

# Reduced Joint Pain after Short-term Duodenal Administration of Seal Oil in Patients with Inflammatory Bowel Disease: Comparison with Soy Oil

Seal and Soy Oils in IBD and Joint Pain

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**Background:** Rheumatic joint pain is a common extraintestinal complication of inflammatory bowel disease (IBD). Because the high ratio of n-6 to n-3 fatty acids (FAs) of the Western diet might promote rheumatic disorders, we wanted to compare the effects of short-term duodenal administration of n-3 rich seal oil and n-6 rich soy oil, on IBD-related joint pain. **Methods:** Nineteen patients with IBD-related joint pain were included, 9 had Crohn's disease and 10 had ulcerative colitis. Ten ml of seal oil (n = 10) or soy oil (n = 9) was self-administered through a nasoduodenal feeding tube 3 times daily for 10 days. **Results:** Compared with soy oil treatment, seal oil significantly reduced the duration of morning stiffness ( $P = 0.024$ ), number of tender joints ( $P = 0.035$ ), intensity of pain ( $P = 0.025$ ) and the doctor's scoring of rheumatic disease activity ( $P = 0.025$ ) at end of the 10 days' treatment period. Analysing the effects as area under the curve (area between the curve and baseline, zero) for the entire period from start of treatment until 6 months' post treatment, suggested a long-lasting beneficial effect on joint pain of seal oil administration, while soy oil tended (not significantly) to aggravate the condition. Consistently, the serum ratios of n-6 to n-3 FAs ( $P \ll 0.01$ ) and arachidonic acid to eicosapentaenoic acid ( $P \ll 0.01$ ) were reduced after treatment with seal oil. **Conclusion:** The results suggest distinctive differential prolonged effects on IBD-related joint pain of short-term duodenal administration of n-3 rich seal oil (significant improvement) and n-6 rich soy oil (tendency to exacerbation).

**Key words:** Arthritis; duodenal administration; inflammatory bowel disease; joint pain; seal oil; short-term treatment; soy oil

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## Introduction

Rheumatic arthritis is a commonly observed extraintestinal complication of inflammatory bowel disease (IBD) (1, 2). An even higher percentage of IBD-patients complain of joint pain (arthralgia) despite no objective clinical findings in the joints (3-6). Several tender joints (polyarthralgia), morning stiffness and disturbed sleep are typical for patients with IBD-related joint pain. Conventional non-steroidal anti-inflammatory drugs (NSAIDs) and selective cyclooxygenase-2 (COX-2) inhibitors have both been implicated in aggravation of experimental colitis (7, 8). Consistently, conventional NSAIDs and possibly also selective COX-2 inhibitors might activate IBD (9, 10). These patients therefore have few options to control their joint pain.

The high ratio of n-6 to n-3 fatty acids (FAs) of the western diet leads to a high ratio of arachidonic acid (20:4 n-6, AA) to eicosapentaenoic acid (20:5 n-3, EPA) in the blood and tissues, which may promote IBD and rheumatic disorders by facilitating the production of pro-inflammatory eicosanoids (11, 12). Of the n-3 FAs, only EPA, docosapentaenoic acid (22:5 n-3, DPA) and docosahexaenoic acid (22:6 n-3, DHA) are “marine” n-3 polyunsaturated fatty acids (PUFAs). The term “marine” denotes that EPA, DPA and DHA accumulates in the marine food chain and are present in high concentrations in seafood. Consistently, orally administered fish oil, rich in n-3 PUFAs, ameliorates IBD and rheumatoid arthritis (RA) after long-term treatment (2-12 months) (11, 13). In a recent pilot study we found a beneficial effect on IBD-related joint pain of duodenally administered n-3 PUFA rich seal oil already after 10 days (14). Seal oil contains slightly less EPA and DHA than fish oil, but approximately 4 fold more DPA (15). In fish oil, the n-3 PUFAs are mainly located in the middle position (sn-2) of the triacylglycerol (TAG) molecule, while they are located almost exclusively in the sn-

1/sn-3 position of TAG from seal oil (16, 17). Pancreatic and lipoprotein lipases are both sn-1/sn-3 position specific (18). Therefore, both in the intestine and through the circulation, the n-3 PUFAs in TAG from seal oil may be more readily available for lipolysis than those in TAG from fish oil. Hence, lessons learned from studying absorption and metabolism of fish oil may not apply to seal oil.

Based on the promising results of our uncontrolled pilot study (14), we wanted to do a controlled study comparing the effects of short-term duodenal administration of n-3 PUFA rich seal oil and n-6 rich soy oil, on IBD-related joint pain.

## **Materials and methods**

### *Patients*

Nineteen patients with IBD-related joint pain were included in the study between January 2002 and June 2002 (Table I). Ten of the 19 patients had objective arthritis, defined as joint swelling, definite arthritis or ankylosing spondylitis. Two of the CD patients and one of the UC patients had been operated on with bowel resection. Fifteen of the 19 patients were on the following stable medications: 7 on 5-aminosalicylic acid (5-ASA), 3 on immune-suppressive medication with azathioprine, 2 on both 5-ASA and azathioprine, one on both 5-ASA, corticosteroid and central muscle-relaxing medicine, one on both 5-ASA and corticosteroid and one on a non-steroidal anti-inflammatory drug (NSAID). The remaining 4 patients received no medication.

### *Study design*

The patients were randomly allocated to treatment with either seal oil (n = 10, CD:UC = 5:5, 6 of 10 had arthritis) or soy oil (n = 9, CD:UC = 4:5, 4 of 9 had arthritis). After an overnight fast, a nasoduodenal feeding tube (Freka<sup>®</sup> Feeding Tube, Fresenius Kabi, GmbH, Germany) was inserted by aid of fluoroscopy until its tip was located in the distal part of the duodenum. Ten ml of seal oil (Rieber Skinn A/S, Bergen, Norway) or soy oil (Mills DA, Oslo, Norway) was self-administered through the feeding tube before meals 3 times daily for 10 days. Fatty acid composition, levels of vitamin A and E and lipid peroxidation assessed by an in vitro method determining thiobarbituric acid reactive substances (TBARS) in the seal oil and soy oil are presented in Table II. Two of the patients refused using the feeding tube and preferred to drink the soy oil. The seal oil group thus received 2.0 grams of EPA, 0.9 grams of DPA and 2.2 grams of DHA per

day while the soy oil group received 14.9 grams of linoleic acid (18:2 n-6, LA) per day. The seal oil was a mixture of crude oil from harp seal (*Phagophilus groenlandicus*) and hooded seal (*Cystophora cristata*). The patients were assessed before and after the treatment period and then 1, 2, 4 and 6 months post treatment. No changes in diet or medication were made during the entire period from start of treatment until 6 months' post treatment.

### *Ethical considerations*

The study was approved by the Regional committee for medical research ethics and all patients gave written informed consent before inclusion.

### *Methods*

The joint pain was quantified as follows: Duration of morning stiffness (min) during the last week. Number of palpation-tender, swollen and subjectively painful joints using a 28 joint count (19), with the addition of ankle joints and toes, toes scored as one. A 100 mm horizontal Visual Analogue Scale (VAS) ranging from 0 (very well) to 100 (very poor) was applied for doctor's scoring of rheumatic disease activity, patient's scoring of rheumatic disease activity and intensity of pain last week (20). The patients filled in a modified health assessment questionnaire (MHAQ) (21). The score in 8 questions about functioning in daily life, with 4 alternative answers, were added and divided by 8, giving scores from 1 (very well) to 3 (very poor).

IBD-index, a measure of IBD-activity, was evaluated by Harvey-Bradshaw simple index in CD (22) and Walmsley simple clinical colitis activity index in UC (23). These IBD-indexes consist of four clinical criteria; symptoms, physical signs, general

well being and extraintestinal complications. A score equal to or higher than 6 indicates an active disease.

Faecal calprotectin concentration, also a measure of IBD-activity (24), was determined according to the Eurospital Calprest<sup>®</sup>, code 9031 (Medinor, Oslo, Norway), an enzyme-linked immunosorbent assay (ELISA) kit for determination of calprotectin in stools.

Venous blood samples were collected in vials with no anticoagulant (gel vial). Serum FA composition was analysed by gas liquid chromatography (Trace GC 2000) according to previously described methods (14, 25), with some modifications; the FAs were esterified in 20 % boron trifluoride (BF<sub>3</sub>) in methanol (w/w) and biological sample parallels were analysed.

Lipid peroxidation was analysed by an in vitro method determining TBARS in serum (26, 27).

A simple self-constructed questionnaire about intake of marine food (n-3 supplement and fish) was filled in by the patients at inclusion. There were 6 alternative answers for each meal (breakfast, lunch and dinner); every day = score 6, 3-4 days a week = score 5, 1-2 days a week = score 4, 3-4 days a month = score 3, 1-2 days a month = score 2 and never = score one.

### *Statistics*

Data were analysed and displayed using the GraphPad Prism 4 (GraphPad Software Inc, San Diego, USA) statistical software package. Values were expressed as mean  $\pm$  standard error of the mean (SEM). Effect of treatment was calculated as change (in absolute values) from baseline. Area under the curve (AUC) (area between the curve

and baseline, zero) for the entire period from start of treatment until 6 months post treatment was calculated by the trapezoid method. Normality of data was tested with Komogorov-Smirnoff test. Group differences were compared by unpaired Student's t-test (two-sided). Differences from baseline to end of treatment were evaluated by paired t-test. *P* values < 0.05 were regarded as statistically significant.



## Results

### *Patient status at baseline*

The soy oil group had a significantly higher intake of marine food compared with the seal oil group ( $9.8 \pm 1.0$  vs  $7.0 \pm 0.8$ ,  $P = 0.04$ ). Consistently, the soy oil group had lower ratios of n-6 to n-3 FAs ( $P = 0.047$ ) and AA to EPA ( $P < 0.01$ ) in serum (Table III). As a result of the lower n-3 content in blood, the soy oil group had a lower joint pain- and IBD-activity compared with the seal oil group (significant for duration of morning stiffness;  $P \ll 0.01$  and number of tender joints;  $P = 0.045$ ) (Table IV). Seven out of 10 patients receiving seal oil and 3 out of 9 patients receiving soy oil had an IBD-index equal to 6 or higher, indicating active IBD (Table IV). Baseline faecal calprotectin values were low (Table IV). The patients were therefore regarded as having mild to moderately active IBD. Due to the significantly group differences at baseline, the effects of treatment were displayed as change from baseline.

### *Joint pain*

#### *At end of treatment*

At end of the 10 days' treatment period, the patients receiving seal oil had significantly reduced duration of morning stiffness ( $P = 0.024$ ), number of tender joints ( $P = 0.035$ ), intensity of pain ( $P = 0.025$ ) and doctor's scoring of rheumatic disease activity ( $P = 0.025$ ) compared with the patients receiving soy oil (Fig. 1a-d). Also compared with baseline, treatment with seal oil reduced the duration of morning stiffness ( $P = 0.015$ ), intensity of pain ( $P < 0.01$ ), doctor's scoring of rheumatic disease activity ( $P < 0.01$ ), MHAQ score ( $P < 0.01$ ), number of subjectively painful joints ( $P = 0.03$ ) and patient's scoring of rheumatic disease activity ( $P < 0.01$ ). Soy oil therapy tended (not significantly) to increase the joint pain (Fig. 1a-e).

### *During the entire observation period*

Comparison of AUC for the entire period from start of treatment until 6 months' post treatment yielded significantly group differences for change from baseline of duration of morning stiffness ( $P = 0.02$ ), doctor's scoring of rheumatic disease activity ( $P = 0.03$ ) and MHAQ score ( $P = 0.03$ ) (Fig. 1a, b, e). The seal oil group's AUC for intensity of pain ( $P = 0.02$ ), doctor's scoring of rheumatic disease activity ( $P = 0.01$ ) and MHAQ score ( $P = 0.02$ ) was significantly negative (i.e., reduced joint pain), while the soy oil group's AUC was (not significantly) positive (i.e., increased pain) (Fig. 1a-e).

### *Fatty acid composition*

#### *Group comparisons*

There were significant group differences at end of treatment (calculated as change from baseline) for  $\sum$  n-6 FAs ( $P < 0.01$ ), LA ( $P < 0.01$ ), 20:3 n-6 ( $P < 0.01$ ),  $\sum$  n-3 FAs ( $P < 0.01$ ), EPA ( $P \ll 0.01$ ), DPA ( $P = 0.01$ ), DHA ( $P = 0.01$ ), and ratios of n-6 to n-3 FAs ( $P \ll 0.01$ ) and AA to EPA ( $P \ll 0.01$ ) (Table III, Figure 2).

#### *Compared to baseline*

Compared to baseline, reduced ratios of AA to EPA, n-6 to n-3 FAs and  $\sum$  n-6 FAs (LA and 20:3 n-6) and increased  $\sum$  n-3 FAs (EPA, DHA and DPA) were observed at end of treatment with seal oil (Table III, Figure 2). Increased level of n-6 FAs (mainly LA) was observed at end of treatment with soy oil (Table III).

### *IBD-activity*

Comparison of AUC for the entire period from start of treatment until 6 months post treatment yielded no significant group differences for IBD-index (Figure 3). Compared with baseline, a

significant improvement in IBD-index was observed at end of treatment with seal oil ( $P = 0.02$ ).

#### *Adverse effects*

No significant change in TBARS was seen (data not shown). Soy oil treatment caused nausea in two patients and reduced food intake in one of these two patients. One patient experienced burping and abdominal pain during treatment with seal oil. These adverse effects were mild and did not result in treatment termination.

## Discussion

Compared with soy oil, duodenal administration of seal oil for 10 days significantly improved IBD-related joint pain, and the effect persisted several months post treatment. While improvement was seen after treatment with seal oil, soy oil tended (not significantly) to deteriorate the condition. The present study confirmed the promising results from our pilot study. Hence, both studies suggest that short-term duodenal administration of seal oil is able to ameliorate IBD-related joint pain substantially.

Most nutritional research concerning IBD and rheumatic disorders have focused on the effects of orally administered fish oil, either in form of capsules or liquid oil (11, 13). In fish oil, the n-3 PUFAs are mainly located in the middle position (sn-2) of the TAG molecule, while they are located almost exclusively in the sn-1/sn-3 position of TAG from seal oil (16, 17). Digestion of TAG in the duodenum by pancreatic lipases specifically acting on the sn-1/sn-3 positions yields two free FAs and 2-monoacylglycerol which are taken up by the enterocyte, followed by re-esterification into TAG and incorporation into chylomicrons designated for the lymphatic route (18). During digestion of TAG in the duodenum it has been estimated that approximately 75% of the FAs in the sn-2 position remain in this position (28). The resultant chylomicrons reflect the dietary TAGs with respect to both the fatty acid composition and location of the n-3 PUFAs on the TAG molecule (17). This implies a general conservation of the FAs in the sn-2 position, which is important considering the possible advantages of structurally different oils and in tailor making fats with particular TAG-structures and maintaining the location of FAs in specific positions following absorption (14, 29). Lipoprotein lipases in the circulation also digest TAG by specifically acting on the sn-1/sn-3 positions (18). The rapid effect on joint pain from seal oil treatment might therefore in part be explained by readily available free n-3 PUFAs (EPA) competing with AA as substrate for eicosanoid production as suggested by the decreased ratio of AA to EPA in serum ( $P \ll$

0.01), resulting in a shift to a less pro-inflammatory eicosanoid profile. Eicosanoid production was not assessed in the present study, however a decreased production of prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) was observed in rats fed EPA or DHA in the sn-1/sn-3 position but not in the sn-2 position of structured TAG (30). Also, seal oil is superior to fish oil in reducing AA content in plasma and liver phospholipids (17, 31). Thus, the different positional distribution of n-3 FAs on the TAG molecule in seal and fish oils may be important in order to achieve an “optimal” eicosanoid profile.

Duodenal administration of the oils might ensure not only rapid absorption by yielding a much higher bolus of n-3 PUFAs into the circulation as compared to drinking, as the former avoids the mixing and dilution in the stomach, but also correct dosing and avoiding of the smell and taste of the crude seal oil. Duodenal administration and sn-1/sn-3 distribution of n-3 FAs may therefore partly explain the rapid joint pain ameliorating effect of seal oil. The much less marked effect on IBD-activity by seal oil, consistent with the pilot study (14), suggests that the intestines and the joints are affected by different disease mechanisms. As also suggested by former studies, the joint pain was largely independent of IBD-activity (3, 14), thus the seal oil probably acted directly on the joints and not indirectly through any improvement of IBD-activity. Due to the rapid relief of joint pain, duodenally administrated seal oil might represent a nutritional treatment of joint pain/arthritis without the adverse gastrointestinal effects of NSAIDs and selective COX-2 inhibitors. In this study with mild to moderately active IBD-patients, the experienced adverse effects were mild, however before recommending widespread use of seal oil in more active IBD, the potential of an increased lipid peroxidation should be addressed.

Increased intake of n-6 FAs and a concomitant increased ratio of n-6 to n-3 FAs have been correlated to increased occurrence of CD (32). In a recent study comparing different enteral feeds for the treatment of active CD, remission rates fell with increasing soy oil

content (33). The higher (not significant) ratio of AA to EPA after treatment with soy oil, might explain the tendency (not significant) to deterioration of joint pain. This tendency is worrying in view of the wide use of soy oil in the western diet. Thus, it may not be the fat content but rather the type of fat that is important, particularly for patients dependent on enteral or parenteral nutrition.

The major limitation of the present study was that unfortunately, in spite of random allocation, the treatment groups differed significantly at baseline. Consistent with a lower intake of marine food in the seal oil group ( $P = 0.04$ ), the ratio of AA to EPA in serum was almost twice higher in this group ( $P < 0.01$ ). Interestingly, the low ratio of n-6 to n-3 FAs in the background diet and the consequent low ratio of AA to EPA in the blood, might explain the unbalances in joint pain and IBD activity between the groups. Also, the small number of patients having different rheumatic problems might be a reason for the group differences, even though the data were normally distributed. A consequence of the group differences for our study could be that the seal oil group would be easier to treat simply because this patient group had more of what we aimed to treat (the IBD-related joint pain). However, it might not be clinically relevant to treat the patients in the soy oil group based on their low disease activity. Therefore, instead of philosophicating about what would happen if the treatment groups had been opposite, we may conclude that seal oil treatment had a positive health effect in those patients that really suffered from joint pain. The effect of treatment was similar in the CD and UC patients (data not shown), justifying pooling the two patient groups to one IBD group. The IBD-indexes for CD (22) and UC (23) are based on relatively similar questionnaires of IBD-activity. We therefore pooled the CD and UC index-scores in one IBD-index. High oral doses of n-3 PUFA for 6 weeks are required to ensure maximum FA incorporation into cell membranes of red blood cells (34). In view of the short-term treatment, we reported serum FA levels only, which reflect the dietary FA intake (35).

In conclusion, a distinctive differential prolonged effect on IBD-related joint pain was observed after short-term (10 days) duodenal administration of seal oil or soy oil. While seal oil improved IBD-related joint pain significantly, soy oil tended (not significantly) to exacerbate the condition. Consistently, ratios of n-6 to n-3 FAs and AA to EPA in serum were significantly decreased after treatment with seal oil and tended to increase (not significantly) after treatment with soy oil.

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Table I: Characteristics of the patients

<u>Disease</u>	<u>n</u>	<u>Male</u>	<u>Female</u>	<u>Range age (yrs)</u>	<u>Mean age (yrs)</u>
CD	9	4	5	21 - 44	33.1
UC	10	4	6	16 - 55	40.8

CD = Crohn's disease, UC = ulcerative colitis and n = number of patients.

Table II: Major fatty acids, vitamins A and E and TBARS

	<u>Seal oil</u>	<u>Soy oil</u>
	<u>g/100 g</u>	<u>g/100g</u>
∑ saturated	12.9	13.4
16:1n-7	11.6	n.d
18:1n-9	16.3	17.5
20:1n-9	7.5	0.2
∑ monoenes	47.6	19.0
18:2n-6	1.4	49.7
20:4n-6	0.4	n.d
∑ ω-6	1.8	49.7
18:3n-3	0.7	5.5
20:5n-3	6.6	n.d
22:5n-3	3.1	n.d
22:6n-3	7.4	n.d
∑ ω-3	21.0	5.5
n-6/n-3	0.1	9.0
Sum vitamin A	1.4 mg/100g	n.d
α-tocopherol	5.4 mg/100g	17.1 mg/100g
TBARS	15.3 nmol/g DW	n.d

Sum vitamin A = all-trans retinol + 13-cis retinol + 3-Dehydroretinol. TBARS = thiobarbituric acid reactive substances. n.d = not detected. DW = dry weight.

Table III: Serum fatty acid composition (%) before and after treatment with seal oil or soy oil

Fatty acid	<u>Seal oil group</u>		<u>P-value</u>	<u>Soy oil group</u>		<u>P-value</u>
	<u>Before</u>	<u>After</u>		<u>Before</u>	<u>After</u>	
$\Sigma$ saturated	29.5 $\pm$ 1.0	29.0 $\pm$ 1	0.64	28.4 $\pm$ 0.7	27.4 $\pm$ 0.7	0.18
$\Sigma$ monoenes	24.2 $\pm$ 1.1	23.3 $\pm$ 1.1	0.61	22.7 $\pm$ 1.4	21 $\pm$ 1.1	0.07
18:2 n-6†	32.2 $\pm$ 1.8	29.6 $\pm$ 1.5	0.04	33.8 $\pm$ 2.5	37.9 $\pm$ 1.9	0.02
20:3 n-6†	1.6 $\pm$ 0.1	1.0 $\pm$ 0.1	$\ll$ 0.01	1.4 $\pm$ 0.1	1.3 $\pm$ 0.1	0.45
20:4 n-6*	5.6 $\pm$ 0.4	5.5 $\pm$ 0.3	0.59	4.4 $\pm$ 0.3	4.6 $\pm$ 0.4	0.45
$\Sigma$ n-6†	39.9 $\pm$ 1.8	36.9 $\pm$ 1.4	0.02	34.6 $\pm$ 4.6	38.5 $\pm$ 4.9	0.02
18:3 n-3*	0.59 $\pm$ 0.04	0.54 $\pm$ 0.04	0.27	0.9 $\pm$ 0.1	0.9 $\pm$ 0.1	0.54
20:5 n-3†	1.1 $\pm$ 0.3	4.2 $\pm$ 0.4	$\ll$ 0.01	1.7 $\pm$ 0.4	1.3 $\pm$ 0.3	0.28
22:5 n-3†	0.50 $\pm$ 0.03	0.82 $\pm$ 0.04	$\ll$ 0.01	0.7 $\pm$ 0.2	0.53 $\pm$ 0.03	0.29
22:6 n-3†	2.2 $\pm$ 0.3	4.0 $\pm$ 0.3	$\ll$ 0.01	3.6 $\pm$ 0.9	2.7 $\pm$ 0.2	0.31
$\Sigma$ n-3†	4.2 $\pm$ 0.5	9.4 $\pm$ 0.7	$\ll$ 0.01	7.1 $\pm$ 1.5	5.5 $\pm$ 0.6	0.31
n-6/n-3*†	10.0 $\pm$ 0.6	4.0 $\pm$ 0.3	$\ll$ 0.01	7.2 $\pm$ 1.1	8.6 $\pm$ 0.8	0.15
20:4 n-6/20:5 n-3*†	7.0 $\pm$ 0.8	1.5 $\pm$ 0.1	$\ll$ 0.01	3.8 $\pm$ 0.7	4.9 $\pm$ 0.8	0.21

Data expressed as % of total fatty acids (FAs). Percent identified FAs ranged between 94.9-99.3 %.

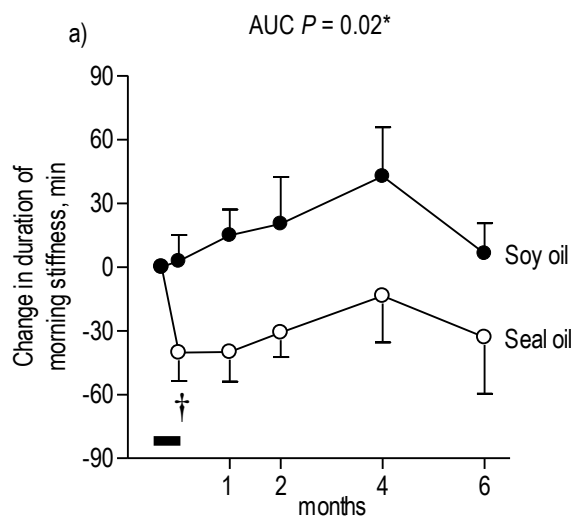
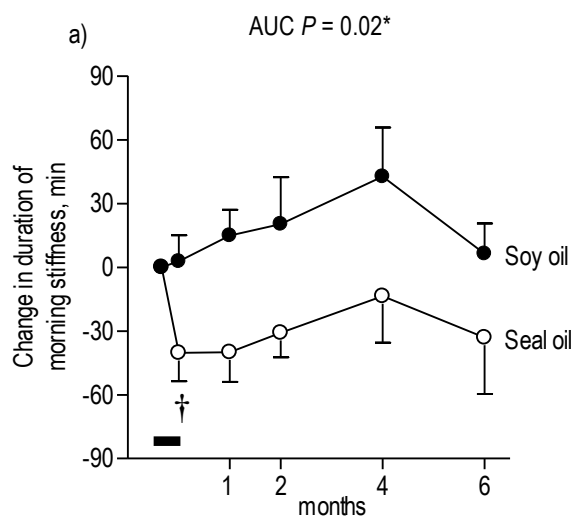
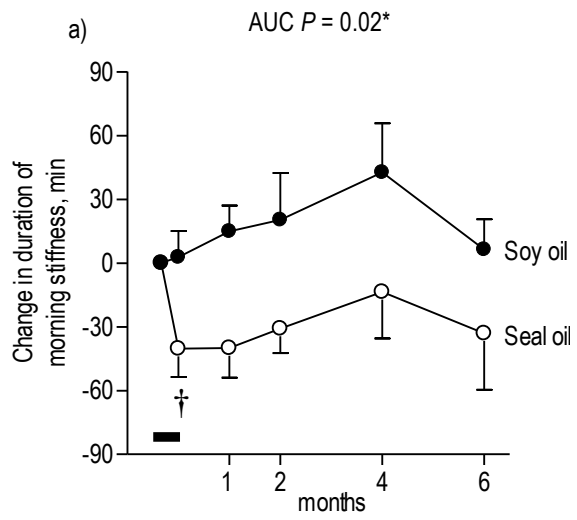
P-values indicate change from before to after treatment in the seal or soy oil groups. \* = significant group difference at baseline. † = significant group difference after treatment.

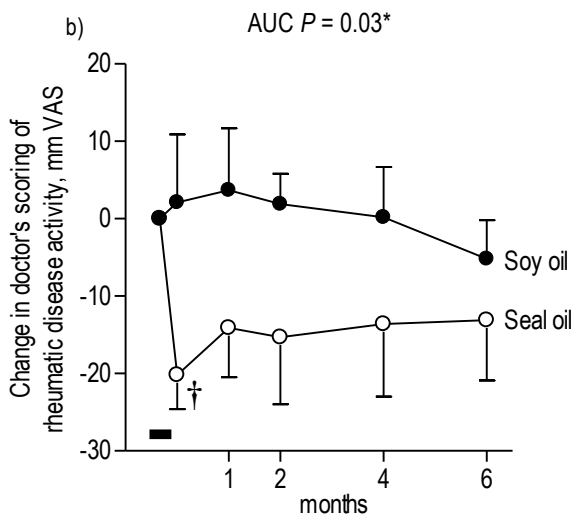
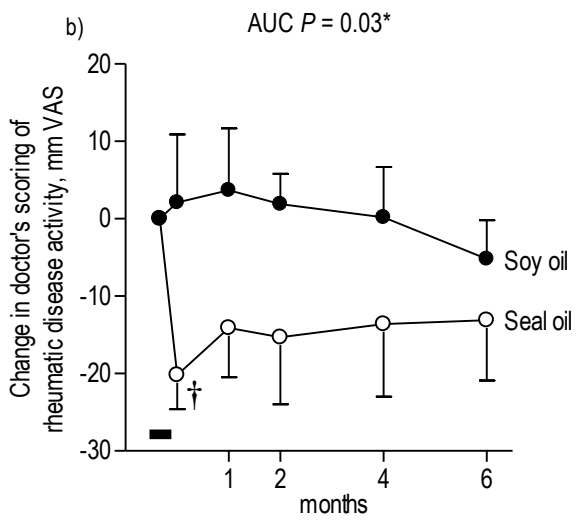
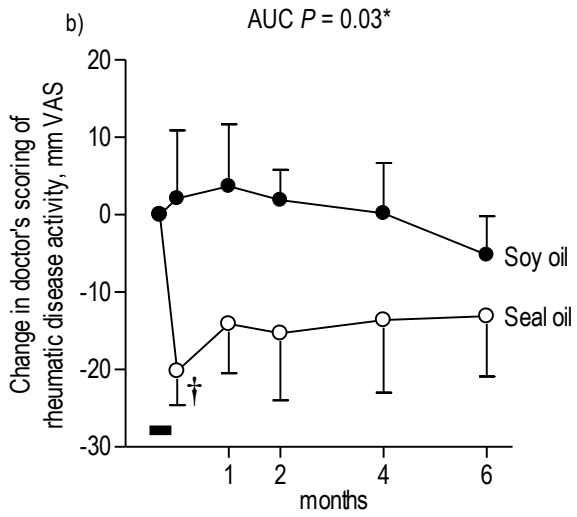
Table IV: Joint pain and IBD-activity at baseline

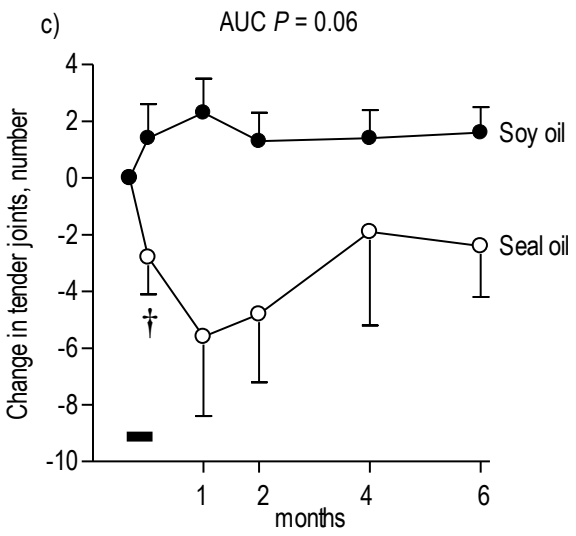
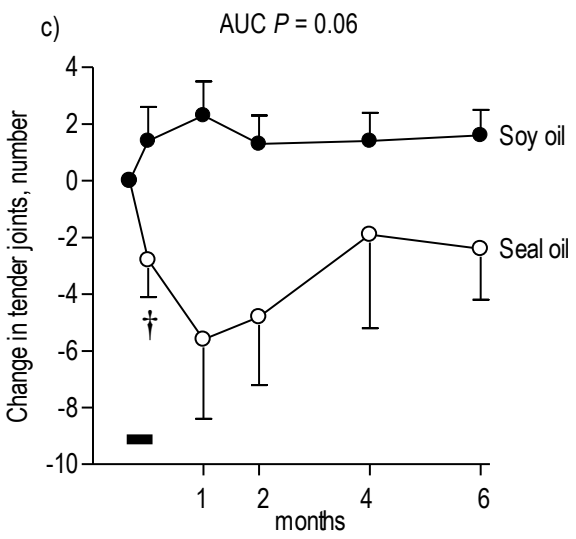
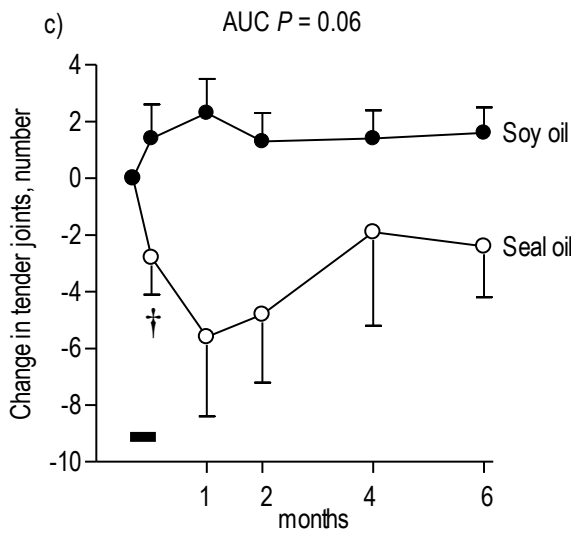
	<u>Seal oil group</u>	<u>Soy oil group</u>	<u>P-value</u>
Morning stiffness (min)*	68.5 ± 13.7	14.5 ± 4.7	≪ 0.01
Tender joints (number)*	7.4 ± 2.2	1.9 ± 0.4	0.045
Swollen joints (number)	1.2 ± 0.6	0.3 ± 0.2	0.18
Painful joints (number)	10.6 ± 3.2	4.5 ± 2.2	0.16
DocVAS (mm)	31.1 ± 5.6	15.6 ± 6.0	0.08
PainVAS (mm)	47.8 ± 7.7	33.3 ± 9.9	0.27
TotVAS (mm)	48.5 ± 8.2	35.3 ± 10.9	0.34
MHAQ (score)	1.320 ± 0.077	1.381 ± 0.150	0.70
IBD-index (score)	6.5 ± 1.1	4.8 ± 0.8	0.22
Calprotectin (mg/kg)	7.3 ± 5.9	4.6 ± 4.6	0.73

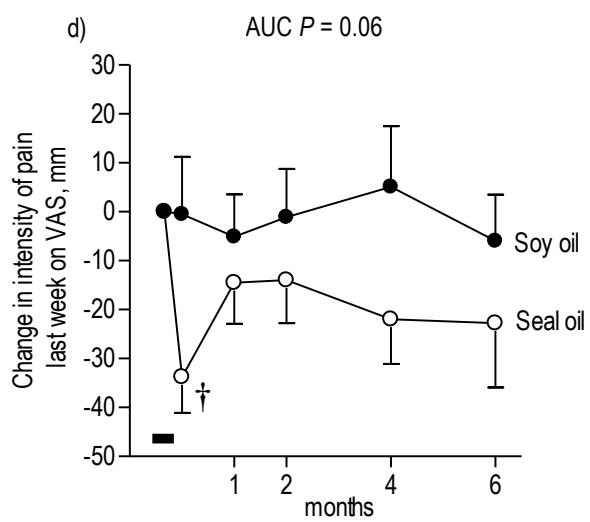
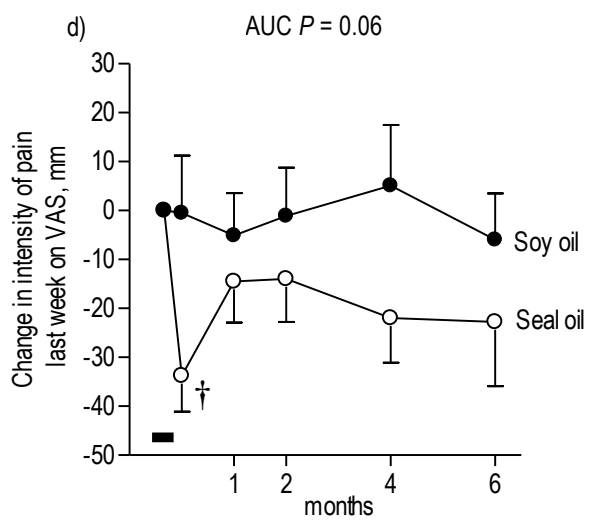
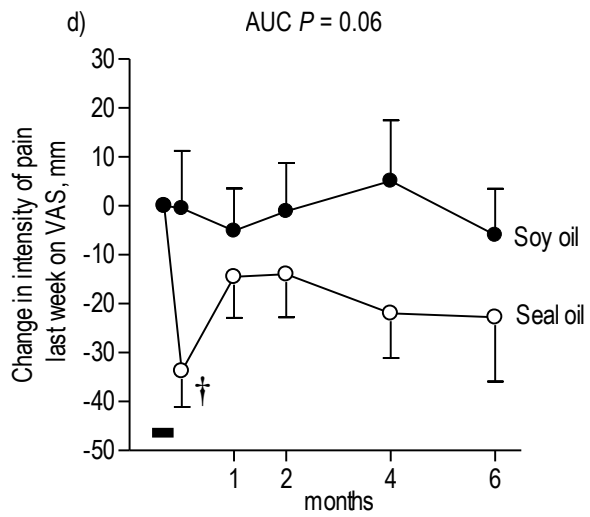
DocVAS = doctor's scoring of rheumatic disease activity. PainVAS = intensity of pain last week. TotVAS = patient's scoring of rheumatic disease activity. MHAQ = modified health assessment questionnaire. IBD-index = sum of Harvey-Bradshaw simple index for Crohn's disease and Walmsley simple clinical colitis activity index for ulcerative colitis. \* = significant group difference at baseline.

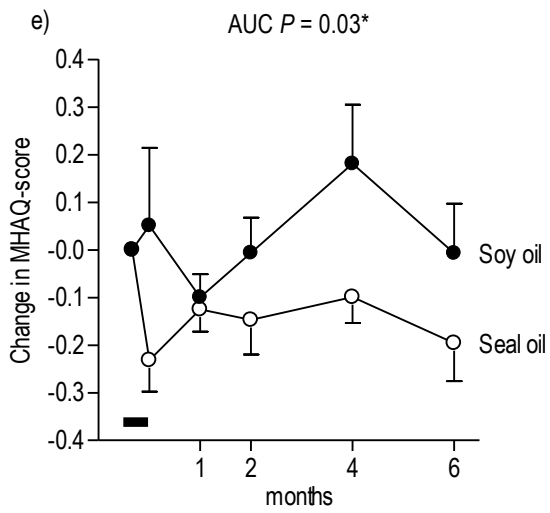
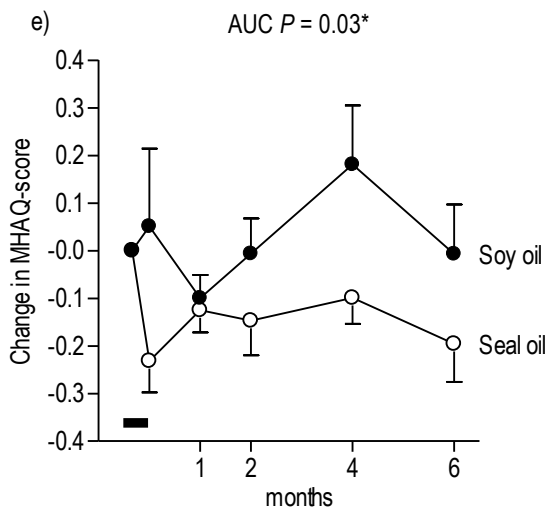
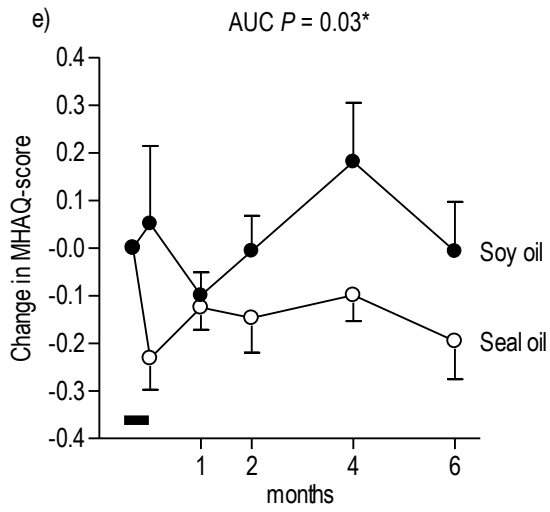


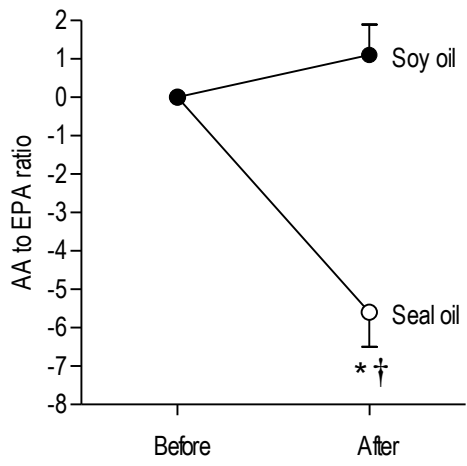
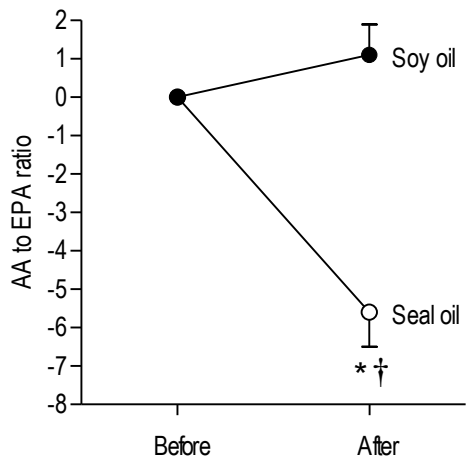
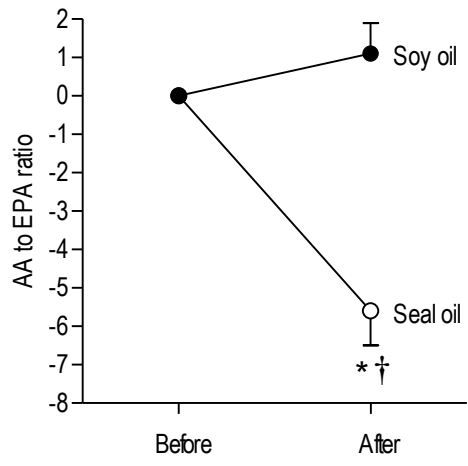












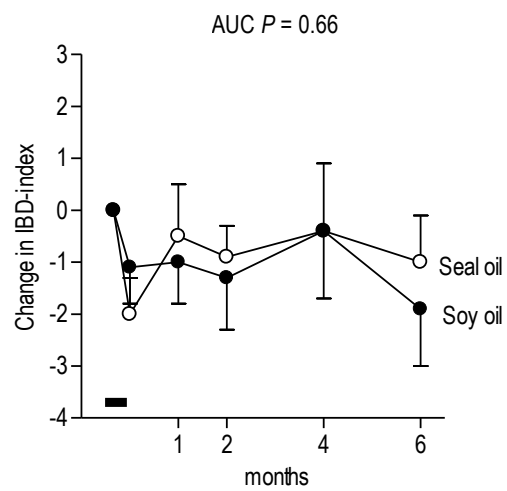
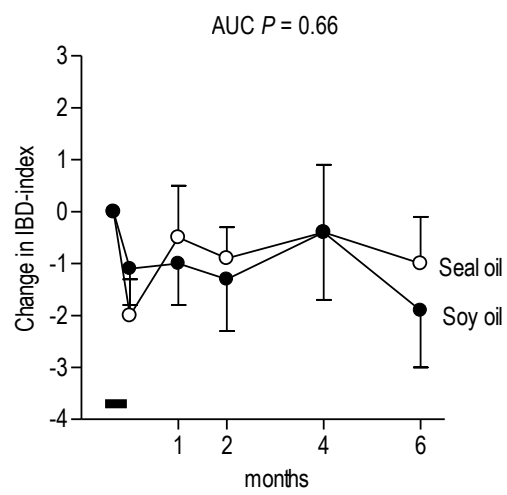
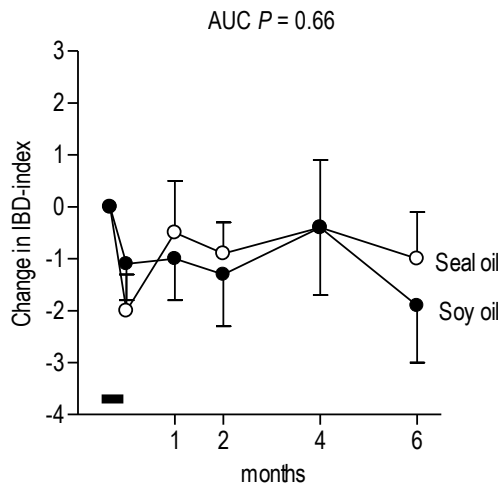


Fig. 1a-e. Change in joint pain from baseline for the entire period from start of treatment with seal oil (○) or soy oil (●) until 6 months' post treatment. Thick horizontal line indicates the treatment period of 10 days. MHAQ = modified health assessment questionnaire. AUC = area under the curve (area between the curve and baseline, zero). \* = significant group differences in AUC for the entire period from start of treatment until 6 months post treatment. † = significant group difference at end of treatment.

Fig. 2. Change in serum ratio of arachidonic acid (20:4 n-6, AA) to eicosapentaenoic acid (20:5 n-3, EPA) from baseline to end of treatment with seal oil (○) or soy oil (●). \* = significant group difference ( $P \ll 0.01$ ) and † = significant change from baseline ( $P \ll 0.01$ ).

Fig. 3. Change in IBD-index (sum of Harvey-Bradshaw simple index for Crohn's disease and Walmsley simple clinical colitis activity index for ulcerative colitis) during treatment with seal oil (○) or soy oil (●) and 6 months post treatment. Thick horizontal line indicates the treatment period of 10 days. AUC = area under the curve (area between the curve and baseline, zero).