THE EFFICACY OF OMEGA-3 FATTY ACID SUPPLEMENTATION IN PATIENTS WITH CROHN'S DISEASE: A SYSTEMATIC REVIEW

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Abstract

Background: Crohn's disease (CD) is one of two types of inflammatory bowel disease (IBD), a condition characterised by gastrointestinal tract inflammation that has become more common recently. For patients with IBD, nutrition plays a critical role in maintaining intestinal inflammation as the disease worsens.

Methods: This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews standards. Three databases were used for the research: PubMed, Medline, and Google Scholar. As a result, 5 randomised controlled trials (RCTs) were identified for review.

Results: After the review of the 5 RCTs regarding the use of omega-3 fatty acid intervention in patients with CD, especially focusing on the primary outcome, which was maintaining remission, the results from the 5 studies were somewhat contradictory. Nevertheless, overall, the intervention tended to have no significant effect on remission and could have other negative side effects on patients.

Conclusion: This review suggests that the use of omega-3 supplementation as an intervention for patients with CD is not very promising. More research is needed to confirm its usefulness as a long-term intervention for patients with CD, with caution to side effects.

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DOI: 10.53555/ecb/2023.12.3.228

Introduction

Crohn's disease (CD) is one of two types of inflammatory bowel disease (IBD), a disorder marked by inflammation of the gastrointestinal tract, particularly the small and/or colon. The two primary types of IBD are CD and ulcerative colitis (UC) (Limketkai et al., 2019). CD is a chronic inflammatory gastrointestinal disorder whose incidence rate has been increasing globally recently. The causes of CD are unclear, but it can be caused by several factors such as intricate interactions of altered gut microbiota, environmental circumstances, and genetic predisposition, which may cause dysregulated innate and adaptive immune responses, ultimately leading to CD (Torres et al., 2017). Most patients with CD manifest several symptoms and clinical signs, including abdominal pain, diarrhoea, exhaustion, weight loss, and malnutrition, which eventually significantly lower their quality of life. Moreover, some patients may develop disorders beyond the gastrointestinal system. They can also experience other symptoms and health issues such as anaemia;, inflammation of the skin, eyes, and joints; functional restrictions; emotional distress; unsatisfactory body image; and difficulties in sexual interactions (Varma et al., 2022).

Nutrition is crucial for patients with IBD, especially for maintaining intestinal inflammation as the illness progresses. Recent research indicates that the most effective diet for inducing remission in patients with CD is still exclusive enteral nutrition, whether in the form of polymeric, semi-elemental, or elemental formulas (Damas et al., 2019). In recent studies, many nutritional interventions such as the use of probiotics, prebiotics, or synbiotics have been tested and have attracted more attention owing to their potential usefulness for reducing the gut inflammatory response and subsequently easing the gastrointestinal symptoms in patients with IBD. Other nutritional interventions include a low-carb diet and supplementation with omega-3 polyunsaturated fatty acids or glutamine (Yamamoto et al., 2017).

Owing to its involvement in the control of immunological and inflammatory responses, long-chain dietary n-3 has been demonstrated to have anti-inflammatory qualities in many chronic inflammatory illnesses. Clinical data remain unclear despite the experimental evidence that suggests biological plausibility, particularly in CD (Scaioli et al., 2017). Polyunsaturated fatty acids have a methyl end, referred to as the omega end, and an acid end that contains a functional carboxylic acid group called omega fatty acids. The first desaturation site in omega-3 (ω-3) and omega-6 (ω-6) fatty acids is found after the third and sixth carbons from the omega end. This is where their significance lies, as the body is unable to generate most of these acids and must obtain these through diet (Tortosa-Caparrós et al., 2017). They can be found in certain foods such as flaxseed and fish, and in dietary supplements such as fish oil. Research has associated omega-3 fatty acids, specifically docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA), to numerous health benefits, including the mitigation of some chronic diseases (Armenta and Valentine, 2013).

Among the many health benefits and qualities of omega-3 acids, most are related to the prevention of certain diseases and the improvement of nutritional overall status. However, some reviews have addressed the use of omega-3 fatty acids as a dietary intervention in patients with CD to reduce the intensity of symptoms, especially during remission. In a recent review by Marton et al. (2019) on the effect of omega-3 fatty acids on IBD, the 15 reviewed papers, which included randomised controlled, cross-sectional, cohort, and case-control and experimental studies, all related to the role of omega-3 in patients with IBD, but only four of them included trials on active CD in adults. The studies included in the review presented findings that indicated improved quality of life, decreased disease activity, and maintenance of remission in adult patients with active CD. In their report, Marton et al. suggested that omega-3 supplementation can be an effective intervention for the treatment of CD on the basis of previous trials. However, it can be argued that these trials showed inconsistent results and included relatively small numbers of patients, with only up to 20 patients. In addition, they differed in the types of formulas given to patients with CD, which could significantly impact the findings.

Another systematic review by Swan and Allen (2013) focused on the use of omega-3 fatty acid supplementation for the treatment of CD. Five studies observed CD relapse rates, and three studies examined biochemical changes. They showed contradictory information regarding the efficacy of omega-3 for the treatment of CD. Some studies have shown sustained remission of the disease with omega-3 supplementation, whereas others found no correlation between omega-3 supplementation and improved remission rates. Although some results showed sustained remission in some patients, it is important to mention the limitations that led the authors to conclude that the results of omega-3 supplementation in patients with CD were not significant, such as the small number of

participants and short duration of the trials. Overall, the current literature on omega-3 supplementation for the treatment of CD is inconclusive, and the results of previous studies remain contradictory regarding the effectiveness of omega-3 supplementation for patients with CD, especially as a measure to improve symptoms in terms of maintaining remission, decreasing disease activity, the effect on pro-inflammatory cytokines, and improving quality of life. This paper presents findings from several RCTs to further discuss and investigate the effectiveness of omega-3 supplementation and the aforementioned measures for the treatment of CD in symptomatic patients, especially in maintaining remission, as evaluated using the Cronh's Disease Activity Index (CDAI), where an index level of ≤150 is defined as inactive, >150 indicates active CD, and >450 is considered severe (Freeman, 2008).

Methods

The search strategy was used on two databases: PubMed and Medline. The following keywords were used in the search: (Omega-3 Fatty Acids) OR (Fish Oil) AND (Crohn's Disease) OR (Inflammatory Bowel Disease) OR (IBD). The studies included were selected in accordance with the Preferred Reporting Items for Systematic Reviews guidelines (PRISMA, 2020), as shown in Figure 1.

The PICO model was followed in this review:

- Population: adult patients with CD
- Intervention: omega-3 fatty acid or fish oil supplementation
- Comparison: placebo
- Outcome: maintained remission

- Inclusion Criteria

1. RCTs
2. Published between 1995 and 2022
3. Adults only
4. Studies that used omega-3 or fish oil as an intervention
5. Studies written and published in English

- Exclusion Criteria:

1. Non-RCT studies
2. Published before 1995
3. Studies in children
4. Studies not in English
5. Studies in animals

Primary Outcome

The focus of this study was primarily on maintaining remission as assessed using the CDAI, which is commonly used to measure disease activity in patients with CD.

Secondary Outcomes

The secondary outcomes were improvement in quality of life as assessed using the Inflammatory Bowel Disease Questionnaire (IBDQ) and diarrhoea frequency.

Quality Assessment

The quality assessment was conducted using the modified Cochrane Collaboration tool to evaluate the risk of bias of RCTs (high, low, or unclear) on five domains (randomization process, intended intervention, missing outcome, outcome measurement and selection of results). (Sterne et al., 2019). See table1.

Table1.

Biases / Authors	Randomization process	Intended intervention	Missing outcome	Outcome measurement	Selection of results	Overall risk of bias
Feagan et al. (2008)	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wiese et al. (2011)	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Belluzzi et al. (1996)	Low risk	Some concerns	Low risk	Low risk	Low risk	Some concerns
Yasueda et al. (2016)	High risk	Some concerns	High risk	High risk	High risk	High risk

Results

From 5 RCTs published between 1995 and 2020 that investigated the effect of omega-3 supplementation as an intervention for patients with CD to maintain remission and monitor changes in CDAI scores due to the lack of recent primary research studies investigating the relationship between omega-3 supplementation and CD remission, a total of 849 patients with CD were evaluated using CDAI to measure remission

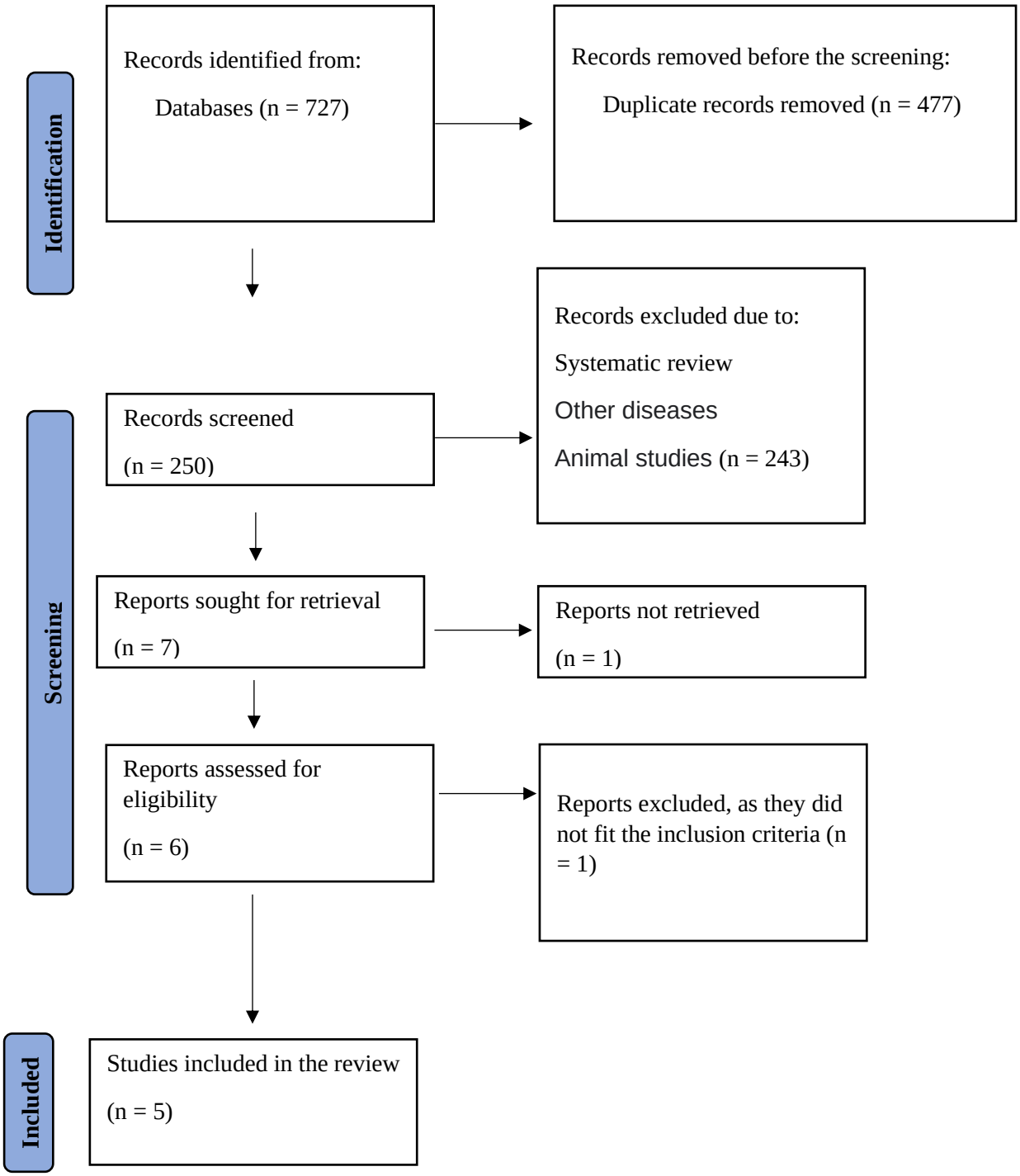
or improvement in quality of life, and the frequency of diarrhoea after receiving omega-3 supplementation, as shown in Table 2.

Table 2.

Authors	Intervention	No. of participants	Outcome	Comments
Feagan et al. (2008), EPIC1	183 patients with CD received four 1-g gelatine capsules of o-3\d for 52 weeks, and 180 patients with CD received 4 capsules of placebo\d.	363 patients with CD whose CDAI scores were <150	CDAI: $P = 0.30$	- Large number of participants - Adherence was evaluated through clinical interviews - No data for improving quality of life
Feagan et al. (2008), EPIC2	187 patients with CD received four 1-g gelatine capsules of o-3\d for 58 weeks, and 188 patients with CD received 4 capsules of placebo\d	375 patients with CD whose CDAI scores indicated active CD	CDAI: $P = 0.48$	- Large number of participants - Patients at baseline were at a high risk of relapse
Wiese et al. (2011)	For 4 months, patients were given 16 oz. of IBDNF per day (each 8 oz. contained 1.09-g EPA and 0.46-g DHA	28 patients with CD at baseline, but only 20 completed the study, with a CDAI score of >150.	CDAI: $P = 0.049$ in patients with higher EPA levels	- Blood tests were performed to measure changes - The formula was not pure fish oil but contained other nutrients such as prebiotics and antioxidants - No other control group for comparison
Belluzzi et al. (1996)	For a year, 39 patients received 3 capsules containing 1.8-g EPA and 0.9-g DHA daily 39 received 3 placebo capsules\d	78 patients with CD whose CDAI scores were <150 in the last 3 months	CDAI: Comparison between 2 intervention groups in maintaining remission after 1 year ($P = 0.003$)	- Sufficient number of participants - Old trial date - No mention of the adherence process
Yasueda et al. (2016)	100 mL o-3 formula\d for 28 days. After a 1-month washout period, patients drank two bottles of the formula every day for another 28 days 100 ml = 0.6-g EPA and 0.26-g DHA	Of 5 patients with CD, 4 started the trial with a CDAI score < 150	CDAI: No report of the score for each patient, but the median CDAI score at the baseline was 105.7, which tended to decrease to 66 at the end	- Very small number of participants - Multiple blood tests were taken to measure changes - No other control group

Key words: o-3: omega-3 fatty acid, EPA: Eicosapentaenoic acid, DHA: Docosahexaenoic acid, CDAI: Cronh's Disease Activity Index, CD: Crohn's disease, IBDNF: Inflammatory bowel disease nutrition formula. P values < 0.05 are considered significant.

Figure 1: PRISMA flowchart demonstrating the selection of articles included in the review



Primary Outcome

All 5 trials investigated the effect of omega-3 supplementation on remission in patients with CD by measuring the patients CDAI scores before and after the intervention. The multicentre, randomised, double-blind, placebo-controlled study by Feagan et al. (2008) (EPIC1) included 363 randomised patients and was conducted between January 2003 and February 2007 at 98 locations in Canada, Europe, Israel, and the United States. In the study, 183 patients with CD received four 1-g gelatine capsules of omega-3 per day, and 180 patients with CD received 4 identical-looking placebo capsules per day for 52 weeks. Compared with 75.6% of patients who received placebo, 79.2% of patients who received omega-3 free fatty acid supplementation demonstrated appropriate adherence to the study intervention. At every clinic appointment, patient adherence to the prescribed study intervention was assessed through interviews and capsule counts. The participants were considered adherent when they had taken at least

75% of the capsules during two clinic visits and had not missed taking their prescription for more than 14 days.

The findings of the study demonstrated that administration of a large dose of omega-3 free fatty acid to patients with CD did not lower their risk of relapse, as 62 patients who received placebo and 54 patients who received omega-3 free fatty acids had relapsed. The percentage of patients who were given omega-3 free fatty acids and relapsed within 360 days was 31.6%, whereas that of the patients who received placebo was 35.7% (P = 0.30).

As for the multicentre, randomised, double-blind, placebo-controlled trial by Feagan et al. (2008) (EPIC2), 375 patients with CD had a CDAI score of >150 at baseline, which indicates a high risk of relapse; 187 patients with CD received four 1-g gelatine capsules of omega-3 per day; and 188 patients with CD received 4 identical-looking placebo capsules per day for 58 weeks. The percentage of adherence was 75.4% in the omega-3 intervention group and 81.4% for the placebo group. Relapse occurred in 84 patients who received omega-3 free fatty acid treatment and in 94 patients who received placebo. The percentage of patients who were given omega-3 free fatty acids and relapsed within 360 days was 47.8%, whereas that of the patients who received placebo was 48.8% (P = 0.48).

In the RCT conducted in the United States by Wiese et al. (2011), only 20 patients completed the study with a CDAI score of >150 for all. For 4 months, the patients consumed 16 oz. of IBD nutrition formula per day, with each 8 oz. containing 1.09-g EPA and 0.46-g DHA. Blood tests were performed before and after the intervention, which revealed a reduction in arachidonic acid levels in plasma phospholipids and elevated DHA and EPA levels. Ten participants showed an increase in EPA concentration of >2% and had lower CDAI scores than those who had EPA concentrations < 2% (P = 0.0049).

In a double-blind trial for 1 year in Italy by Belluzzi et al. (1996), 39 patients received three capsules of fish oil three times a day, and 39 patients received three capsules of placebo three times a day. Three fish oil capsules contained 1.8-g EPA and 0.9-g DHA. Of the 39 patients in the fish oil group, 23 (59%) remained in remission after a year of treatment, and 11 patients relapsed (28%), compared with only 10 of the 39 patients (26%) in the placebo group remaining in remission and 27 (69%) who relapsed (P = 0.003).

As for the open-label clinical trial conducted by Yasueda et al. (2016) in Japan, patients were given only one bottle (100 ml) of the test formulation per day for 4 weeks. After a 1-month washout period, the patients received two bottles of the formula per day for another 4 weeks. The formula contained 0.6-g EPA and 0.26-g DHA per bottle (100 ml). The trial included only 6 patients with CD, but one of them withdrew from the study. The remaining five patients had a CDAI score of <150, except for one patient with a CDAI score of 324. The results regarding remission indicated that all patients in remission at baseline remained in remission, and the CDAI score tended to decrease after consuming only one bottle in the first 4 weeks (median, 61.5) compared with consuming two bottles after a 1-month washout period (median, 66).

Secondary Outcomes

- Improvement in quality of life

The IBDQ includes 32 multiple-choice questions designed to evaluate the quality of life of patients with IBD. A score of <170 is considered a low quality of life, and it was only carried out in the study by Wiese et al. (2011).

The participants had a low quality of life at baseline. After 4 months of intervention, the patients with EPA concentrations of >2% had higher IBDQ scores than those with EPA concentrations of <2% (P = 0.001).

- Frequency of Diarrhoea

Feagan et al. (2008) (EPIC1) provided information about the incidence of diarrhoea but without any further details regarding its frequency. Diarrhoea was reported in 35 (18.7%) of the 183 patients with CD who received omega-3 supplementation and in 21 (11.4%) of the 180 patients with CD who received placebo.

While 44 (23.3%) of the 187 patients who received omega-3 supplementations in the study by Feagan et al. (2008) (EPIC2) reported diarrhoea, 37 (19.7%) of the 188 patients who received placebo had diarrhoea.

Belluzzi et al. (1996) measured the frequency of diarrhoea if more than 4 liquid stools were passed per day in patients who relapsed in the two groups. Of the 11 patients who had a relapse in the fish oil group, 10 experienced diarrhoea (91%). Four of the 39 patients in the fish oil group withdrew from the study because of diarrhoea, whereas 1 patient in the placebo group withdraw from the study because of diarrhoea. Among the 27 patients who had a relapse, 23 experienced diarrhoea (85%). Yasueda et al. (2016) reported that few patients experienced diarrhoea but provided no exact data.

Discussion

With the growing interest in the different types of nutritional intervention for CD, this review examined the possibility of using omega-3 fatty acid supplementation to improve the nutritional and pathogenic statuses of patients with CD, especially in maintaining remission and improving their quality of life. The primary focus of this study was to determine whether omega-3 intervention can help patients with CD remain in remission. The results of the five studies provided valuable insights into the use of omega-3 fatty acid supplementation in patients with CD. Each study offers unique findings and considerations that contribute to our understanding of the potential benefits and limitations of omega-3 supplementation in patients with CD.

In the study by Feagan et al. (2008) (EPIC1 and EPIC2), the purpose was to investigate whether high-dose omega-3 free fatty acid supplementation could sustain remission in patients with CD, offering a safe and affordable therapeutic option. The EPIC1 trial did not find a significant difference in relapse rate between the substantial omega-3 intervention and placebo groups, which suggests that omega-3 supplementation did not provide a substantial protective effect against relapse. In the EPIC2 study, which included patients with CD at high risk of relapse (CDAI score > 150) despite the longer intervention period of 58 weeks, the results were in accordance with those of EPIC1, with no statistically significant difference in relapse rate between the omega-3 and placebo groups. The adherence rates were comparable, emphasising the challenges of achieving meaningful clinical outcomes with omega-3 supplementation in this context. In the United States, Wiese et al. (2011) conducted a RCT with a smaller sample size of 20 people who consumed an IBD nutrition formula high in EPA and DHA. Significant decreases in arachidonic acid levels and increases in EPA and DHA levels were observed in the study. However, given the small sample size, how these alterations affect disease relapse and their clinical importance are still unclear, considering that the formula used in this intervention contained many nutrients and did not depend exclusively on omega-3 fatty acids. A year-long double-blind trial conducted in Italy by Belluzzi et al. (1996) compared fish oil supplementation with placebo. When compared with the placebo group, the fish oil group showed a noticeably lower rate of relapse. These results raise the possibility that fish oil supplementation helps keep patients with CD in remission. However, while compliance was assessed on the basis of pill counts, this may not fully capture the variations in the actual intake of capsules, potentially affecting the accuracy of the results.

Despite having a small sample size, the open-label clinical research by Yasueda et al. (2016) in Japan provides information about the effects of short-term omega-3 supplementation. After taking one bottle of the omega-3 formulation, a decrease in CDAI score was detected, which indicates a possible quick-acting effect on disease activity. However, careful interpretation is required because of the short study period and small number of participants. The findings of all trials point to the complexity of CD and the variation in patient responses to omega-3 supplementation by showing a general tendency towards non-significant differences in relapse rates between the omega-3 and placebo groups.

Each study had a different adherence rate, which might have had an impact on the results. It is important to take adherence patterns into account when evaluating results, as demonstrated by the stronger adherence to the placebo in the study of Feagan et al. (2008) (EPIC2). In addition, the observed discrepancies in the results could be explained by differences in study designs, including differences in the duration and formulation of the intervention. For example, the longer intervention period in EPIC2 did not produce outcomes different from those in EPIC1, indicating that longer intervention periods would not always result in more benefits. The improvement in quality of life after omega-3 intervention was only measured in the trial by Wiese et al. (2011). The researchers found that higher EPA concentrations (>2%) might correlate with better IBDQ scores (P = 0.001), which may indicate a connection between the improved quality of life and biochemical changes induced by omega-3 supplementation. As for the side effects of this intervention, one focus was on the frequency of diarrhoea in the participants.

In both the EPIC1 and EPIC2 studies by Feagan et al., the reported incidence of diarrhoea was an essential indicator of disease activity and treatment response. In EPIC1, 18.7% of patients who received omega-3 supplementation experienced diarrhoea compared with 11.4% of the patients in the placebo group. Similarly, in EPIC2, 23.3% of patients who received omega-3 supplementation reported diarrhoea, whereas the placebo group had a slightly lower incidence of 19.7%. While these differences did not reach statistical significance, they suggest a trend towards a higher frequency of diarrhoea in the omega-3 groups. However, the precise nature of the diarrhoea, whether in terms of severity or duration, would be valuable information

if mentioned in detail in both trials. Belluzzi et al. (1996) provided valuable insights into the relationship between fish oil supplementation, relapse, and diarrhoea. The higher incidence of diarrhoea (91%) among those who experienced relapse in the fish oil group is noteworthy. In addition, the withdrawal of some participants from the fish oil group due to diarrhoea (4 of 39) highlights the clinical relevance of this side effect. By contrast, the placebo group had a lower incidence of diarrhoea among those who relapsed (85%), and only one participant withdrew from the study because of diarrhoea. This raises questions about the tolerability and potential gastrointestinal side effects associated with fish oil supplementation. The consistency in reporting diarrhoea as an adverse event across multiple studies shows its relevance as a possible side effect associated with omega-3 supplementation and emerges as a notable consideration in the evaluation of omega-3 supplementation in CD patients. Marton et al. claims that omega-3 supplements intervention on CD patients can decrease disease activity and increase the quality of life for the patients. However, there is many limitations to his findings such as the small numbers of participants in the papers he reviewed, the components of the dietary intervention and duration of the trials. These can result in different outcomes in each trial, it also complies with the trials reviewed in this systematic review.

Conclusion

In light of the comprehensive review of the available studies on omega-3 fatty acid supplementation in patients with CD, it is more likely that the current body of evidence does not support the significant efficacy of this intervention in maintaining remission or improving clinical outcomes, particularly the rates of relapse, consistently showing non-significant differences between the patients with CD who received omega-3 supplementation and those who received placebo. The EPIC1 and EPIC2 trials by Feagan et al. (2008), which was comprised of substantial patient populations, failed to demonstrate a clear protective effect of omega-3 against disease relapse. The absence of a significant impact on relapse rates was further emphasised by the findings of the trial by Wiese et al. (2011), although with a smaller sample size. Moreover, the observed trends in the incidence of diarrhoea across multiple studies add an additional layer of concern. Although not reaching statistical significance, the higher frequency of diarrhoea in the patients with CD who received omega-3 supplementation raises questions about the tolerability and potential adverse effects associated with this intervention. In light of these findings, health practitioners may need to exercise caution when considering omega-3 fatty acid supplementation as a possible intervention for patients with CD. The current evidence base does not offer a compelling case for its inclusion in standard treatment regimens. Instead, resources and efforts might be better directed towards exploring alternative therapeutic options or refining existing strategies that have demonstrated more consistent and clinically meaningful outcomes. Future research should explore whether specific subgroups of patients with CD, based on disease characteristics or biomarker profiles, could benefit more from omega-3 supplementation. While the idea of using omega-3 fatty acids in the management of CD holds promise, the current evidence suggests that caution is warranted. Health practitioners and researchers should carefully weigh the limited and non-significant benefits against potential risks and consider alternative strategies until more robust and conclusive evidence emerges from well-designed studies. More research is needed in this area, especially long-term trials, to better understand the potential adverse effects associated with omega-3 use in CD patients.

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