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Omega-3 fatty acids and inflammatory bowel diseases – a systematic review

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Abstract

Background & Aim: Despite their well known anti-inflammatory actions, the clinical usefulness of omega-3 PUFA in inflammatory bowel disease is controversial. We aimed to systematically review the available data on the performance of omega-3 PUFA as therapeutic agents in these patients. Methods: Electronic databases were systematically searched for RCT of fish oil or omega-3 PUFA therapy in both active and inactive ulcerative colitis or Crohn's disease, without limitation on either the length of therapy or the form it was given, including nutritional supplements and enteral formula diets. Eligible articles were assessed for methodological quality on the basis of the adequacy of the randomisation process, concealment of allocation, blinding of intervention and outcome, possible biases, and completeness of follow-up. The five-point Oxford quality score was calculated. Results: A total of 19 RCT were finally selected for this review. Overall, available data do not allow to support the use of omega-3 PUFA supplementation for the treatment of both active and inactive inflammatory bowel disease. Negative results are quite consistent in trials assessing the use of omega-3 PUFA to maintain disease remission, particularly ulcerative colitis, and to a lesser extent Crohn's disease. Trials on their use in active disease do not allow to draw firm conclusions mainly because the heterogeneity of design (ulcerative colitis) or their short number (Crohn's disease). In most trials, the appropriateness of the selected placebo is questionable. Conclusion: The present systematic review does not allow to make firm recommendations about the usefulness of omega-3 PUFA in inflammatory bowel disease.

Key words: **Ulcerative colitis: Crohn's disease: Omega-3 fatty acids: EPA: DHA: Fish oil**

Ulcerative colitis (UC) and Crohn's disease (CD) are chronic idiopathic inflammatory disorders of the gastrointestinal tract, collectively termed as Inflammatory Bowel Diseases (IBD). They are relatively common in developed countries, with reported prevalences and incidences in the USA of 200–250, and 7–9 per 100 000 people for UC, and 130–200 and 6–8 per 100 000 people for CD, respectively[1,2]. In Europe, a North-South gradient has been described, but the incidence appears to have increased in Southern and developing countries in recent years[3,4]. While UC involves exclusively the mucosa of the colon in a variable continuous extent, CD may occur in any part of the digestive tract in a segmental transmural fashion, with the ileum and colon being the most often involved segments. Although IBD is thought to occur as a result of an inadequate and sustained immune response against luminal (most probably bacterial) antigens, its precise aetiology remains elusive[5]. Therefore, there is no curative therapy (except for total proctocolectomy in UC) for these diseases, and patients should receive medical treatment for both controlling the inflammatory flares and preventing further bouts of the disease, since they typically have a relapsing and remitting course. Surgery is reserved for life-threatening acute severe refractory colitis, chronic disease unresponsive to any medical therapy, or for the treatment of local complications such as strictures, fistulas or intraabdominal abscesses. Drugs effective for inducing and/or maintaining remission in IBD include aminosalicylates, corticosteroids, immunesuppressants (such as thiopurines, cyclosporin, or methotrexate), and biologic agents (mainly anti-TNF monoclonal antibodies)[6,7]. However, the use of many of these drugs encompasses an increased risk for infections (mainly opportunistic)[8], and concerns about the possibility of developing malignancies have also been raised[9,10]. Therefore, alternative approaches to IBD therapy, including nutritional ones, should be looked for.

Fish oil-derived omega-3 polyunsaturated fatty acids (PUFA) – namely, EPA and DHA – are good candidates for this purpose as they may exert several anti-inflammatory biological actions[11,12]. Fish oil intake results in EPA incorporation, and arachidonic acid decrease in membrane phospholipids, thereby leading to a decreased synthesis of proinflammatory eicosanoids and enhanced production of they less proinflammatory or even anti-inflammatory counterparts[11,12]. Also, increased generation of EPA- and

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DHA-derived resolvins, with anti-inflammatory or inflammation resolving actions has been described[13]. Other anti-inflammatory actions of omega 3 PUFA include a) down regulation of proinflammatory cytokine synthesis (such as TNF-α, IL-1β, IL-6 and IL-8) through either a decreased activation of some nuclear transcription factors (e.g. NF-κB) or enhanced PPAR-γ activation, b) decreased leukocyte chemotaxis, and c) decreased T-cell reactivity[11,12]. In the last two decades, several trials assessing the effect of omega-3 PUFA on IBD have been reported with variable results. The purpose of the present study was to systematically review the available data on the performance of fish-oil derived omega-3 PUFA as therapeutic agents for UC and CD.

Materials and methods

Search strategy

A literature search for published full articles was performed, without language restrictions, using the following databases (from inception to April 2011): Medlars Online International Literature (MEDLINE) via PubMed©, EMBASE©, and Latin American and Caribbean Heath Sciences Literature (LILACS). The following sets of keywords – including both text words and Medical Subject Heading (MeSH) terms, and adapted for each database as appropriate – combined with the boolean operator 'OR', were used:

Set #1: Fish oils [MeSH] OR Fatty acids, omega-3 [MeSH] OR Eicosapentaenoic acid [MeSH] OR Docosahexaenoic acid [MeSH] OR Fatty acids, essential [MeSH] OR EPA OR DHA OR *n*-3 fatty acids OR *n*-3 PUFA.

Set #2: Crohn disease [MeSH] OR Colitis, ulcerative [MeSH] OR Inflammatory Bowel Diseases [MeSH] OR Ileitis [MeSH] OR Pouchitis [MeSH] OR Crohn's OR ileocolitis OR enteritis, regional OR ileitis, regional OR rectocolitis.

Both sets of keywords were the combined with the boolean operator 'AND'. The search was not restricted to study design, since the overall literature concerning IBD and omega-3 PUFA is not very extensive. No specific search for studies published only as abstract was performed; however, abstract studies reported in the most recent systematic reviews[14–16] on the field were also included in the present one. No search for ongoing studies was performed.

Eligibility

Every randomised controlled trial (RCT) of fish oil or omega-3 PUFA therapy in both active and inactive UC or CD, reporting at least one of the primary or secondary outcomes (see below), was considered potentially eligible for this systematic review. Since the broadest qualitative review (without meta-analysis) was intended, there was no limitation on either the length of therapy or the form it was given (capsules, liquid, enteric coated preparation), including nutritional supplements and enteral formula diets. Concomitant IBD therapies were allowed if they were balanced between the study groups. Studies dealing with conventional diets enriched with fish foods were not considered eligible since the dose of omega-3 PUFA is not clear in these studies. Papers reporting pooled results in UC and CD, or in active and inactive patients were also excluded.

Outcomes

Primary outcomes were remission rate (for active patients) and relapse rate (for patients in remission) during the observation period. Possible secondary outcomes included change in disease activity scores (either clinical or endoscopic), time to remission, time to first relapse, adverse events, hospitalisation rate, steroid sparing effect, disease activity at the end of follow-up period, and quality of life. Studies reporting only surrogate outcomes, such as serum/tissue levels of cytokines, eicosanoids or other inflammatory markers, were excluded.

Methods of review and data extractions

All abstracts identified by the search strategy were assessed for eligibility by one author (E. C.). Full-text studies were retrieved if they were potentially eligible or if they were relevant systematic review articles. The full-text articles were independently reviewed by two authors (E. C. and M. M.) for eligibility. Disagreements were resolved by consensus.

E. C. and M. M. also assessed eligible articles for methodological quality on the basis of the adequacy of the randomisation process, concealment of allocation, blinding of intervention and outcome, possible biases, and completeness of follow-up. The five-point Oxford quality score[17] was calculated. Final decisions for eligibility were done by mutual agreement.

For every eligible article the following data were extracted: (a) Design of the study (i.e. parallel groups, cross-over), (b) Number and characteristics of participant subjects with particular reference to activity, and extension/location and of the disease according to the Montreal classification of IBD[18], time in remission (for patients with inactive IBD), (c) details on both the therapeutic intervention and that used for comparison (i.e. placebo or other widely accepted therapy for IBD), and (d) the reported outcomes.

Results

The initial search yielded a total of 284 articles, 28 of which being considered potentially eligible as they reported results of clinical trials. Of these, one was an open trial[19], six reported pooled results of UC and CD and/or active and inactive patients[20–25], three investigated only surrogate endpoints[26–28], one dealt with omega-3 FA rich conventional foods[29], and two compared enteral formulas not enriched with omega-3 PUFA[30,31]. The remaining 15 articles, as well as three studies published only as abstract and reported in the most recent systematic reviews on the field[14–16], were finally included in the present review for a total of 19 RCT[32–49], since two independent trials were reported in a single paper[48] (Fig. 1). None of the eligible articles was excluded because of poor quality. Details of quality assessment of the included studies are presented in Table 1.

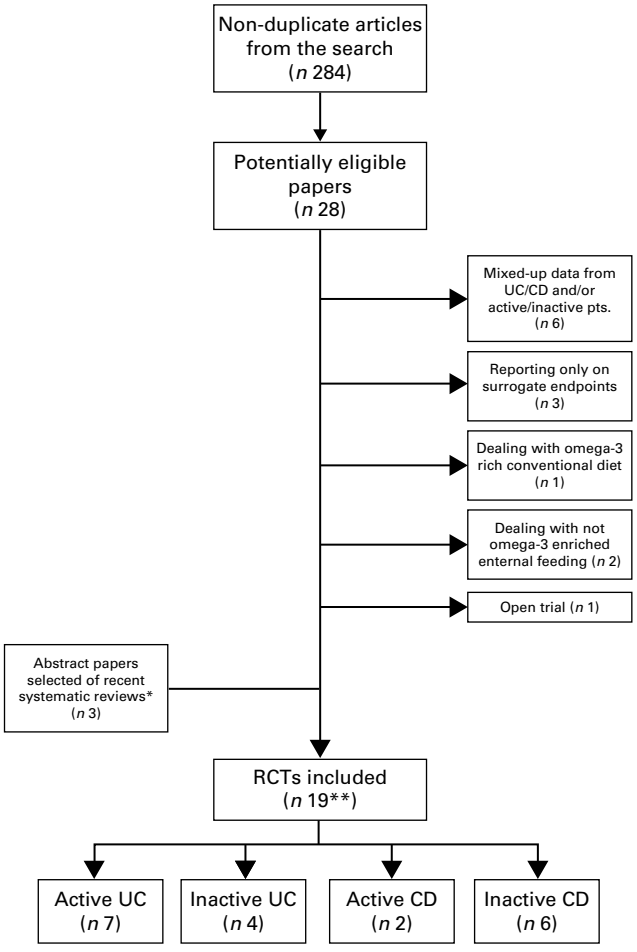

Fig. 1. Disposition of trials in the present systematic review. *De Ley *et al.*[14], Turner *et al.*[15], and Turner *et al.*[16]. **Two independent trials published in the same article[48].

Clinical effectiveness of omega-3 PUFA in IBD

Active ulcerative colitis. Seven out the 19 selected RCT, investigated the effect of omega-3 PUFA in patients with active UC[32,34,40–43,47] (Fig. 1, Table 2). Three trials used a cross-over[32,34,42] and four a parallel-groups design[40,41,43,47]. Liquid fish oil as active treatment, with sunflower oil as placebo, were used in three trials[40,41,43], while fish oil capsules were compared with capsules with a mixture of fatty acids (mostly oleic acid) in two[32,34]. One cross-over trial used sulfasalazine capsules as comparator instead of placebo[42]. Finally, one trial compared a nutritional supplement enriched with omega-3 PUFA, prebiotics (fructooligosaccharides, Arabic gum), and antioxidant micronutrients, with a sucrose-based placebo supplement[47]. Details on the sample size, as well as severity and extension of UC are summarised in Table 2.

Only one small trial in patients with active proctitis or distal UC reported on the primary end-point (i.e. remission rate during the observation period)[41]. After 3 months of treatment, this occurred in 9/9 patients on omega-3 PUFA *v.* 0/9 treated with placebo[41]. Three studies reported a significantly greater improvement in the clinical score with omega-3 PUFA as compared with placebo[32,41,43]. In two of them, this was accompanied with a significant improvement in the endoscopic[41,43] and histological score[41]. A cross-over study did not disclose differences in the clinical and endoscopic scores between fish oil or placebo therapy, but the histological index significantly improved during the fish oil period[34]. Steroid-sparing effect could not be demonstrated in two trials[34,40] while, in the trial where omega-3 PUFA were administered along with probiotics and antioxidants, this was the only benefit of active treatment since similar improvements in clinical, endoscopic and histological indices in both therapeutic arms were found[47]. Finally, in the cross-over study comparing fish oil capsules with sulfasalazine, the former resulted in a significant endoscopic improvement which was paradoxically associated to clinical worsening (as assessed by serum C-reactive protein, ESR and platelet count)[42].

Inactive ulcerative colitis. Four placebo-controlled RCT of parallel groups investigated the effect of omega-3 PUFA therapy for one[33,38,44] or two years[36] in patients with UC in remission (Fig. 1, Table 3). Fish oil – either liquid[33,38] or encapsulated[36] – was used in three trials, whereas in the fourth study the active treatment was a mixture of omega-3 PUFA and the omega-6 gamma-linolenic acid[44]. Olive oil[33,38], corn oil[36], and sunflower oil[44] were used as placebos in these trials. Details on the sample size, time in remission before entry, and extension of UC are summarised in Table 3.

The four trials reported on the primary end-point (i.e. relapse rate during the observation period). This ranged from 27% to 58% in the omega-3 PUFA groups, and from 28% to 55% with placebo (P=non significant in all studies)[33,36,38,44] (Table 3). Of note, in the study by Mantzaris *et al.*, a significant benefit with fish oil was found in the subgroup of patients at high risk of relapse (those with a history of more than two relapses per year) where 3/9 on fish oil relapsed, as compared to 5/7 on placebo ($P<0{\cdot}04$)[38].

Active Crohn's disease. Only two RCT were identified on the effect of omega-3 FA in active CD[45,49] (Fig. 1, Table 4). In both studies, omega-3 FA were included in complete enteral formulas to be used as supplements or total enteral nutrition.

The first trial, conducted in adult patients, assessed the effect of an enteral supplement enriched with omega-3 FA (not only EPA and DHA, but also alpha-linolenic acid), as well as L-arginine, and RNA, as adjuvant therapy of steroid treatment in active CD[45]. Control supplement was an isocaloric standard enteral formula without any of those components, and both formulas were administered for nine weeks[45].

The second trial was conducted in paediatric patients as a trial comparing two enteral formulas as primary treatment for active CD, with no other active therapy allowed, for six weeks[49]. The active formula was a polymeric diet with 1·5% of energy as omega-3 alpha-linolenic acid (with increased amounts of antioxidant vitamins C and E), whereas the control one was an isocaloric, quasi-isonitrogenous elemental diet with only 0·4% of energy as alpha linolenic acid[49]. Details on the sample size, severity, and extension of CD in these trials are shown in Table 4.

Table 1. Methodological quality of included studies

Study	Adequacy of randomisation and allocation concealment	Blinding	Follow-up and adherence	Intention-to-treat analysis	Other possible biases	Oxford quality score[17]
Aslan 1992[32]	Adequate randomisation Unclear allocation concealment	Adequate	35 % drop-out rate Adherence not reported	no	-	5
Stenson 1992[34]	Not described	Adequate	21 % drop-out rate 1 (4 %) non-adherent patient	no	-	4
Stack 1997 (abs)[40]	Not described	Not described	20 % drop-out rate Adherence not reported	yes (but not reported)	-	3
Almallah 1998[41]	Both adequate	Not described	No drop-outs Adherence not reported	yes	-	3
Dichi 2000[42]	Not described	Unblinded (except for endoscopist and pathologist)	10 % drop-outs Adherence not reported	no	-	2
Varghese 2000 (abs)[43]	Not described	Not described	Not reported	unknown	-	2
Seidner 2005[47]	Both adequate	Not described	29 % drop-out rate Similar adherence in completers	yes	Significantly more drop-outs in the active group Other potentially active ingredients (prebiotics, antioxidants) in the active group Significantly higher baseline clinical activity index in the active group	4
Hawthorne 1992[33]	Both adequate	Patients unblinded because of the taste of fish oil	9 % drop-out rate Adherence reported and similar in both groups	no	-	3
Loeschke 1996[36]	Both adequate	Adequate	27 % drop-out rate Adherence data partially reported	yes	-	5
Mantzaris 1996[38]	Not described	Not described	20 % drop-out rate Adherence not reported	no	-	2
Middleton 2002[44]	Not described	Not described	46 % drop-out rate Adherence not reported	no	GLA* associated to omega-3 PUFA capsules Higher drop-out rate in active group	3
Nielsen 2005[45]	Both adequate	Not described	No reported drop-outs Adherence not reported	yes	Active supplement also containing significant amounts of L-Arginine, and RNA	3
Grogan 2011[49]	Both adequate	Adequate	17 % drop-out rate Similar formula intake between groups	yes	-	5
Belluzzi 1996[35]	Not described	Adequate	9 % drop-out rate (assessed as treatment failures) Adherence not reported	no	-	3
Lorenz-Meyer 1996[37]	Both adequate	Not described	11 % drop-out rate Adherence reported	yes	-	4
Belluzzi 1997 (abs)[39]	Not described	Not described	16 % drop-out rate Adherence not reported	no	-	2

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Table 1. *Continued*

Study	Adequacy of randomisation and allocation concealment	Blinding	Follow-up and adherence	Intention-to-treat analysis	Other possible biases	Oxford quality score[17]
Romano 2005[46]	Not described	Not described	No drop-outs Adherence reported as optimal	yes	Extremely high on-year relapse rate with placebo	3
Feagan 2008 (EPIC-1 trial)[48]	Both adequate	Adequate	15 % drop-out rate > 75 % of patients with adequate adherence	yes	-	5
Feagan 2008 (EPIC-2 trial)[48]	Both adequate	Adequate	13 % drop-out rate > 75 % of patients with adequate adherence	yes	-	5

* Gamma-linolenic acid.

The primary end-point (i.e. remission rate during the observation period) was reported only in the paediatric trial. There were no differences in the remission rate between the alpha-linolenic enriched enteral feeding and control groups both on an intention-to-treat (70 *v.* 93 %) and as per protocol analysis (71 *v.* 70 %)[49]. In the adult trial, there were significant reductions in the disease activity index and serum C-reactive protein in both therapeutic groups, but again without significant between-group differences[45]. No endoscopic assessment of the effect of therapy was performed in either trial.

Inactive Crohn's disease. Six out the 19 selected RCT, investigated the effect of omega-3 PUFA in patients with CD in remission[35,37,39,46,48], two of them (EPIC-1 and EPIC-2 trials) being reported in the same article[48] (Fig. 1, Table 5). One trial was conducted in paediatric patients[46]. In five studies, omega-3 PUFA were administered to maintain medically-induced CD remission[35,37,46,48], while in the remaining one they were used to prevent postoperative recurrence of the disease[39] All studies were double-blind, placebo-controlled RCT of parallel groups with 12 months of therapy. Omega-3 PUFA were supplied as free fatty acids in enteric-coated capsules in five trials[35,39,46,48], while non-enteric coated capsules of ethyl esters were used in the remaining one[37]. Capsules of corn oil[37], olive oil[46], and medium-chain triglycerides (MCT)[35,48] were used as placebo in those studies reporting on its composition. One study (published as abstract)[39] did not report on the nature of placebo but it might conceivably be MCT as in the other trial by the same authors[35]. Details on the sample size, time in remission before entry, and location of the disease are summarised in Table 5.

All included trials reported on the primary end-point (i.e. relapse rate during the observation period). Both the study by Lorenz-Meyer *et al.*[37], and the EPIC-2 trial[48] – both including their patients immediately after drug-induced remission – failed to demonstrate any significant difference in the relapse rate between omega-3 PUFA and placebo capsules. There were divergent results in those trials including adult patients with longer-lasting remission; the positive results obtained by Belluzzi *et al.*[35], with a relapse rate of 28 % with fish oil capsules *v.* 69 % with placebo ($P<0{\cdot}001$), could not be confirmed by the much largely sized EPIC-1 trial (31·6 % relapse rate with fish oil *v.* 35·7 % with placebo)[48]. The paediatric study reported a significant benefit with fish oil, but the relapse rate with placebo was unexpectedly high (95 %)[46]. Omega-3 PUFA were unable to significantly reduce the postoperative clinical recurrence rate (8 *v.* 21 % with placebo, $P=0{\cdot}24$) in a small trial of 50 CD patients undergoing bowel resection[39].

Biological effects (UC and CD studies combined)

Some of the included trials also evaluated some biological effects of fish oil supplementation as compared to placebo in these patients. These included: (a) decreased serum concentrations of triglycerides[38,48] and total cholesterol[38]; (b) increased omega-3 PUFA and decreased arachidonic acid content in plasma lipids[36,47,49] and red blood cells[35,46]; (c)

Table 2. Characteristics and outcomes of studies in active ulcerative colitis

Study	Design	Participants	Severity of the disease	Extension of the disease	Interventions	Outcomes
Aslan 1992[32]	Double-blind, placebo-controlled, cross-over study (3 mo. treatment periods, 2 mo. wash-out period)	11 adult patients (from 17 originally randomised)	Mild/moderate	Proctitis (*n* 4) Distal UC (*n* 3) Extensive UC (*n* 4)	Fish oil capsules: 2·7 g EPA + 1·8 g DHA per day Placebo capsules: 10·3 g Oleic acid + 2·1 g Palmitic acid + 1·8 g Linoleic acid (Steroids and 5-ASA allowed if taken at stable doses for more than 4 wk. before inclusion)	56 % mean reduction in DAI* with fish oil *v.* 4 % with placebo ($P < 0·05$)
Stenson 1992[34]	Double-blind, placebo-controlled, cross-over study (4 mo. treatment periods, 1 mo. wash-out period)	18 adult patients (from 24 originally randomised)	Not reported	Not reported	Fish oil capsules: 3·2 g EPA + 2·2 g DHA per day Placebo capsules: 12·4 g Oleic acid + 2·5 g Palmitic acid + 2·2 g Linoleic acid (5-ASA allowed at maintenance dose. Steroid doses adjusted to clinical response)	Greater improvement in histology index with fish oil ($P=0·002$). No differences in clinical and endoscopic response No steroid sparing effect
Stack 1997 (abs)[40]	Double-blind, placebo-controlled, four-arm parallel groups study (4 mo. treatment period)	53 adult patients (from 66 originally randomised)	Not reported	Not reported	Omega-3: 1·5 g EPA per day Omega-6: 2·1 g GLA$ per day Omega-3 + Omega-6 Placebo: Sunflower oil (Steroid doses adjusted to clinical response)	No steroid sparing effect with Omega-3 and Omega-6 (either alone or in combination)
Almallah 1998[41]	Double-blind, placebo-controlled, two-arm parallel groups study (6 mo. treatment period)	18 adult patients	Not reported	Proctitis/Distal UC	Fish oil: 3·2 g EPA + 2·4 g DHA per day Placebo: Sunflower oil (2·6 g Oleic acid + 7·6 g Linoleic acid per day) (5-ASA allowed at maintenance doses)	Improvement in clinical score with fish oil ($p < 0·05$) but not with placebo. All patients on fish oil in remission by month 3. Lower endoscopic ($P=0·013$) and histological ($P=0·016$) scores at 6 mo. with fish oil
Dichi 2000[42]	Sulfasalazine-controlled, cross-over study (2 mo. treatment periods, 2 mo. wash-out period)	10 adult patients	Mild/moderate	Proctitis (*n* 4) Distal UC (*n* 4) Extensive UC (*n* 2)	Fish oil capsules: 3·2 g EPA + 2·2 g DHA per day Sulfasalazine: 2 g per day (No other medications allowed)	Increase in C-reactive protein, ESR and platelet count in the fish oil group. In spite of that, endoscopic score improved with fish oil.
Varghese 2000 (abs)[43]	Double-blind, placebo-controlled, two-arm parallel groups study (6 mo. treatment period)	51 adult patients (21 in the active group)	Not reported	Extensive UC	Fish oil: 5·6 g omega-3 PUFA per day Placebo: /Sunflower oil /(No other medications allowed)	Clinical ($P=0·001$) and endoscopic ($P=0·054$) improvement in the EFA group, but no quantitative data presented
Seidner 2005[47]	Double-blind, placebo-controlled, two-arm parallel groups study (6 mo. treatment period)	121 adult patients (intention-to-treat) 86 completed the study (as per protocol)	Mild/moderate	Distal UC (*n* 75) Extensive UC (*n* 46)	Active treatment: Nutritional liquid supplement with ≈2·5 g EPA and ≈1·0 g DHA per day (plus prebiotics and antioxidant micronutrients) Placebo: Liquid supplement based on sucrose alone (Steroids and 5-ASA allowed, their doses adjusted to clinical response)	Similar improvements in clinical, endoscopic and histological indices in both therapeutic arms (both in intention-to-treat, and as per protocol) Faster reduction in steroid dose with active therapy

*Composite clinical and endoscopic Disease Activity Index.

Table 3. Characteristics and outcomes of studies in inactive ulcerative colitis

Study	Design	Participants	Time in remission	Extension of the disease	Interventions	Outcomes
Hawthorne 1992[33]	Placebo-controlled, two-arm, parallel groups study (12 mo. treatment period)	96 adult patients in remission or 'going into remission' with at least 2 relapses in the previous 3 years Only 34 entered the trial in remission (outcomes refer to them)	> 4 weeks by inclusion criteria	Unknown for the subset of patients in remission	Fish oil: 20 ml/d (5·0 g EPA, 2·1 g DHA) Placebo: 20 ml/d of olive oil (5-ASA maintenance therapy allowed)	Relapse rate: 42 % with fish oil *v.* 48 % with olive oil (P=0·54) Similar time to relapse between groups.
Loeschke 1996[36]	Double-blind, placebo-controlled, two-arm parallel groups study (24 mo. treatment period)	64 adult patients in remission (*n* 55) or minimally active (*n* 9), with at least 1 relapse in the previous 2 years	< 2 years by inclusion criteria	Proctitis (*n* 15) Distal UC (*n* 29) Extensive UC (*n* 17) Partial colectomy (*n* 3)	Fish oil capsules: 5·1 g omega-3 PUFA per day Placebo capsules: Corn oil (5-ASA therapy withdrawn after 3 mo.)	58 % relapse rate with fish oil *v.* 55 % with placebo (P=N.S.)
Mantzaris 1996[38]	Placebo-controlled, two-arm parallel groups study (12 mo. treatment period)	50 adult patients in remission. 10 early drop-outs (outcomes from the 40 remaining patients)	2 to 8 months	Proctosigmoiditis (*n* 11) Distal UC (*n* 16) Extensive UC (*n* 13)	Fish oil: 20 ml/day (3·2 g EPA + 2·2 g) Placebo: 20 ml/day olive oil (All patients received 3·6 g 5-ASA per day)	27 % relapse rate with fish oil *v.* 28 % with placebo (P=N.S.), but significantly lower relapse rate in the subgroup with more than 2 relapses/year in the past.
Middleton 2002[44]	Double-blind, placebo-controlled, two-arm, parallel groups study (12 mo. treatment period)	63 adult patients in remission. 5 early drop-outs (outcomes from the 58 remaining patients)	Not described	Proctitis (*n* 25) Distal UC (*n* 25) Extensive UC (*n* 8)	EFA capsules: 1·62 g GLA*, 0·27 g EPA, 0·05 g DHA per day Placebo capsules: Sunflower oil (All patients were on 5-ASA therapy throughout the study. 16 patients on tapering steroid therapy at entry)	55 % relapse rate EFA *v.* 38 % with placebo (P=N.S.)

* Gamma-linolenic acid.

Table 4. Characteristics and outcomes of studies in active Crohn's disease

Study	Design	Participants	Severity of the disease	Location of the disease	Interventions	Outcomes
Nielsen 2005[45]	Double-blind, controlled, two-arm, parallel groups study (9 wk. treatment period)	31 adult patients	Mild/moderate, as assessed by a CDAI* between 150 and 450	Ileal (*n* 11) Ileo-colonic (*n* 3) Colonic (*n* 17)	Active formula: Nutritional supplement enriched with 3·0 g omega-3 FA (EPA, DHA, ALA$), 11·4 g L-Arginine, and 1·2 g RNA per day Control formula: Nutritional supplement with 7·8 g Linoleic acid (omega-6 FA) per day (All patients received systemic steroid therapy)	Significant decreases in CDAI and C-reactive protein in active and control groups (no differences between groups)
Grogan 2011[49]	Double-blind, controlled, two-arm, parallel groups study (6 wk. treatment period) of enteral feeding as primary treatment	41 newly diagnosed paediatric patients	Moderate/severe as assessed by PCDAI‡	All patients with ileo-colonic involvement	Active formula: Polymeric diet with 1·5 % of energy as omega-3 FA (ALA) and 3 % as omega-6 FA (linoleic acid) Control formula: Elemental diet with 0·4 % of energy as omega-3 FA (ALA) and 5·4 % as omega-6 FA (linoleic acid) (No other active therapy for CD allowed)	Intention-to-treat: 71 % remission rate with active *v.* 70 % with control formula (*P*=N.S.) Intention-to-treat: 79 % remission rate with active *v.* 93 % with control formula (*P*=N.S.)

* Crohn's Disease Activity Index.
$ Alpha-linolenic acid.
‡ Paediatric Crohn's Disease Activity Index.

Table 5. Characteristics and outcomes of studies in inactive Crohn's disease

Study	Design	Participants	Time in remission	Location of the disease	Interventions	Outcomes
Belluzzi 1996[35]	Double-blind, placebo-controlled, two-arm, parallel groups study (12 mo. treatment period)	78 adult patients in remission (CDAI* < 150)	Between 3 and 23 mo.	Ileal (*n* 40) Ileo-colonic (*n* 29) Colonic (*n* 9)	Fish oil capsules: Enteric coated capsules with 1·8 g EPA and 0·9 g DHA per day Placebo capsules: Enteric coated MCT capsules with 2·7 g caprylic and 1·8 capric acid per day (No other medication allowed)	28 % relapse rate with fish oil *v.* 69 % with placebo ($P<0·001$)
Lorenz-Meyer 1996[37]	Double-blind, placebo-controlled, two-arm, parallel groups study (12 mo. treatment period)	135 adult patients in remission (CDAI < 150)	Patients were included immediately after reaching remission with steroids	Ileal (*n* 20) Ileo-colonic (*n* 87) Colonic (*n* 26) Unknown (*n* 2)	Fish oil capsules: Omega-3 PUFA (3·3 g EPA and 1·8 g DHA per day) as ethyl esters Placebo capsules: Corn oil (All patients on a high-fibre, low-arachidonic acid diet. Tapering dose of steroids during the first 3 mo.)	57 % relapse rate with fish oil *v.* 55 % with placebo ($P < 0·84$)
Belluzzi 1997 (abs)[39]	Double-blind, placebo-controlled, two-arm, parallel groups study (12 mo. treatment period)	50 adult patients in remission	Patients included one month after bowel resection	Not described	Fish oil capsules: Enteric coated capsules with 1·8 g EPA and 0·9 g DHA per day Placebo capsules: Not described (No other medication allowed)	8 % clinical recurrence rate with fish oil *v.* 21 % with placebo ($P=0·24$)
Romano 2005[46]	Double-blind, placebo-controlled, two-arm, parallel groups study (12 mo. treatment period)	38 paediatric patients in remission (PCDAI$ < 20)	> 2 mo. by inclusion criteria	Ileal (*n* 17) Ileo-colonic (*n* 14) Colonic (*n* 7)	Fish oil capsules: Enteric coated capsules with 1·2 g EPA and 0·6 g DHA per day Placebo capsules: Olive oil (Both groups on 5-ASA therapy)	61 % relapse rate with fish oil *v.* 95 % with placebo ($P=0·0016$)
Feagan 2008 (EPIC-1 trial)[48]	Double-blind, placebo-controlled, two-arm, parallel groups study (52 wk. treatment period)	363 adult patients in remission (CDAI < 150)	> 3 mo. by inclusion criteria	Not reported	Fish oil capsules: Enteric coated capsules with 2·0–2·4 g EPA and 0·6–1·0 g DHA per day Placebo capsules: Enteric coated capsules with MCT (4 g/d) (No other medication allowed)	31·6 % relapse rate with fish oil *v.* 35·7 % with placebo ($P=0·30$)
Feagan 2008 (EPIC-2 trial)[48]	Double-blind, placebo-controlled, two-arm, parallel groups study (58 wk. treatment period)	375 adult patients in remission (CDAI < 150)	Patients were included immediately after reaching remission with either prednisone or budesonide	Not reported	Fish oil capsules: Enteric coated capsules with 2·0-2·4 g EPA and 0·6-1·0 g DHA per day Placebo capsules: Enteric coated capsules with MCT (4 g/d) (All patients on tapering dose of steroids during the first 8 wk.)	47·8 % relapse rate with fish oil *v.* 48·8 % with placebo ($P=0·48$)

$Paediatric Crohn's Disease Activity Index.
* Crohn's Disease Activity Index.

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increased incorporation of EPA into the rectal mucosa[33]; (d) attenuated proinflammatory eicosanoid profile in stimulated blood neutrophils[33], rectal dialysate[34], and urine[36]; and (e) reductions of circulating CD16 + and CD56 + cells, and the cytotoxic activity of NK cells[41]. One study could not demonstrate a greater reduction of LTB_4 in colonic tissue with fish oil as compared to placebo, in spite of a better clinical performance with the former[32].

Safety issues (UC and CD studies combined)

Safety issues are addressed in some[32,35–38,40,44,46–48] but not all papers included in the review. In general, adverse events related to treatment are scarce and mild – mostly consisting of fishy taste, dyspepsia or diarrhoea – and do not usually lead to treatment discontinuation. In the largest EPIC trials, including 370 patients in the fish oil groups, and 368 in the placebo groups, the rates of discontinuation due to adverse events were 4·86 and 3·26 %, respectively[48].

Discussion

The rationale for using omega-3 PUFA supplementation in the treatment of patients with UC or CD lies in the anti-inflammatory effects of these lipid compounds. The first evidence of the importance of dietary intake of omega-3 PUFA to attenuate intestinal inflammation was drawn from the epidemiological observation of low incidence of IBD in Eskimos[50]. Furthermore, there is strong indirect evidence supporting the potential of fish oil derived fatty acids in modulating intestinal inflammation. Omega-3 PUFA are readily incorporated to inflamed bowel mucosa[51,52] thus decreasing its content of arachidonic acid and increasing the levels of weaker proinflammatory eicosanoids[51]. On the other hand, fish oil have proven to be protective in animal models of bowel inflammation[53–56]. Finally, omega-3 PUFA depletion in IBD patients has been reported by some authors[57,58], but not confirmed in other studies[59–63].

In spite of these arguments, data collected in the present systematic review do not allow to overtly support the use of omega-3 PUFA supplementation for the treatment of both active and inactive IBD. Negative results are quite consistent in trials assessing the use of omega-3 PUFA to maintain disease remission, particularly UC[33,36,38,44], and to a lesser extent CD[35,37,39,46,48]. However, it is harder to reach any conclusion from trials evaluating the role of these lipid compounds for treating active IBD. Most trials carried-out in active UC patients included a quite small number of patients, and some of them had a cross-over design[32,34,42] which does not seem to be the better approach for a disease that exhibits a natural tendency to have a relapsing-remitting course. On the other hand, the largest sized of these trials evaluated the usefulness of omega-3 PUFA associated to prebiotics and antioxidants[47], making difficult to ascertain which of these compounds accounted for the observed therapeutic effect. Finally, only two trials evaluated omega-3 fatty acids for active CD both in the setting of total enteral nutrition; in the first one, omega-3 PUFA were administered in association with other potentially immunomodulatory compounds (i.e. L-arginine, and RNA)[45], whereas the precursor α-linolenic acid, but not their long-chain derivatives (i.e. EPA, DHA), was used in the second one[49].

Other reasons may account for the observed disappointing results. First, the doses of omega-3 PUFA used might have be too low to elicit a clinical therapeutic effect. It would be difficult to ascertain which is the optimal dose of omega-3 PUFA both in active and inactive IBD patients since, as previously mentioned, there is no agreement regarding the PUFA status in these patients[57–63]. Anyway, many studies did not monitorise either dietary omega-6 to omega-3 ratio, or plasma, red blood cell or even mucosal fatty acid profiles. Second, the different formulations used have different pharmacokinetic behaviour. Enteric-coated capsules containing free fatty acids, with a release time of one hour, appear to have a faster blood and cell fatty acid incorporation than other timed release systems or triacylglycerols[64]. Other studies have shown that EPA and DHA are better absorbed when administered as free fatty acids as compared to ethyl esters or triacylglycerols[65,66]. Finally, but not less important, the choice of placebo might have been not optimal in most trials. Some of them used placebos containing significant amounts of olive oil or oleic acid[32–34,38,46]. Oleic acid readily incorporates to intestinal mucosa[51] and exhibits immunomodulatory effects both *in vitro*[67] and *in vivo*[68]. Furthermore, olive oil has been reported to be useful in animal models of intestinal inflammation[55,69]. Other trials, including the largest EPIC trials, have used MCT as placebo[35,48]. Although traditionally considered as immunologically inert, MCT may have anti-inflammatory properties[70]. In the last years, there is growing evidence that MCT may attenuate experimental intestinal inflammation[56,71–74]. Moreover, some clinical data from patients with CD suggest that replacing part of the dietary fat with MCT may help in inducing clinical remission[30,75–77].

In summary, although the available data are in general discouraging, the present systematic review does not allow to make firm recommendations about the usefulness of omega-3 PUFA in IBD. Extra attention about the manufacturing of placebo (perhaps using edible mineral oil) should be paid in future large-sized, high quality trials.

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