (−7.7 ± 3.1; $P = 0.026$).**

Conclusion. **Patients taking dietary supplements of fish oil exhibit improvements in clinical parameters of disease activity from baseline, including the number of tender joints, and these improvements are associated with significant decreases in levels of IL-1β from baseline. Some patients who take fish oil are able to discontinue NSAIDs without experiencing a disease flare.**

Omega-3 fatty acids are highly polyunsaturated long-chain fatty acids derived primarily from marine sources, including fish and shellfish. Eicosapentaenoic acid (EPA), which has 20 carbons and 5 double bonds, may compete with arachidonic acid, which has 20 carbons and 4 double bonds, as a substrate for oxygenation by both the cyclooxygenase and 5-lipoxygenase pathways. These two pathways lead to the production of highly metabolically active eicosanoids, including prostaglandins (PGs) and leukotrienes (LTs), respectively (1). In the absence of fish consumption, the modern Western diet generally lacks a significant con-

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tent of ω3 fatty acids, a reversal of the pattern through most of human history, when ω3 fatty acids were ingested in the fat of game animals (2).

Dietary supplementation with ω3 fatty acids is associated with significant decreases in neutrophil production of LTB_4 (3), a highly potent chemotactic substance, as well as a decrease in the production of interleukin-1 (IL-1) from monocytes (4,5). EPA will also compete with arachidonate for cyclooxygenase, with a consequent decrease in the production of PGE_2 (6).

The beneficial effects of dietary supplementation with ω3 in inflammatory disease have been demonstrated in some (7,8), but not all (9), animal models of inflammatory disease. Because of this and the beneficial changes in eicosanoids, we and others (5,10–19) have studied the effects of dietary fish oil supplements in patients with rheumatoid arthritis (RA).

We describe here the effects of dietary supplementation with doses of ω3 fatty acids that are higher than any previously reported. We also describe the effects of discontinuing therapy with nonsteroidal anti-inflammatory drugs (NSAIDs) on the efficacy of n3 dietary supplements and expand our observations of potential alterations in immune function by reporting on the effects of these supplements on the in vivo production of multiple cytokines.

PATIENTS AND METHODS

Patients. Sixty-six patients with definite or classic RA, according to the criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (20), were recruited from the outpatient clinic of the Division of Rheumatology of Albany Medical College, the Albany Veterans Administration Medical Center, and a private practice of rheumatology in Albany, NY. Patients had active disease, as demonstrated by the presence of 3 of the following 4 criteria: ≥6 tender joints, ≥3 swollen joints, ≥30 minutes of morning stiffness, and a Westergren erythrocyte sedimentation rate of ≥28 mm/hour.

All patients were receiving NSAIDs prior to study inception, 56 patients were also receiving slow-acting antirheumatic drugs (SAARDs; hydroxychloroquine in 16, intramuscular gold in 11, methotrexate in 15, auranofin in 4, D-penicillamine in 3, sulfasalazine in 6, and azathioprine in 1), and 18 patients were receiving prednisone at a dosage of ≤5 mg/day, which was held constant through the duration of the study. The demographic features of the 49 patients completing evaluations at least through week 18 or 22 are presented in Table 1.

Between baseline and either week 18 or week 22 (the maximum duration of diclofenac therapy), there were 10 dropouts from the group receiving fish oil supplements and 7 dropouts from the group receiving corn oil supplements. Four patients receiving fish oil and 3 receiving corn oil dropped out of the study during the 4 weeks after starting the diclofenac placebo. A total of 6 patients in the fish oil group and 5 in the corn oil group had dropped out during the 8-week interval between cessation of diclofenac and discontinuation of fish oil (week 26 or 30). In addition, 4 patients who had received fish oil and 3 who had received corn oil dropped out of the study during the period between discontinuation of fish oil and termination of the study (week 48).

Table 1. Demographic and clinical features of rheumatoid arthritis study patients at baseline, by dietary supplement group*

	Fish oil (n = 23)	Corn oil (n = 26)
Age, mean	58	57
Disease duration, mean years	11	10
Females:males	13:10	14:12
Medication, no		
Prednisone (mean mg/day)	11 (4.9)	6 (4.5)
Methotrexate	9	3
Hydroxychloroquine	8	9
Intramuscular gold	4	3
Auranofin	2	1
D-penicillamine	1	2
Sulfasalazine	3	3
Azathioprine	0	1
Hemoglobin, gm/dl	13.0 ± 0.26	12.0 ± 0.29
Westergren ESR, mm/hour	31 ± 3.9	41 ± 8.1
Tender joint count	15.1 ± 8.5	12.1 ± 8.2
Swollen joint count	10.2 ± 5.6	9.3 ± 6.0
AM stiffness, minutes	108.1 ± 121	128.1 ± 248
Physician's assessment of pain, 0–4 scale	1.8 ± 0.56	1.6 ± 0.64
Physician's global assessment of arthritis activity, 0–4 scale	1.9 ± 0.54	1.6 ± 0.51†
Patient's assessment of pain, 0–4 scale	1.8 ± 0.70	1.7 ± 0.78
Patient's global assessment of arthritis activity, 0–4 scale	2.1 ± 0.74	1.8 ± 0.68
Time to onset of fatigue, hours	8.7 ± 3.9	8.3 ± 3.0
Grip strength, mm Hg	105.8 ± 49.3	124.4 ± 65.0

* Except where noted otherwise, values are the mean ± SEM. ESR = erythrocyte sedimentation rate.
† $P = 0.049$.

Study design. This was a double-blind, placebo-controlled, prospective study. Patients were randomized to receive ω3 fatty acid or corn oil supplements according to age, sex, disease duration, and 3 categories of disease severity: total joint count ≤10, 11–20, and ≥21.

All patients discontinued their previous NSAID for a period of at least 5 half-lives of the drug before being evaluated at a screening visit. Patients who were taking SAARDs were allowed to continue the medication. Immediately after the screening visit, patients were started on diclofenac, 75 mg twice a day, and were reevaluated 2 weeks later (baseline). At the baseline visit, either 130 mg/kg/day of ω3 fatty acid or corn oil was added to the diclofenac and the background SAARD.

Fish oil capsules were the ethyl ester concentrate

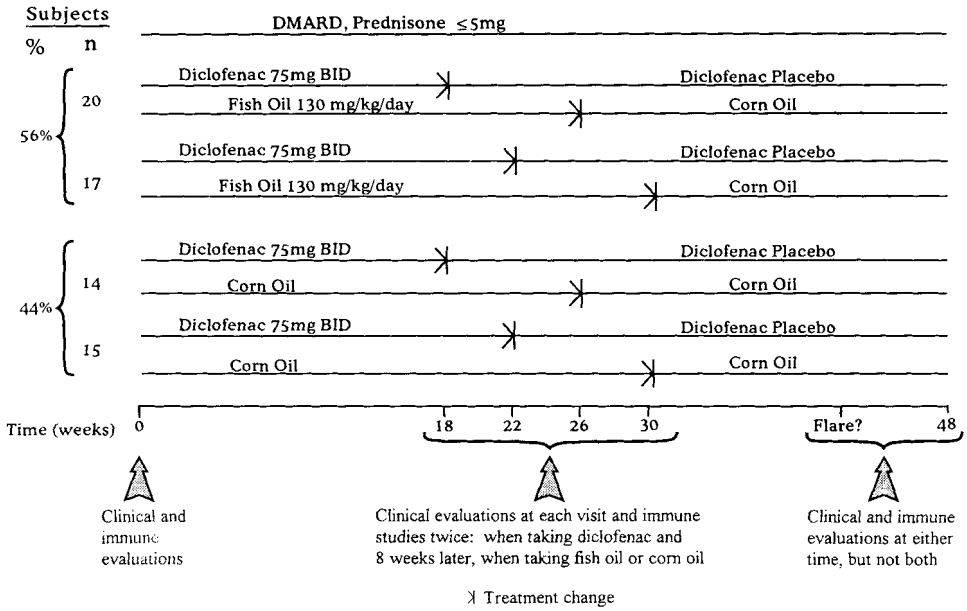

Figure 1. Study design. Prior to the screening visit (not shown), patients discontinued their nonsteroidal antiinflammatory drug for a duration of at least 5 of the drug's half-lives. Background disease-modifying antirheumatic drugs (DMARDs) and prednisone (≤5 mg/day) were continued throughout the study. At the screening visit, patients were given diclofenac, 75 mg twice a day (BID), and 2 weeks later (baseline visit, or week 0), they returned for reevaluation and for randomization to receive fish oil or corn oil supplements. At week 18 or week 22, active diclofenac was changed to diclofenac placebo. The time for this change was staggered, so that at the week-22 or week-26 evaluation, there would be only a 50% chance that the investigators would be able to guess which patients had been switched from the active diclofenac. Patients who were taking fish oil continued those supplements through week 26 or week 30 (8 weeks after discontinuing diclofenac), when they were switched to corn oil supplements. The final study visit was at week 48 or at the time of an arthritis flare after week 30. Immunologic studies were performed 4 times: baseline (week 0); maximum duration of diclofenac (week 18 or 22); maximum duration of fish oil, or for those taking corn oil, 8 weeks after switching to diclofenac placebo (week 26 or 30); and study end (week 48 or at arthritis flare).

supplied by the National Marine Fisheries Association for the National Institutes of Health. The ω3 ethyl ester concentrate is prepared from vacuum-deodorized menhaden oil, using transesterification, urea adduction, and short-path distillation. The concentrate contains ~80% ω3 fatty acid ethyl esters (44% EPA, 24% docosahexaenoic acid, 10–12% other ω3 fatty acid ethyl esters), 3% C18 (other than ω3), 6% C16, and the remainder as other esters. It also contains 0.2 mg/gm of TBHQ (tertiary butyl hydroquinone) as antioxidant, 2 mg/gm of tocopherols, and 2.0 mg/gm of cholesterol. The concentrate is encapsulated in 1-gm soft-gel capsules.

Patients randomized to receive fish oil continued their supplements through either week 26 or week 30, when all who remained in the study were switched to corn oil. At either week 18 or week 22, active diclofenac was replaced with an identical placebo diclofenac (supplied by Ciba-Geigy, Summit, NJ). Half of the patients were switched at week 18 and the other half at week 22 so that the investigators would not be unblinded to NSAID usage at the time of the first evaluation after week 18, when half of all patients would still be receiving active diclofenac and half would be receiving placebo diclofenac. Patients receiving fish oil continued these supplements for a full 8 weeks after discontinuing active diclofenac at either week 18 or week 22. After week 30, all subjects were taking both corn oil and placebo diclofenac, the latter having been taken since week 18 or week 22.

Clinical evaluations after baseline were done at weeks 18, 22, 26, and 30 in all patients. After week 30, evaluations were performed at the time of a disease flare, which served as a termination visit, or at week 48, which was the study termination. Individual patients were evaluated by the same investigator for the duration of the study. A schema of the study design is shown in Figure 1. The clinical evaluations performed at each visit have been described previously (5). Consistency of nutrient intake was analyzed as previously described (5).

Outcome measures were also calculated using the criteria of Paulus et al (21) and OMERACT (Outcome Measures in Rheumatoid Arthritis Clinical Trials) (22). Seven binary (0/1) improvement scores were constructed: 1 overall Paulus Index, and an OMERACT score for each of the 6 outcomes. The Paulus Index is scored as 1, if 4 of the 6 following measures show ≥20% improvement: tender joint

count, swollen joint count, duration of morning stiffness, grip strength, and physician and patient's evaluation of global arthritis activity. The percentages of improvement necessary for a score of 1 on the OMERACT measures are as follows: 27% for tender joint count, 17% for swollen joint count, 25% for morning stiffness, 25% for grip strength, 39% for physician's global evaluation, and 35% for patient's global evaluation.

The time intervals examined were baseline to maximum duration of diclofenac, baseline to maximum duration of fish oil, and maximum duration of diclofenac to maximum duration of fish oil. The chi-square statistic was computed to test for a significant association between study group (fish oil/corn oil) and the Paulus and OMERACT scores for each time period.

Laboratory evaluations. Laboratory studies performed at baseline, at the maximum duration of diclofenac (week 18 or 22), at the maximum duration of fish oil (week 26 or 30), and at disease flare after week 30 or at study termination (week 48). Evaluations were the same as those previously described (5).

Immunologic studies. Immunologic studies were performed at the same times as the laboratory evaluations (baseline, week 18 or 22, week 26 or 30, and between week 30 and week 48 or at week 48). Serum enzyme-linked immunosorbent assays (ELISAs) were performed to assess the following levels: IL-1β, IL-2, IL-6, IL-8, and tumor necrosis factor α (TNFα). All ELISAs were run on sera that had been stored at −80°C and processed simultaneously.

Statistical analysis. Several types of analysis were performed on the data for this study, each using SPSS Version 5.0.1 for Windows on an IBM 80386 computer. To determine whether changes in clinical and other parameters over the course of the study were statistically significant from zero, 2-tailed *t*-tests were performed with data from the fish oil and corn oil supplement groups. For these tests, a dummy variable, equal to zero for all cases, was created to use in the Paired Comparisons option in the SPSS T-Test command. A number of changes were examined in the study: changes from baseline to week 18, from baseline to week 26, from week 18 to week 26, from week 18 to week 22, and from the screening visit to week 22.

To compare the fish oil and corn oil supplement groups, 2-tailed independent-sample *t*-tests were performed using the SPSS T-Test command. For these comparisons, a dummy variable fish oil (−0 for the corn oil group and −1 for the fish oil group) was used to define the independent groups. The following changes were compared: from baseline to week 18, from baseline to week 26, from week 18 to week 26, from week 18 to week 22, and from the screening visit to week 26. Correlation coefficients were calculated using both Pearson and Spearman computations.

RESULTS

The changes in clinical parameters after discontinuation of active diclofenac are reported in the following ways: 1) the change 4 weeks after discontinuation; 2) the change 8 weeks after discontinuation; 3) the change from baseline to maximum duration of fish oil after stopping active diclofenac; 4) the change from the screening visit to the first visit after stopping active diclofenac.

Table 2. Mean change from maximum duration of diclofenac to first visit while taking diclofenac placebo*

	Fish oil (n = 19)		Corn oil (n = 20)	
	Mean ± SEM change	*P*	Mean ± SEM change	*P*
Tender joint count	3.7 ± 1.3	0.008	3.0 ± 3.0	0.34
Swollen joint count	0.11 ± 1.1	0.93	1.1 ± 1.0	0.29
AM stiffness, minutes	43.1 ± 21.4	0.06	100.2 ± 53.0	0.08
Patient's assessment of pain, 0–4 scale	0.21 ± 0.16	0.22	0.58 ± 0.19	0.007
Physician's assessment of pain, 0–4 scale	0.37 ± 0.14	0.02	0.47 ± 0.23	0.06
Grip strength, mm Hg	−13.1 ± 5.3	0.02	−6.4 ± 6.1	0.31
Patient's global assessment of arthritis activity, 0–4 scale	0.37 ± 0.16	0.03	0.53 ± 0.21	0.02
Physician's global assessment of arthritis activity, 0–4 scale	0.15 ± 0.12	0.19	0.26 ± 0.10	0.02
Interval to onset of fatigue, hours	−0.19 ± 0.40	0.64	−0.76 ± 0.56	0.19
Diastolic BP, mm Hg	−2.0 ± 2.1	0.35	0.4 ± 2.1	0.84
Systolic BP, mm Hg	−5.1 ± 3.2	0.13	1.7 ± 2.8	0.56

* Patients received diclofenac through either week 18 or week 22. The first visit while taking diclofenac placebo occurred at either week 22 or week 26, respectively. Patients taking fish oil received these supplements for 8 full weeks after beginning diclofenac placebo (see Patients and Methods). BP = blood pressure.

Effect of dietary oil supplements on RA flare after discontinuation of diclofenac: change from maximum duration of active diclofenac to first visit while taking diclofenac placebo. The mean changes in clinical parameters between the time of the evaluation after the maximum duration of diclofenac to the first visit while taking the diclofenac placebo are shown in Table 2. In patients consuming fish oil, significant worsening was observed in patient's global evaluation, grip strength, physician's evaluation of pain, and the tender joint count. Patients consuming corn oil showed significant worsening in both the physician's and the patient's evaluation of global arthritis activity and in the patient's evaluation of pain, but not in the number of tender joints.

Morning stiffness showed a trend toward significant prolongation in both groups. Patients consuming fish oil also exhibited a nonsignificant decrease in both systolic and diastolic blood pressure after discontinu-

Table 3. Mean change from baseline to maximum duration of fish oil supplementation while receiving diclofenac placebo for 8 weeks*

	Fish oil (n = 15)		Corn oil (n = 14)	
	Mean ± SEM change	*P*	Mean ± SEM change	*P*
Tender joint count	−7.8 ± 2.6	0.01†	−6.4 ± 2.2	0.78
Swollen joint count	−4.7 ± 2.7	0.10	−5.6 ± 1.7	0.004
AM stiffness, minutes	−71.3 ± 41.5	0.12	−2.1 ± 14.9	0.89
Patient's assessment of pain, 0–4 scale	0.10 ± 0.35	0.78	−0.08 ± 0.31	0.80
Physician's assessment of pain, 0–4 scale	−0.40 ± 0.22	0.10	0.08 ± 0.26	0.75
Grip strength, mm Hg	17.5 ± 13.6	0.23	−1.5 ± 11.5	0.90
Patient's global assessment of arthritis activity, 0–4 scale	−0.10 ± 0.28	0.73	−0.17 ± 0.27	0.55
Physician's global assessment of arthritis activity, 0–4 scale	−0.40 ± 0.16	0.04	−0.17 ± 0.21	0.44
Interval to onset of fatigue, hours	0.23 ± 0.67	0.74	−0.63 ± 0.46	0.20
Diastolic BP, mm Hg	−8.6 ± 8.5	0.04	−2.3 ± 2.0	0.28
Systolic BP, mm Hg	−2.1 ± 17.0	0.24	−0.28 ± 4.7	0.95

* Patients in the fish oil group took the supplement through week 26 or week 30, which was 8 weeks after beginning diclofenac placebo (see Patients and Methods). BP = blood pressure.
† $P = 0.043$ versus corn oil group.

ing diclofenac. None of the clinical changes in the fish oil group versus the corn oil group during this time were significant.

Change 8 weeks after discontinuing diclofenac. After switching to diclofenac placebo at week 18 or 22, patients consuming fish oil continued these supplements for a full 8 weeks (Figure 1). Nonsignificant decreases in both systolic and diastolic blood pressure continued to be seen in those who were taking fish oil, but not in those who were taking corn oil. None of the changes during this period achieved significance when patients receiving fish oil were compared with those receiving corn oil.

Change from baseline to maximum duration of fish oil (week 26 or week 30). In patients consuming fish oil, the week-26 or week-30 change from baseline in the physician's global evaluation of disease activity achieved significance (−0.40 ± 0.16; $P = 0.04$), as did the decrease in the tender joint count (−7.8 ± 2.6; $P = 0.01$) (Table 3). The change in the number of swollen joints from the number at baseline achieved significance in patients taking corn oil (−5.6 ± 1.7; $P = 0.004$) (Table 3). The improvements in the tender joint count and physician's global evaluation of disease activity from baseline in patients taking fish oil and the decrease in the swollen joint count in those taking corn oil were achieved despite their having taken placebo diclofenac for 8 weeks at the time of this evaluation. The decrease in the tender joint count at this time in patients consuming fish oil was significant compared with the tender joint count in patients consuming corn oil ($P = 0.043$).

Changes induced by dietary oil supplementation: evaluations from baseline to maximum duration diclofenac (week 18 or week 22). In patients ingesting fish oil, significant improvements from baseline were observed after the maximum duration of diclofenac at weeks 18 or 22 in the physician's and patient's global evaluation of disease activity (−0.33 ± 0.13; $P = 0.017$ and −0.38 ± 0.17; $P = 0.036$, respectively), physician's evaluation of pain (−0.38 ± 0.12; $P = 0.004$), duration of morning stiffness (−67.7 ± 23.3 minutes; $P = 0.008$), and the number of tender joints (−5.3 ± 0.835; $P < 0.0001$). The decrease in diastolic blood pressure in patients taking fish oil showed a trend toward significance (−5.4 ± 2.7 mm Hg; $P = 0.06$).

None of the changes in the patients receiving corn oil achieved significance during this time, although there was a trend toward a decrease in the number of swollen joints (−1.3 ± 0.68; $P = 0.06$). During this period, none of the changes from baseline in the fish oil group achieved significance when compared with the corn oil group.

Results by Paulus and OMERACT criteria. When analyzed by the Paulus criteria (21), there were no significant changes in disease activity between the fish oil and corn oil groups for any of the time periods evaluated ($P > 0.20$). By the OMERACT criteria (22) for the outcome measure, physician's global assessment, there were significantly more responders from baseline to the maximum duration of diclofenac in the fish oil group than in the corn oil group (7 responders of 20 patients taking fish oil; 1 responder of 21 patients taking corn oil; $P = 0.02$). For the same time period, for the tender joint count, there were more responders in the fish oil group than in the corn oil group, but the difference did not reach statistical significance (14 responders of 20 patients taking fish oil; 10 responders of 21 patients taking corn oil; $P = 0.146$). By OMERACT criteria, there were no significant between-group differences ($P > 0.20$) for any of the variables for either of the remaining time intervals analyzed.

Change in IL-1β from baseline to maximum duration of diclofenac. A significant decrease from baseline was observed in IL-1β levels in patients

receiving fish oil at this time (-7.7 ± 3.1; $P = 0.026$). None of the other within-group changes in cytokine levels from baseline achieved significance. None of the changes from baseline were significant when patients taking fish oil were compared with patients taking corn oil.

Change in cytokine levels from maximum duration of diclofenac to maximum duration of fish oil. We compared the change in cytokine levels between the maximum duration of diclofenac and 8 weeks later, which was the maximum duration of fish oil in patients in this group. None of the changes were significant within or among groups.

Change in cytokine levels from baseline to maximum duration of fish oil. From the baseline evaluation to the maximum duration of fish oil at week 26 or 30, there was a significant increase in TNFα levels in the patients taking fish oil (45.1 ± 13.6; $P = 0.013$) and in those taking corn oil (65.8 ± 27.5; $P = 0.038$). None of the other within-group changes from baseline to this time were significant. No significant changes in cytokines were observed when patients taking fish oil were compared with those taking corn oil at this time.

We also examined the effects of discontinuing diclofenac on the production of cytokines in all study patients combined, and found no significant differences between weeks 18 or 22 and weeks 26 or 30.

Analysis of the 3-day food diaries revealed a consistent pattern of nutrient intake throughout the study in both study groups (data not shown). Pill counts showed a 93% overall compliance rate in patients consuming fish oil and 88% in those taking corn oil supplements.

DISCUSSION

In the present investigation, we were interested in expanding the observations of the effects of fish oil to include an examination of the effects of $\omega 3$ fatty acids on the production of other cytokines in patients with RA. We also used a higher dose of $\omega 3$ supplements than any previously reported. The high-potency capsules enabled us to give a person weighing 75 kg a total daily dose of 9.75 gm of $\omega 3$ supplements at our study dosage of 130 mg/kg/day. Since dose-dependent effects of $\omega 3$ supplements have previously been reported in hypertension (23) as well as in RA (5), we were interested in whether the higher dose used here would result in further clinical benefit. In addition, by substituting a visually identical placebo diclofenac for the active drug, both patients and investigators could remain blinded; this would allow us to assess whether background dietary manipulation would allow patients to successfully discontinue this class of medication.

Our results confirm that fish oil dietary supplementation results in significant improvement in tender joint counts and other clinical parameters of disease activity from baseline activity. However, none of the improvements in the patients receiving fish oil achieved significance at the time of the maximum duration of diclofenac therapy (at 18 or 22 weeks) compared with patients receiving corn oil. During this time interval, patients receiving corn oil also exhibited many improvements which did not achieve statistical significance. In addition, the magnitude of the improvement from baseline that we observed in patients taking high-dose fish oil was indistinguishable from those previously reported in patients consuming total doses of $\omega 3$ fatty acids that ranged from 3 to 6 gm/day (5,11). We cannot therefore recommend further investigations with the doses we used, which resulted in the daily ingestion of 9 gm of $\omega 3$ supplements in a person weighing 70 kg.

Improvements from baseline in patients with RA who take fish oil often do not achieve statistical significance compared with other dietary fatty acid interventions. This may be because the biologic effects are not powerful enough or because of either a placebo effect or real biologic effects induced by the so-called "placebo fatty acids." We have previously wrestled with the issue of an ideal control fatty acid to compare with fish oil (5) and in this investigation, chose corn oil, having used olive oil in 2 previous studies (5,11). It is not unlikely that there are some mono- or polyunsaturated fatty acids that have potentially significant immunologic effects (24–27). We believe that the issue of the ideal placebo dietary intervention to compare with fish oil has not yet been settled.

After switching from active diclofenac to diclofenac placebo, it was apparent that patients in both the fish oil and the corn oil groups exhibited significant flares when examined 4 weeks after discontinuation of this NSAID (Table 2). Yet, none of these flares remained significant in either group at the time of the evaluation 8 weeks after stopping active diclofenac. This could be because 5 patients in each group dropped out of the study at the time of their first visit after discontinuing active diclofenac (4 weeks after diclofenac was discontinued), leaving in the study only those patients who were better able to tolerate the discontinuation of this NSAID.

The patients' clinical status after discontinuing

diclofenac and while receiving fish oil and corn oil was examined in several ways. We examined their clinical status while off diclofenac after the maximum duration of fish oil exposure (week 26 or 30) and compared this with their baseline status while receiving diclofenac. We believe it is meaningful that the improvement in the number of tender joints was significant in the patients remaining on the fish oil supplementation regimen at this time when compared both with their baseline status and with the patients receiving corn oil supplementation during the same period. The patients' status after stopping diclofenac was also compared with their status after stopping their previous NSAID at the time of the screening visit. Most evaluations showed that the character of the flare was worse at the screening visit, when patients were not consuming dietary fatty acid supplements (data not presented).

Other investigators have reported on whether dietary supplements of fish oil can affect NSAID requirements in patients with RA (15,16,18,28). We believe that our data support the previous observations that selected individuals with RA may discontinue NSAID therapy while consuming $\omega 3$ supplements.

We also observed reductions in blood pressure that were consistently greater in patients taking fish oil than in those taking corn oil. The reduction in diastolic pressure achieved significance 8 weeks after stopping diclofenac in patients who continued to receive fish oil supplementation. There are well-described effects of dietary supplementation with $\omega 3$ fatty acids on the vascular system (29), which have been documented in patients with primary Raynaud's phenomenon (30) as well as hypertension (24,31).

We were unable to demonstrate an inhibitory effect of dietary fish oil supplementation on the serum concentrations of IL-2, IL-6, IL-8, or TNFα. We confirmed our previous observation that fish oil supplementation inhibits the production of IL-1β (5), which others have also reported in patients with RA (19). Meydani et al (32) also reported an inhibitory effect of fish oil on the production of TNFα and IL-6, although they used an in vitro system of mitogen-stimulated peripheral blood mononuclear cells derived from normal volunteer donors. We actually observed an increase in TNFα levels 8 weeks after diclofenac was discontinued in patients who continued to take fish oil and corn oil. The significance of this observation is presently unclear.

In summary, we have demonstrated that patients with active rheumatoid arthritis who consume high-dose fish oil supplements exhibit improvements over baseline in multiple clinical parameters, improvements that are not seen in patients who consume corn oil supplements. Only the improvement in the tender joint count achieved significance ($P = 0.04$) compared with those taking corn oil; however, the magnitude of the changes did not differ from that found in previous investigations employing lower doses. Therefore, the actual mechanism(s) of the improvements observed remains imperfectly defined. The benefits are associated with a significant decrease in IL-1β. Although some patients in either dietary supplement group exhibited significant worsening of clinical parameters after stopping diclofenac, the flare was not associated with significant changes in serum cytokine concentrations. Although patients taking high-dose fish oil exhibited significantly fewer tender joints 8 weeks after stopping diclofenac than they did at baseline while taking the drug, and this effect was significant compared with the group taking corn oil, we were nevertheless unable to demonstrate a clinically important NSAID-sparing effect of fish oil immediately after discontinuation of diclofenac. Our results suggest a possible modest NSAID-sparing effect of fish oil dietary supplements, which should be further explored in well-designed clinical trials.

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