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


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Rheumatic arthritis is a commonly observed extra-intestinal 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 could 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 accumulate 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 of duodenally administered n-3 PUFA-rich seal oil on IBD-related joint pain after as early as 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 located mainly 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.


Background: Rheumatic joint pain is a common extra-intestinal 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 sought 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 in the study; 9 had Crohn disease and 10 had ulcerative colitis. Ten millilitres 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 the end of the 10-day treatment period. Analysis of 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 of seal oil administration on joint pain, whereas soy oil tended (not significantly) to aggravate the condition. Consistently, the serum ratios of n-6 to n-3 FAs (P < 0.01) and arachidonic acid to eicosapentaenoic acid (P < 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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Based on the promising results of our uncontrolled pilot study (14), we sought 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 Crohn disease (CD) patients and one of the ulcerative colitis (UC) patients had been operated on with bowel resection. Fifteen of the 19 patients were receiving the following stable medications: 7 on 5-amino salicylic acid (5-ASA), 3 on immune-suppressive medication with azathioprine, 2 on both 5-ASA and azathioprine, 1 on 5-ASA, corticosteroid and central muscle-relaxing medicine, 1 on both 5-ASA and corticosteroid and 1 on a NSAID. The remaining 4 patients were not receiving any 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® Feeding Tube, Fresenius Kabi, GmbH, Germany) was inserted with the aid of fluoroscopy until its tip was located in the distal part of the duodenum. Ten millilitres 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 to use the feeding tube and preferred to drink the soy oil. The seal oil group thus received 14.9 g linoleic acid (18:2 n-6, LA) per day. Two patients refused to use the feeding tube and preferred to drink the soy oil. The seal oil group received 2.0 g EPA, 0.9 g DPA and 2.2 g DHA per day while the soy oil group received 14.9 g linoleic acid (18:2 n-6, LA) per day.

Seal and Soy Oils in IBD and Joint Pain

Table I. Characteristics of the patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>n</th>
<th>Male</th>
<th>Female</th>
<th>Range age (years)</th>
<th>Mean age (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>21–44</td>
<td>33.1</td>
</tr>
<tr>
<td>UC</td>
<td>10</td>
<td>4</td>
<td>6</td>
<td>16–55</td>
<td>40.8</td>
</tr>
</tbody>
</table>

CD = Crohn disease; UC = ulcerative colitis; n = number of patients.

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

<table>
<thead>
<tr>
<th></th>
<th>Seal oil g/100 g</th>
<th>Soy oil g/100 g</th>
</tr>
</thead>
<tbody>
<tr>
<td>Σ saturated</td>
<td>12.9</td>
<td>13.4</td>
</tr>
<tr>
<td>16:1n-7</td>
<td>11.6</td>
<td>nd</td>
</tr>
<tr>
<td>18:1n-9</td>
<td>16.3</td>
<td>17.5</td>
</tr>
<tr>
<td>20:1n-9</td>
<td>7.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Σ monoenes</td>
<td>47.6</td>
<td>19.0</td>
</tr>
<tr>
<td>18:2n-6</td>
<td>1.4</td>
<td>49.7</td>
</tr>
<tr>
<td>20:4n-6</td>
<td>0.4</td>
<td>nd</td>
</tr>
<tr>
<td>Σ ω-6</td>
<td>1.8</td>
<td>49.7</td>
</tr>
<tr>
<td>18:3n-3</td>
<td>0.7</td>
<td>5.5</td>
</tr>
<tr>
<td>20:5n-3</td>
<td>6.6</td>
<td>nd</td>
</tr>
<tr>
<td>22:5n-3</td>
<td>3.1</td>
<td>nd</td>
</tr>
<tr>
<td>22:6n-3</td>
<td>7.4</td>
<td>nd</td>
</tr>
<tr>
<td>Σ ω-3</td>
<td>21.0</td>
<td>5.5</td>
</tr>
<tr>
<td>n-6/6-3</td>
<td>0.1</td>
<td>9.0</td>
</tr>
<tr>
<td>Sum vitamin A</td>
<td>1.4 mg/100 g</td>
<td>nd</td>
</tr>
<tr>
<td>z-tocoerophol</td>
<td>5.4 mg/100 g</td>
<td>17.1 mg/100 g</td>
</tr>
<tr>
<td>TBARS</td>
<td>15.3 nmol/g DW</td>
<td>nd</td>
</tr>
</tbody>
</table>

Sum vitamin A = all-trans retinol + 13-cis retinol + 3-dehydroretinol; TBARS = thiobarbituric acid reactive substances; nd = not detected; DW = dry weight.

Ethical considerations

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

Methods

The joint pain was quantified as follows: duration of morning stiffness (min) during the past 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 the previous week (20). The patients completed a modified health assessment questionnaire (MHAQ) (21). The score in 8 questions about functioning in daily life, with 4 alternative answers, was added and divided by 8, giving scores from 1 (very well) to 3 (very poor).

An IBD index, a measure of IBD activity, was evaluated using the Harvey-Bradshaw simple index in CD (22) and the Walmsley simple clinical colitis activity index in UC (23). These IBD indexes consist of four clinical criteria; symptoms, physical signs, general well-being and extra-intestinal complications. A score equal to or higher than 6 indicates active disease.

Faecal calprotectin concentration, also a measure of IBD activity (24), was determined according to the Eurospital Calprotect®, 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 modifica-
Table III. Serum fatty acid composition (%) before and after treatment with seal oil or soy oil

<table>
<thead>
<tr>
<th>Fatty acid</th>
<th>Seal oil group Before</th>
<th>Seal oil group After</th>
<th>P-value</th>
<th>Soy oil group Before</th>
<th>Soy oil group After</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>∑ saturated</td>
<td>29.5 ± 1.0</td>
<td>29.0 ± 1</td>
<td>0.64</td>
<td>28.4 ± 0.7</td>
<td>27.4 ± 0.7</td>
<td>0.18</td>
</tr>
<tr>
<td>∑ monoenes</td>
<td>24.2 ± 1.1</td>
<td>23.3 ± 1.1</td>
<td>0.61</td>
<td>22.7 ± 1.4</td>
<td>21 ± 1.1</td>
<td>0.07</td>
</tr>
<tr>
<td>20:3 n-6†</td>
<td>1.6 ± 0.1</td>
<td>1.0 ± 0.1</td>
<td>&lt;0.01</td>
<td>1.4 ± 0.1</td>
<td>1.3 ± 0.1</td>
<td>0.45</td>
</tr>
<tr>
<td>20:4 n-6*</td>
<td>5.6 ± 0.4</td>
<td>5.5 ± 0.3</td>
<td>0.59</td>
<td>4.4 ± 0.3</td>
<td>4.6 ± 0.4</td>
<td>0.45</td>
</tr>
<tr>
<td>∑ n-6†</td>
<td>39.9 ± 1.8</td>
<td>36.9 ± 1.4</td>
<td>0.02</td>
<td>34.6 ± 4.6</td>
<td>38.5 ± 4.9</td>
<td>0.02</td>
</tr>
<tr>
<td>18:3 n-3*</td>
<td>0.59 ± 0.04</td>
<td>0.54 ± 0.04</td>
<td>0.27</td>
<td>0.9 ± 0.1</td>
<td>0.9 ± 0.1</td>
<td>0.54</td>
</tr>
<tr>
<td>20:5 n-3†</td>
<td>1.1 ± 0.3</td>
<td>4.2 ± 0.4</td>
<td>&lt;0.01</td>
<td>1.7 ± 0.4</td>
<td>1.3 ± 0.3</td>
<td>0.28</td>
</tr>
<tr>
<td>22:5 n-3†</td>
<td>0.50 ± 0.03</td>
<td>0.82 ± 0.04</td>
<td>&lt;0.01</td>
<td>0.7 ± 0.2</td>
<td>0.53 ± 0.03</td>
<td>0.29</td>
</tr>
<tr>
<td>22:6 n-3†</td>
<td>2.2 ± 0.3</td>
<td>4.0 ± 0.3</td>
<td>&lt;0.01</td>
<td>3.6 ± 0.9</td>
<td>2.7 ± 0.2</td>
<td>0.31</td>
</tr>
<tr>
<td>∑ n-3†</td>
<td>4.2 ± 0.5</td>
<td>9.4 ± 0.7</td>
<td>&lt;0.01</td>
<td>7.1 ± 1.5</td>
<td>5.5 ± 0.6</td>
<td>0.31</td>
</tr>
<tr>
<td>n-6/n-3†</td>
<td>10.0 ± 0.6</td>
<td>4.0 ± 0.3</td>
<td>&lt;0.01</td>
<td>7.2 ± 1.1</td>
<td>8.6 ± 0.8</td>
<td>0.15</td>
</tr>
<tr>
<td>20:4 n-6/20:5 n-3*†</td>
<td>7.0 ± 0.8</td>
<td>1.5 ± 0.1</td>
<td>&lt;0.01</td>
<td>3.8 ± 0.7</td>
<td>4.9 ± 0.8</td>
<td>0.21</td>
</tr>
</tbody>
</table>

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

*Significant group difference at baseline.
†Significant group difference after treatment.

Statistics

Data were analysed and displayed using the GraphPad Prism 4 (GraphPad Software Inc., San Diego, Calif., USA) statistical software package. Values were expressed as the mean ± s.e. (standard error of the mean). Effect of treatment was calculated as change from baseline (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 using the trapezoid method. Normality of data was tested with the Kolmogorov-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 ± 1.0 versus 7.0 ± 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 lower joint pain- and IBD activity compared with the seal oil group (significant for duration of morning stiffness; P < 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. Owing 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-day 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
Fig. 1. a–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. VAS = visual analogue scale; 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.
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 significant 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 ($P = 0.01$), 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).

Fatty acid composition

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

Compared to baseline. Compared to baseline, reduced ratios of AA to EPA, n-6 to n-3 FAs and $\Sigma$ n-6 FAs (LA and 20:3 n-6) and increased $\Sigma$ n-3 FAs (EPA, DHA and DPA) were observed at the end of treatment with seal oil (Table III, Fig. 2). An increased level of n-6 FAs (mainly LA) was observed at the 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 did not yield any significant group differences for IBD index (Fig. 3). Compared with baseline, a significant improvement in IBD index was observed at the 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 for several months post-treatment. While improvement was seen after treatment with seal oil, soy oil tended (not significantly) to exacerbate 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 can substantially ameliorate IBD-related joint pain.

Most nutritional research concerning IBD and rheumatic disorders have focused on the effects of orally administered fish oil, either in the 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
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 tailoring the location of 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 be explained partly 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 as compared to drinking, as the latter prevents the mixing and dilution in the stomach, but also correct dosing and avoidance 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 of seal oil on IBD activity, 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. Therefore, instead of philosophizing about what would have happened if the treatment groups had been the opposite, we can 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 the pooling of the two patient groups into one IBD group. The IBD indexes for CD (22) and UC (23) are based on relatively similar questionnaires on IBD activity. We therefore pooled the CD and UC index scores into one IBD index. High oral doses of n-3 PUFAs 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 significantly improved IBD-related joint pain, 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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