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ORIGINAL ARTICLE

Salmon diet in patients with active ulcerative colitis reduced the simple clinical colitis activity index and increased the anti-inflammatory fatty acid index – a pilot study

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Abstract

Objective. Data concerning the anti-inflammatory effect of dietary n-3 polyunsaturated fatty acids (PUFAs) in patients with ulcerative colitis (UC) are inconsistent. Salmon fillet contains n-3 PUFAs and bioactive peptides that may improve its effects compared to fish oil alone. We assessed the efficacy of a salmon-rich diet in patients with mild ulcerative colitis. ***Methods***. An 8-week intervention pilot study was designed to assess the effects of 600 grams Atlantic salmon consumption weekly in 12 UC patients. Simple clinical colitis activity index (SCCAI), a dietary questionnaire, sigmoidoscopy, selected serum inflammatory markers, fecal calprotectin, and plasma and rectal biopsy fatty acid profiles were assessed before and after intervention. ***Results.*** The levels of C20:4n-6 arachidonic acid in biopsies after dietary intervention were correlated with histology and endoscopy scores. The concentrations of n-3 PUFAs, C20:5n-3 eicosapentaenoic acid, C22:6n-3 docosahexaenoic acid, and the n-3/n-6 ratio increased in plasma and rectal biopsies. The anti-inflammatory fatty acid index (AIFAI) increased both in biopsies and plasma accompanied with a significantly reduced SCCAI. ***Conclusion.*** Based on evidence of SCCAI and AIFAI and a tendency of decreased levels of CRP and homocysteine, intake of Atlantic salmon may have beneficial effects on disease activity in patients with mild ulcerative colitis.

Key Words: *Ulcerative colitis, omega-3 fatty acids, fish oils, inflammatory bowel diseases, diet therapy*

Introduction

Ulcerative colitis (UC) is an inflammatory bowel disease (IBD) characterized by colonic inflammation associated with frequent bloody diarrhea. Although the etiology of IBD remains unknown, proposed pathogenic mediators include microbial agents, immune dysfunction, genetic susceptibility, and various environmental factors [1]. Fish oil has been reported by some authors to be beneficial in UC, but results are inconsistent [2–4]. Some reports suggest lower disease activity with a daily intake of $>$ 2 grams of eicosapentaenoic acid (EPA, C20:5n-3) and docosahexaenoic acid (DHA, C22:6n-3) evidenced by decreased symptom score, endoscopic score, histological score, relapse rate, or corticosteroid requirement [5]. Oral n-3 PUFA intake may also decrease the levels of several pro-inflammatory cytokines involved in IBD-mediated inflammation [6]. A Western diet, which supplies a surplus of omega-6 (n-6) polyunsaturated fatty acids (PUFAs), provides arachidonic acid (AA, C20:4n-6) as the main substrate for the cyclooxygenase and lipoxygenase enzyme pathways, which catalyse the formation of highly active inflammatory substances such as prostaglandin (PG)E_2 and leukotriene (LT)B_4. Moreover, a high intake of linoleic acid (LA, C18:2n-6), a dietary n-6 PUFA, was associated with an increased risk of developing UC, suggesting that LA may have an aetiological role [7].

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The hypothesized mechanism underlying the anti-inflammatory effect of dietary fish oil is that alteration of substrate from AA to EPA/DHA in cell membrane phospholipids provides eicosanoids that have lower inflammatory potential, such as PGE_3 and LTB_5 [8]. Dietary n-3 PUFAs in forms of DHA and EPA may also protect against UC [9]. Fish fillets are of interest as dietary intervention instead of pure fish oil because they contain a wide variety of potentially bioactive substances, such as peptides and phospholipids in addition to n-3 PUFAs. These compounds may have additional positive biological effects. A previous study also showed that fish consumption was a more efficient administration of n-3 PUFAs than fish oil capsules [10].

The main objective of this pilot study was thus to investigate the influence of regular high intake (600 grams each week) of Atlantic salmon fillet on disease activity, inflammatory and biochemical markers in blood and tissue samples in patients with mild UC.

Methods

Patients

Twenty-three patients were consecutively recruited from the outpatient clinic of Stavanger University Hospital. Inclusion criteria were a confirmed diagnosis of UC by colonoscopy with biopsies, a SCCAI of ≥ 4 and a fecal calprotectin of > 50 mg/kg. Exclusion criteria were considerable organ disorder such as lung disease, heart failure, or liver failure. Patients with diabetes, hypercholesterolemia (total cholesterol > 8 mmol/l), regular intake of n-3 fatty acids supplements or fish (> 30 g fat fish weekly), treatment with corticosteroids (prednisolone ≥ 7.5 mg daily), and patients receiving treatment with a tumor necrosis factor (TNF)-α inhibitor or azathioprine within the last three months were excluded.

Study design

The study was as an open, 12-week single centre pilot study in which each patient consumed 200 grams of Atlantic salmon fillet 3 times a week. Four weeks of wash out were followed by 8 weeks of intervention. Visit zero was at inclusion, visit one at start of the intervention and visit two at the end of the intervention period. At inclusion, patients filled in a food frequency questionnaire and screening blood tests were taken. During the wash out period, dietary restrictions included no intake of omega-3 (n-3) PUFA dietary supplements and < 0.25 grams of daily long chain n-3 PUFA content in the diet. At visit one and visit two, laboratory tests in the fasting state, including selected cytokines, C-reactive protein (CRP), fatty acid profile, and fecal calprotectin were assessed, and sigmoidoscopy with biopsies from the rectum was performed. The patients filled in a food frequency questionnaire for the second time at visit two. Patients completed the simple clinical colitis activity index (SCCAI) questionnaire at visits one and two.

Study diet

The Atlantic salmon was produced by EWOS innovation AS, Dirdal, Norway. The salmon feed contained a mixture of vegetable oil and fish oil in a 1:1 ratio. Analysis of salmon muscle has shown a content of 4–4.5 g n-3 PUFAs in 100 g of fillet, which provides a daily average of 3.4–3.9 g of n-3 PUFA when consuming 600 g salmon a week. The canteen at Haukeland University Hospital prepared study meals. The fillets were cooked and vacuum packed, ready for consumption at home. Durability of the fillets was 4 weeks when stored at 4°C.

Medication

All patients except one (who was given topical 5-aminosalisylic acid (5-ASA) due to a flare up of distal colitis) maintained their individual medication throughout the study period (Table I).

Fatty acids in plasma and rectal specimen

These were analysed as previously described [11]. The same method was used for analysis of fatty acid profile in plasma and homogenized biopsy samples taken from rectal mucosa. EPA, DHA, docosapentaenoic acid (DPA, C22:5n-3), AA, total n-3 and total n-6 PUFAs were analysed. An anti-inflammatory fatty-acid index (sum of EPA, DHA, and dihomo-gamma-linolenic acid (DGLA, C20:3n-6) divided by AA) and an n-3/n-6 ratio were calculated [12].

Table I. Characteristics at baseline for intervention patients ($n = 12$) with mild ulcerative colitis.

Gender	
Male/Female	5/7
Age, years, median (range)	50 (35–65)
Disease duration, years, median (range)	20 (8–26)
Simple Clinical Colitis Activity Index, median (range)	5 (4–8)
Disease location (at diagnosis)	
Distal colitis	7
Subtotal colitis	2
Total colitis	3
Medication	
5-ASA*/Sulphasalazine use	9
topical	2
oral	7
Corticosteroids	0

*ASA = aminosalicylic acid.

Diet questionnaire

A validated food frequency questionnaire (FFQ) was filled in at the start and at the end of the study [13,14]. The FFQ was semi-quantitative and designed to capture dietary habits and intake of dietary supplements. At the start of the study, the participants gave information about their diet over the last year. At the end of the study, the questions encompassed their diet since inclusion in the study. The FFQ included questions about intake of 255 food items. The questionnaires were optically read. Consumption frequencies were converted into food amounts (g/day) by the use of standard Norwegian portion sizes.

Simple Clinical Colitis Activity Index (SCCAI)

This symptom-based index is an instrument for evaluation of disease activity in UC patients [15]. The method is based on six items: general well-being, day- and night-time stool frequency, urgency of defecation, amount of blood in the stool, and extra-intestinal complications. Maximum score is 20, and a score of four or more is suggestive of active colitis.

Inflammatory markers

A 21-plex kit from LINCO® (Millipore Corporation, Billerica, MA 01821, USA), including interleukin (IL)-1b, IL-2, IL-6, IL-10, and TNF-α was used for analysis of plasma cytokines. Analyses from the kits were performed on a Bio-plex 200 suspension array system from Bio-Rad® (Bio-Rad Life Science Research Group, Hercules, CA 94547, USA) and further processed by a Bio-plex manager 4.1 software supplied from Bio-Rad®. CRP was analysed in the hospital's routine laboratory. Homocysteine and malondialdehyde (MDA) levels were analysed in plasma samples as markers of oxidation. Fecal calprotectin was analysed by the PhiCal Test® (NovaTec Immunodiagnostica GmbH, Dietzenbach, Germany). Results are expressed as mg calprotectin/kg faeces. Fecal calprotectin > 50 mg/kg was regarded as objective evidence of active colon inflammation [16].

Sigmoidoscopy

Inflammation scores were rated from 0 to 3 according to the following scale: Grade 0 (no inflammation) – normal mucosa; Grade 1 (mild inflammation) – mucosal oedema and changes in vascular pattern; Grade 2 (moderate inflammation) – mucosal oedema, lack of vascular pattern, and erosions; Grade 3 (high grade inflammation) - spontaneous mucosal bleeding and ulcerations [17].

Histological investigations

Four biopsies were taken from the rectal mucosa, 8 cm from the anus, and were immediately frozen unfixed at −70°C for later lipid profile assessments. Two additional biopsies were fixed in formalin and processed for histological evaluation of inflammation. One blinded senior pathologist evaluated the biopsies. Inflammation was rated as follows: Grade 0 – normal mucosa; Grade 1A – chronic inflammatory infiltration of the lamina propria, no effect on the mucosal lining or crypts, no or mild architectural disorder; Grade 1B – chronic inflammatory infiltration of the lamina propria not excluding the mucosal lining, no or mild architectural disorder; Grade 2 – mild crypt injury with acute inflammatory cell infiltration; Grade 3 – extensive crypt injury with crypt abscesses and ulcerations. Grade 0 implies clinically inactive disease, grade 1 mild disease, grade 2 moderate, and grade 3 severe disease [17].

Routine laboratory tests

Blood samples were collected after an overnight fast. Routine laboratory analyses included haemoglobin, leukocytes, platelets, creatinine, alanine aminotransferase (ALAT), alkaline phosphatase (ALP), albumin, and electrolytes.

Statistical analysis

For normally distributed data, parametric statistics by paired samples t-test were applied and mean and 95% confidence intervals are reported. Data not normally distributed were analysed by non-parametric statistics using Wilcoxon matched-pairs/signed rank test, and median and ranges given. Data were analysed using the SPSS 14.0 for Windows statistical software package. No corrections for multiple analyses were performed. Rank correlation coefficients were calculated using Spearman's method and p-values < 0.05 were considered statistically significant.

Ethical considerations

This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures were approved by the Regional Committee for Medical Research Ethics. Written informed consent was obtained from all patients.

Results

Patient characteristics

Of the 23 patients, six patients withdrew because of loss of motivation to follow the prescribed diet. Five patients had a normal fecal calprotectin and were

excluded. Thus, 12 patients were included in the final analyses. Baseline data are given in Table I.

Fatty acid profile and anti-inflammatory fatty-acid index (AIFAI) in plasma and rectum

The levels of n-3 PUFAs in plasma and rectal biopsies were significantly increased after intervention (Table II), reflecting an elevated content of EPA and DHA, but not n-6, resulting in an increased ratio of n-3 to n-6 (Table II). Although the amount of n-6 PUFAs was not significantly affected after intervention, it is worth noting that the concentration of AA in plasma was significantly reduced. No changes in AA level were found in rectal biopsies. DPA was increased in plasma, but not in rectal biopsies. Thus, AIFAI increased both in plasma and rectal biopsies (Table II).

Diet questionnaire

Estimations based on the food frequency questionnaire showed a statistically significant increase in the intake of EPA, DHA, DPA, and total n-3 PUFAs at visit two compared with baseline. Despite an unchanged level of n-6 fatty acids, the estimated ratio of n-3 to n-6 was significantly increased (Table III).

Simple clinical colitis activity index

The SCCAI was significantly reduced from median (range) 3.0 (0–7) at visit one to 1.5 (0–6) at visit two, $p = 0.007$.

Assessment of inflammation

There was a tendency towards lower S-CRP after treatment ($p = 0.066$). Moreover, plasma homocysteine was reduced, but did not reach statistical significance. Plasma cytokines including TNF-α, and MDA, as well as histology score were not changed after consumption of the fish fillets. Fecal (f)-calprotectin increased non-significantly from median (range) 556 (96–5290) mg/kg at visit one to 1105 (35–3640) mg/kg at visit two, $p = 0.6$.

Correlations

Histology score and endoscopy score correlated with AA content in rectal biopsies at visit two ($r = 0.82$, $p = 0.001$ and $r = 0.90$, $p < 0.001$), but not at visit one ($r = 0.36$, $p = 0.2$ and $r = 0.53$, $p = 0.07$). No significant correlation was found between histological inflammation and SCCAI at either visit. SCCAI correlated with endoscopy score at visit one ($r = 0.65$, $p = 0.02$) but not at visit two ($r = 0.50$, $p = 0.097$). No statistically significant correlations between plasma or biopsy levels of fatty acids and disease activity markers (SCCAI, f-calprotectin and endoscopy score) were identified.

Adverse effects of intervention

During the study period, one patient reported transient nausea following salmon intake. No other adverse effects were recorded.

Discussion

The main finding in this study was a significantly reduced SCCAI in patients with mild UC after consumption of Atlantic salmon fillets. In addition we observed a non-significant reduction in CRP and homocysteine levels. The AIFAI was significantly increased in both plasma and rectal biopsies and AA level decreased significantly in plasma after intervention. Based on these findings, intake of Atlantic salmon fillets seems beneficial, and the improved

Table II Fatty acids (FA) in plasma (μg FA/ml plasma) and rectal biopsies (μg FA/gram tissue) and Anti-inflammatory fatty-acid index (AIFAI) in plasma and rectal biopsies at visits 1 and 2 in 12 patients with mild ulcerative colitis (Mean values and 95% confidence intervals).

	Plasma					Biopsies				
	Visit 1		Visit 2			Visit 1		Visit 2		
Variable	Mean	95% CI	Mean	95% CI	P-value*	Mean	95% CI	Mean	95% CI	*P*-value*
20:5n-3	24.1	16.8–31.5	52.2	39.1–65.2	<0.001	73.7	60.4–87.1	163	131–194	<0.001
22:5n-3	16.1	13.5–18.8	18.9	16.3–21.5	0.005	164	126–202	204	145–263	0.19
22:6n-3	78.3	62.3–94.3	116.9	94.2–139.6	<0.001	355	275–435	520	415–624	0.007
20:3n-6	50.5	40.4–60.6	44.1	33.5–54.8	0.001	340	224–456	263	210–315	0.08
20:4n-6	214	167–260	196	160–231	0.035	1827	1538–2117	1706	1440–1973	0.4
Total n-3	143	118–168	213	173–252	<0.001	649	525–773	965	763–1166	0.008
Total n-6	1215	1081–1348	1186	1037–1335	0.25	4476	4108–4844	4608	3668–5548	0.8
n-3/n-6 ratio	0.12	0.10–0.14	0.18	0.15–0.21	<0.001	0.14	0.12–0.16	0.21	0.19–0.24	<0.001
AIFAI†	75.1	61.4–88.8	111.3	93.8–128.8	<0.001	42.9	32.9–52.9	56.2	49.9–62.5	<0.001

*Paired samples t-test.

†Anti-inflammatory fatty-acid index = ((20:5n-3 + 20:3n-6 + 22:6n-3)/20:4n-6)) × 100.

Table III. Estimated daily intake of polyunsaturated fatty acids (mg) based on a food frequency questionnaire, at baseline and after intervention in 12 patients with mild ulcerative colitis (median values and ranges).

	Visit 0		Visit 2		
Variable	Median	Range	Median	Range	*p*-value*
18:3n-3	2070	940–4630	2350	1910–4040	0.084
20:5n-3	162	20–890	877	790–1310	0.002
22:5n-3	64	20–170	340	320–430	0.002
22:6n-3	355	320–430	1365	1200–1870	0.003
18:2n-6	12850	690–31480	12430	10160–25300	0.93
Total n-6	14150	7020–31640	12850	10270–27410	0.86
Total n-3	2490	1250–7280	5250	4390–7190	0.002
n-3/n-6 ratio	0.17	0.10–0.35	0.40	0.28–0.51	0.002

*Wilcoxon signed rank test.

health effects on disease activity might be ascribed to changes in the pro-inflammatory status. The SCCAI score reduction occurring during the washout period could be due to the statistical phenomenon 'regression towards the mean', which is often seen in intervention studies.

Fish fillet consumption altered the fatty acid composition both in plasma and in the rectal biopsies. The prescribed salmon diet provided a daily intake of 3.4–3.9 g of n-3 PUFAs based on analysis of salmon muscle, while the background diet supplied 2.5 g daily as estimated by the FFQ. The amount of n-3 PUFAs provided by the intervention is in line with previous trials where 2.7–5.6 grams were sufficient to achieve a beneficial effect [8]. Whether the high n-3 content in the background diet could influence/obscure the clinical effects from the salmon consumption despite the 4-week washout period, is possible.

As expected, the content of EPA and DHA in plasma and rectal biopsies increased. The synthesis of prostaglandins depends on the availability of the 20 carbon polyunsaturated fatty acids, either from the circulation or from local production catalysed by delta 6 and delta 5 desaturasis. We found that Salmon ingestion affected the delta 6 and delta 5 desaturase indexes (data not shown) as well as the content of AA in plasma, but not in rectal biopsies, making it likely that the biosynthesis of C20:4n-6 locally could not contribute to inflammation. The fatty acid composition in the biopsies was changed and accompanied by increased AIFAI. Thus, locally EPA, DHA, and not AA, may contribute to an increased anti-inflammatory effect under the present condition. However, these findings were not supported by significant changes in other disease activity markers. Although CRP was reduced from 6.4 to 4.3, significant changes in TNF-α or other selected cytokines in plasma did not occur. The non-significant CRP reduction might be due to a poor association between CRP and the degree of colonic inflammation or few patients [18]. Moreover, conflicting results have been reported not only on TNF-α, but also on IL-6 levels [19]. Thus, the association between several classical cytokines and IBD disease activity is uncertain [19]. Fecal calprotectin was not significantly altered after regular salmon intake, and did not indicate a beneficial effect. However, regression of symptoms usually precedes changes in endoscopic and/or histological grade of inflammation [20]. This might also explain our findings of reduced SCCAI, and increased AIFAI, but unchanged endoscopy findings and histology score. This is in contrast to previous reports, which found fish oil supplementation to be associated with less endoscopic signs of inflammation [2,21] and a reduced histological score [21]. However, in these studies the intervention periods were either substantially longer (6–7 months) or the sample size was larger. It appears, also considering the high drop-out rate during our 12-week study, that a diet of 600 g of salmon weekly for a longer period than 8 weeks seems unacceptable for many patients.

In conclusion, this pilot study suggests that a regular intake of Atlantic salmon in patients with active UC is beneficial based on improved SCCAI and AIFAI in colonic mucosa. The tendency of decreased CRP and lower homocysteine add value to an increased anti-inflammatory/antioxidative state following consumption of salmon fillets, although other disease activity measures did not support these findings. There are other limitations to this study. The small sample size could obscure clinical or biological effects from the intervention, the study is open, non-randomized and a control group is missing. Larger studies are therefore needed to confirm whether fat fish fillet consumption is truly beneficial in active ulcerative colitis patients.

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