

Diet and Gut Inflammation: The Effect of Diet on Inflammatory Markers in Inflammatory Bowel Disease – A Scoping Review

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ABSTRACT

Background & Aims: Inflammatory bowel disease (IBD) is a chronic inflammatory disorder of the gastrointestinal tract. Studies evaluated the effect of several diets on inflammatory markers in IBD patients. Nevertheless, the results have been inconsistent. Therefore, we conducted this review to evaluate the effectiveness of dietary interventions on inflammatory markers in IBD.

Methods: A comprehensive electronic literature search strategy using the PubMed, Embase, and Scopus was conducted in March 2023 and evaluated inflammatory markers included C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin (FC), as well as disease severity scores. We included full-text articles that met our inclusion and exclusion criteria. To evaluate the included studies, we used the NHLBI quality evaluation tools.

Results: A total of 16 studies were included in our qualitative synthesis. Elemental and polymeric diets showed similar efficacy in reducing Crohn's disease activity index (CDAI) and CRP levels. On the other hand, most studies evaluating the effects of omega 3 fatty acids reported no significant improvement. Moreover, protein supplementation was not seen to improve ESR or CRP levels. Except for improvements in FC levels with IgG4-guided exclusion diet in CD patients with elevated CDAI levels, restrictive diets were successful in controlling functional abdominal symptoms but did not appear to have an impact on inflammation in most studies. Furthermore, disease severity scores, CRP, ESR, and FC levels did not significantly change when eating a high-fiber, low-refined-carb, low-fat diet.

Conclusions: Diet plays a vital role in managing IBD by impacting the inflammatory response. Among the interventions studied, enteral nutrition showed the most promising results, improving patients' inflammatory status. Restrictive diets effectively managed symptoms and clinical remission but had limited impact on inflammatory markers. Supplementing the diet with fatty acids, omega 3, or proteins did not definitively improve patients' condition or inflammation.

Key words: inflammatory bowel disease – anti-inflammatory diet – C-reactive protein – erythrocyte sedimentation rate – fecal calprotectin.

Abbreviations: CD: Crohn's disease; CDAI: CD activity index; CDAS: CD activity score; CRP: C-reactive protein; CT: computed tomography; ED: elemental diet; ESD: erythrocyte sedimentation rate; FC: fecal calprotectin; FODMAP: low low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet; IBD: inflammatory bowel disease; iSAD: improved standard American diet; MD: Mediterranean diet; MRI: magnetic resonance imaging; PD: polymeric diet; SCD: specific carbohydrate diets; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic and recurrent inflammatory disorder affecting the gastrointestinal tract, which encompasses both Crohn's disease (CD) and ulcerative colitis (UC), with different

pathology and clinical features. Despite the extensive research conducted on IBD, its etiology and pathogenesis are not yet completely understood. However, it is generally accepted that the development of IBD involves the interplay of genetic and environmental factors [1]. Dietary factors have been identified as a potential risk factor for developing IBD. Several epidemiological studies have demonstrated that a diet rich in fruits and vegetables and low in animal fats and sugars could potentially decrease the incidence of IBD [2]. The underlying

hypothesis is that reduced consumption of microbiota-accessible carbohydrates, such as fiber, may adversely affect the gut microbiota and host, leading to dysbiosis and a proinflammatory state.

Evidence is increasing that specific enteral regimens may be therapeutically beneficial for CD [1]. There are also indications that diet may contribute to the initial development of IBD. However, due to a lack of robust studies, there are few clear recommendations for nutrition care in IBD, and many of the following conclusions are the authors' opinions based on their interpretation of the literature and experience in patient care.

While the exact contribution of diet in the development of IBD remains uncertain, epidemiological evidence suggests that the increasing incidence of this condition is, in part, influenced by changes in dietary patterns. Specifically, a shift away from a primitive, „aboriginal” diet towards a more refined and processed „Western” diet appears to be a contributing factor [3]. Despite significant advances in the understanding of IBD pathogenesis and the development of novel therapies, its management remains challenging. The current standard of care for IBD includes the use of immunosuppressive and biological therapy, but these treatments are not always effective and are associated with significant side effects and risks. Therefore, there is growing interest in the role of dietary interventions in the management of IBD.

This article aims to review the current evidence on the effectiveness and safety of dietary interventions in IBD, with a particular focus on their impact on inflammatory markers. We will discuss the results of recent studies investigating the effects of specific carbohydrate diets (SCD), low low-fermentable oligosaccharides, disaccharides, monosaccharides, and polyols diet (FODMAP), enteral nutrition (EN), fiber supplementation, and protein intake modulation on inflammatory markers in patients with IBD.

METHODS

This scoping review was written according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement [4].

Data Sources and Search Strategy

A comprehensive computerized literature search strategy, having used the electronic database search engines PubMed, Embase and Scopus was conducted on the 29th of March 2023. The search strategy applied for PubMed was as follows: ((„Diet”[Mesh]) OR („Diet”[All Fields]) OR („Immunonutrition Diet”[Mesh]) OR („Immunonutrition Diet”[All Fields])) AND ((„Inflammatory Bowel Diseases”[Mesh]) OR („Inflammatory Bowel Diseases”[All Fields])) AND ((„Randomized Controlled Trial” [Publication Type])) AND ((„Leukocyte L1 Antigen Complex”[Mesh]) OR („Leukocyte L1 Antigen Complex”[All Fields]) OR („C-Reactive Protein”[Mesh]) OR („C-Reactive Protein”[All Fields]) OR („Blood Sedimentation”[Mesh]) OR („Blood Sedimentation”[All Fields])), for Embase was (Diet/exp OR ,Diet’ OR ,Immunonutrition Diet’/exp OR ,Immunonutrition Diet’) AND (Inflammatory Bowel Diseases’/exp OR ,Inflammatory Bowel Diseases’) AND (Randomized Controlled Trial’) AND (Leukocyte L1 Antigen Complex’/exp

OR, Leukocyte L1 Antigen Complex’ OR, C-Reactive Protein’/exp OR, C-Reactive Protein’ OR, Blood Sedimentation’/exp OR ,Blood Sedimentation’) and the following search string for Scopus ((„Diet”[Mesh]) OR („Diet”[All Fields]) OR („Immunonutrition Diet”[Mesh]) OR („Immunonutrition Diet”[All Fields])) AND ((„Inflammatory Bowel Diseases”[Mesh]) OR („Inflammatory Bowel Diseases”[All Fields])) AND ((„Randomized Controlled Trial” [Publication Type])) AND ((„Leukocyte L1 Antigen Complex”[Mesh]) OR („Leukocyte L1 Antigen Complex”[All Fields]) OR („C-Reactive Protein”[Mesh]) OR („C-Reactive Protein”[All Fields]) OR („Blood Sedimentation”[Mesh]) OR („Blood Sedimentation”[All Fields])). A similar search was used for the other two electronic databases. To minimize result bias, the reference lists of relevant articles were manually searched to identify any missed publications. We included full articles that satisfied the inclusion and exclusion criteria.

Study Selection and Eligibility Criteria

Original articles were included in the qualitative assessment and scoping review if they met the following inclusion criteria: (1) interventional and observational studies; (2) IBD confirmed according to each study criteria based on one of the following methods: endoscopic procedures biopsy, capsule endoscopy, imaging techniques such as computed tomography (CT), magnetic resonance imaging (MRI), validated markers, or codes such as International Classification of Diseases (ICD); (3) studies that objectively evaluate the effect of diet on the inflammatory status, using markers such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), fecal calprotectin (FC), and disease severity scores; (4) studies conducted on humans only.

Exclusion criteria included the following: (1) studies published in languages other than English, German, French and Romanian; and (2) case reports, reviews, practice guidelines, commentaries, opinions, letters, editorials, short surveys, articles in press, conference abstracts, conference papers, and abstracts published without a full article.

Two investigators (C.M.S. and C.S.) separately conducted a screening evaluation based on the aforementioned eligibility requirements by carefully reading titles and abstracts and rejecting any papers that seemed to be irrelevant. The whole text of a few carefully chosen articles that met the inclusion and exclusion requirements was then carefully examined for further evaluation. Discussion was held to resolve any disagreements regarding study eligibility, and a consensus was eventually established.

Data Extraction

We extracted the following information from eligible studies: author's name, publication year, study location, study population, the source of cohort, sample size, mean age, diet type, duration, outcome. The data was extracted by two investigators (C.M.S. and C.S.) using an electronic spreadsheet and reviewed by another investigator (A.I.) for accuracy. Any discrepancies were resolved through discussion. The extracted data was entered into tables and presented in the manuscript text.

Quality Assessment

To assess bias risk and internal validity in individual studies similarly, two researchers (C.M.S. and C.S.) used

the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tools according to the study design to independently carry out the quality evaluation for included studies. Answers to the questions on the evaluation assessment tool included „yes,” „no,” „not applicable,” „cannot determine,” or „not reported.” Discussion was used to resolve any differences between the two investigators’ outcomes of the quality assessment evaluation. The findings of the methodological quality evaluation had no bearing on the studies’ eligibility.

RESULTS

Literature Search

The literature search identified 31, 142 and 438 records on PubMed, Embase and Scopus, respectively. Following the removal of 64 duplicates, we obtained a total of 547 records that were carefully reviewed through the assessment of the titles and abstracts, of which a total of 495 records were excluded due to the following reasons: irrelevant studies (n=391), reviews (n=35), letters, editorials, conference abstract (n=44), book chapters (n=20), languages (n=5). The eligibility of the remaining 49 articles according to the inclusion and exclusion criteria was evaluated through assessing the full text, of which seven records were excluded due to the following: abstracts without full text (n=8), pediatrics (n=6), no matching diet (n=19). Hence, a total of 16 articles fulfilled our criteria and were included in our scoping review as outlined in Fig. 1.

Quality Assessment

We used the NHLBI quality assessment tools to evaluate the methodological quality of eligible studies included in our qualitative synthesis as demonstrated in Supplementary file (Tables I and II). A total of eight studies had an overall rating of “good” [5-12] six studies were rated “fair” [13-18], and three studies were rated “poor” [19-21].

Generally, all included studies clearly stated a research question or objective. The study population was specified and defined in all studies. There was a high adherence to the intervention and no study had an overall drop-out rate greater than 20% at endpoint. The studies evaluated as “good” showed an improvement of the clinical result and the inflammatory status in enteral, exclusion diets and diets high in fiber [6, 9, 10, 12], but not after the diet supplemented with fish oil, omega 3 or proteins [5, 7, 8, 11].

Included Studies

The main characteristics of the total included studies are summarized in Supplementary file (Table III). Moreover, Table I summarizes the different evaluated diets and their effects on inflammatory makers in IBD patients. A total of approximately 1,000 subjects were included in this review with a follow-up period ranging from 9 days to 54 months in the included studies. We evaluated enteral nutrition (n=4), protein supplementation (n=2), omega 3, fish oil supplementation (n=2), fiber diets (n=3), and restrictive diets (n=6). Eight studies were conducted in Europe (UK n=4, Italy n=2, Germany n=1, Denmark n=1), three studies in Asia (Japan

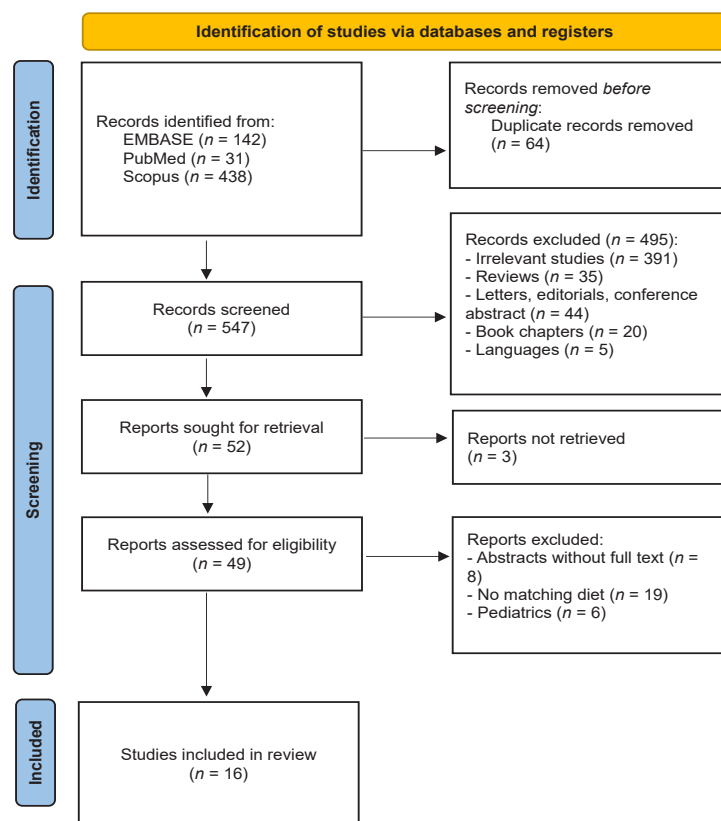


Fig. 1. PRISMA flow diagram for the identification, screening, and inclusion phases of our systematic review.

Table I. Summary of the different evaluated diets and their effects on inflammatory makers in IBD patients

Diet type	Country	Study population	Evidence of association	Observation
Enteral	Zoli, 1997 Italy [13]	22 patients	+	The diet group showed a significant improvement in CDAS and ESR after 2 weeks of treatment.
	Verma, 2000 UK [6]	21 patients	+	Demonstrated a significant decrease of CRP levels after elemental diet.
	Sakurai, 2002 Japan [20]	36 patients	+	Short-term treatment with enteral nutrition induced clinical remission and normalized CRP levels in about two-thirds of patients.
	Bamba, 2003 Japan [21]	36 patients	-	The CRP levels in the enteral low-fat group decreased (non-significant level) after one week.
Protein supplementation	Machado, 2015 Brazil [9]	68 patients	-	No significant differences were observed in terms of CRP or CDAI before, during, or after the protein supplementation.
	Zhao, 2022 China [18]	28 patients	-	There was no significant change observed for ESR and CRP after 4 and 8 weeks of intervention.
Omega 3 & fish oil	Barbosa, 2003 Brazil [7]	9 patients	+	Noticed a significant decrease in ESR compared to initial values without endoscopic or histological improvement.
	Treble, 2005 USA [8]	61 patients	-	There were no significant differences in the response of absolute values for CDAI, CRP or ESR to fish oil plus antioxidants and placebo at 24 weeks.
Fiber diets	Jones, 1985 UK [19]	20 patients	+	Dietary manipulation showed significant reduction in ESR levels among CD patients in remission for 6 months.
	Brotherton, 2014 USA [14]	22 patients	-	There were no statistically significant differences between groups in either CRP or ESR at week four.
	Fritsch, 2021 USA [12]	17 patients	-	FC and CRP decreased during treatment, but not significantly.
Restrictive Diets	Gunasekera, 2016 UK [10]	98 patients	+	A significant reduction in FC levels in the diet group was seen only in a subset analysis of patients with CDAI greater than 150 compared to the control group.
	Cox, 2017 UK [11]	32 patients	-	Fermentable carbohydrates diet was associated with no significant difference in CRP between the start and end of the intervention, and increased FC levels in CD patients.
	Pedersen, 2017 Denmark [15]	89 patients	-	There was no significant difference observed in mean CRP and FC levels between the LFD group at 6 weeks and at 0 weeks.
	Bodini, 2019 Italy [16]	55 patients	+	Following the intervention, low-fat diet group showed a significant decrease in median FC values.
	Lewis, 2021 USA [2]	191 patients	+	The SCD group, not the Mediterranean diet group, was associated with a significant reduction in FC concentration. However, there was no significant difference in CRP levels and clinical or symptomatic remission between both groups.

n=2, China n=1), three studies in North America (USA n=3) and two studies in South America (Brazil n=2).

Enteral Diet

In a randomized controlled study comparing elemental diet (ED) and steroid treatment in CD, Zoli et al. [13] observed that the diet group showed a significant improvement in CD activity score (CDAS) and ESR after two weeks of ED ($p < 0.01$). It was concluded that the elemental diet was equally effective as steroids in inducing remission, and both treatment groups exhibited a significant improvement in disease activity.

Verma et al. [6] found in a randomized, double-blind trial that 80% of patients in the ED group and 55% of patients in the polymeric diet (PD) group achieved clinical remission, but this difference was not statistically significant with a p -value of 0.1. During the 4-week enteral nutrition study, both the ED and PD groups showed similar reductions in CD activity index (CDAI) and CRP levels. Specifically, the CDAI levels decreased significantly from pre-trial levels of 359 ± 67 to

112 ± 19 ($p \leq 0.0002$) for the ED group and 303 ± 27 to 97 ± 11 ($p \leq 0.0005$) for the PD group. Similarly, CRP levels decreased from pre-trial levels of 16 ± 5 to 4 ± 1.6 ($p < 0.1$) for the ED group and from 62 ± 20 to 9 ± 6 ($p < 0.04$) for the PD group [6].

Sakurai et al. [20] analyzed Elental (Synthetic amino acids, Dextrin, Soy oil) (ED) and Twinline (Milk protein hydrolysates, amino acids, oligopeptide, polypeptide Dextrin, Tricaprilin and sunflower oils) on 36 patients with CD [20]. After 6 weeks of therapy, the high CDAI levels in both groups were significantly reduced to 102 and 82, respectively. The therapy also normalized CRP levels, and there was no significant difference observed between the two groups. Moreover, therapy improved ESR, which became nearly normal at 6 weeks.

Bamba et al. [21] studied low-fat, medium-fat, and high-fat enteral diets. The CRP levels in the low-fat group decreased after one week and remained low throughout the study ($p = 0.254$). However, in the medium- and high-fat groups, CRP levels fluctuated during the study, and in some patients, they remained high after four weeks. Although the ESR values

decreased in most patients in the low-fat group, in many patients in the medium- and high-fat groups, they remained high or increased during the study ($p=0.243$) [21].

Protein Supplementation

Machado et al. [9] conducted a study involving 68 patients with CD patients randomly assigned into two groups: a whey protein group and a soy protein group. No significant differences were observed between the two groups in terms of albumin, pre-albumin, CRP, or CDAI before, during, or after the nutritional supplementation [9].

Zhao et al. [18] performed a randomized, double-blinded, placebo-controlled trial including IBD patients that were assigned randomly to receive either whey protein (10 g/d) or placebo (10 g/d) for 8 weeks while participating in a resistance training program (3 times a week) [18]. Hemoglobin, creatinine, ESR, C-reactive protein, and albumin were collected from venous blood after fasting for at least 8 hours. The above information was measured and collected again after 4 and 8 weeks of intervention. The authors reported that there was no significant change observed regarding ESR and CRP levels, indicating that neither intervention had an effect on these markers.

Omega 3, Fish Oil Supplementation

Barbosa et al. [7] in a randomized, crossover study, assigned patients to one of two groups: fish oil and sulfasalazine or placebo and sulfasalazine. After two months, there were no significant changes observed in any laboratory indicators, sigmoidoscopy, or histological scores, except for a decrease in ESR ($p<0.05$) compared to initial values.

Treble et al. [8] investigated high-dose fish oil in IBD relapse and inflammatory markers. At baseline, there were no significant differences between fish oil plus antioxidants and placebo groups in terms of CRP ($p=0.233$), ESR ($p=0.486$), or CDAI ($p=0.515$). Furthermore, there were no significant differences in the response of absolute values for CDAI ($p=0.459$), CRP ($p=0.994$), or ESR ($p=0.283$) to fish oil plus antioxidants and placebo at 24 weeks compared to baseline values.

Fiber Diets

In Brotherton's et al. [14] study about high-fiber and low refined carbohydrate diet including consumption of whole wheat bran cereal, systemic inflammation levels were evaluated using CRP and ESR. These markers were collected and measured at baseline and after four weeks. Analysis of covariances were performed separately for CRP and ESR results and there were no statistically significant differences between groups in either CRP ($p=0.125$) or ESR ($p=0.788$) in week four.

In another study, Fritsch et al. [12] investigated the effects of a low-fat, high-fiber diet (LFD) versus an improved standard American diet (iSAD) on quality of life, inflammation markers, and fecal markers of intestinal dysbiosis in UC patients [12]. Results showed that FC and CRP levels were low at baseline and after iSAD, but decreased further after LFD, although not significantly.

A controlled trial conducted by Jones et al. [19] involving 20 patients with CD was conducted to investigate whether an

unrefined carbohydrate fiber-rich diet or a diet that excluded specific intolerant foods could maintain remission. Of the 10 patients on the exclusion diet, 7 remained in remission for 6 months, while none of the 10 on the unrefined carbohydrate fiber-rich diet did so (p -value <0.05). The ESR was measured at relapse in the unrefined carbohydrate fiber-rich (41.3 ± 28.04 mm/h) and exclusion diet (30.8 ± 25.7 mm/h) groups. Among patients on the exclusion diet who remained in remission for 6 months, the ESR decreased from 39.7 ± 21.7 mm/h before the intervention to 16.1 ± 8.8 ($p<0.05$) at 3 months and to 16.2 ± 12.5 ($p<0.05$) at 6 months [19]. This study suggests that dietary manipulation may be a practical long-term management strategy for many patients with CD.

Restrictive Diets

Lewis et al. [17] compared the efficacy of the SCD and Mediterranean diet (MD) in treating CD with mild to moderate symptoms [17]. From screening to week 6, there was no significant change in hs-CRP concentration in either group. However, the SCD group had a significant reduction in FC concentration (median reduction, -140 $\mu\text{g/g}$; IQR, -321 to 0 $\mu\text{g/g}$; $p=0.0001$ within group, $p=0.44$ between groups), while the MD group did not. After a 12-week follow-up, there was no significant difference between the two groups in the percentage of participants who achieved symptomatic remission (42.4% with the SCD and 40.2% with the MD, $p=0.87$) or clinical remission (40.4% with the SCD and 46.7% with the MD, $p=0.28$) [17].

Cox et al. [11] aimed to investigate whether fermentable carbohydrates exacerbate functional gastrointestinal symptoms in IBD through a randomized, double-blinded, placebo-controlled, re-challenge trial. The authors found that there was no significant difference in CRP between the start and end of the intervention ($p=0.797$), but FC increased significantly between baseline and end of the intervention (29.5 $\mu\text{g/g}$ vs 72.9 $\mu\text{g/g}$, $p=0.018$). When sub-group analyses were performed individually for CD and UC, the difference in FC was significant only for CD (16.8 $\mu\text{g/g}$ vs 46.4 $\mu\text{g/g}$, $p=0.026$). However, only a small proportion of participants ($n=2$) had a FC level greater than 250 $\mu\text{g/g}$ at the end of the trial [11].

In a 6-week, randomized, open-label study, Pedersen et al. [15] evaluated the effect of FODMAP diet on IBS-like symptoms in IBD patients with quiescent or mild-to-moderate activity. At baseline and week 6, CRP levels were measured in 75 (96%) and 74 (95%) patients, respectively, with the majority having levels <10 mg/L. There was no significant difference observed in mean CRP levels between the low FODMAP diet (LFD) group at 6 weeks (2.8 ; 95% CI: 2.2 - 3.5) and at 0 weeks (2.7 ; 95% CI: 2.2 - 3.2) ($p=0.57$). Additionally, there was no significant difference in the change of CRP levels between the LFD group and the normal diet group at the end of the study with a p -value of 0.23 . Of the 73 (94%) patients who collected FC at baseline, the majority had levels <100 $\mu\text{g/g}$ (UC patients) or <200 $\mu\text{g/g}$ (CD patients). There was no significant difference in geometric mean FC between the LFD and ND groups at week 6 compared to week 0 (53 ; 95% CI: 30 - 93 vs. 65 ; 95% CI: 37 - 113 , $p=0.75$ and 46 ; 95% CI: 27 - 81 vs. 44 ; 95% CI: 23 - 83 , $p=0.46$, respectively) [15].

Bodini's et al. [16] prospective study aimed to evaluate the safety and effect of a low-fat diet on clinical and biochemical

disease activity. At the initial visit (T0), all patients underwent a complete blood examination and FC assessment and were evaluated by a gastroenterologist and a dietitian. For the entire UC patient cohort, median FC levels were significantly higher at T0 than at the end of the 6-week dietary intervention (T1: 55 mg/kg; $p=0.002$). There was no significant difference in median FC values at T0 between the low-fat diet and standard diet groups. However, after the intervention, they observed a significant decrease in median FC values in the low-fat group (T1: 50 mg/kg; $p=0.004$) but not in the SD group (T1: 87 mg/kg; p -value=0.175). Overall, median FC values decreased by 34.7% and 4.4% in the low-fat diet and standard diet groups, respectively, between T0 and T1. There was no significant difference in median CRP values between T0 and T1 for the entire cohort or between the low-fat diet and standard diet groups at either time point ($p=0.637$) [16].

Gunasekeera et al. [10] conducted a double-blinded randomized sham-controlled study to determine whether an IgG4-guided exclusion diet could improve the quality of life in patients with CD. While there was no significant difference in FC and CRP levels between the groups, a subset analysis of patients with CDAI greater than 150 showed a significant reduction in FC levels in the diet group compared to the control group.

DISCUSSION

Several studies evaluated the effects of different diets on inflammatory markers in IBD. However, these results were inconclusive with conflicting findings. Therefore, we conducted this comprehensive scoping review to evaluate the role of several diets and inflammatory markers including CRP, ESR, and FC in IBD patients. We found that EN was effective in inducing clinical remission in active CD and significantly reduced inflammatory markers. The consumption of omega 3 fatty acids has been linked to anti-inflammatory properties, but their effect on inflammatory markers in IBD patients remains inconclusive where most studies demonstrated no significant improvement. Protein supplementation was not found to be associated with improvements in ESR and CRP levels. Restrictive diets were effective in managing functional abdominal symptoms, but the effects on inflammation were not seen in most studies, except in improvements in FC levels with IgG4-guided exclusion diet in CD patients with increased CDAI levels. Moreover, high-fiber, low refined carbohydrate, low fat diet was not associated with any significant improvements in CRP, ESR, FC levels and clinical scores.

Inflammatory bowel disease includes a collection of heterogeneous conditions characterized by both acute and chronic inflammation in the small and/or large intestines. The increasing prevalence and incidence of IBD worldwide suggests that environmental factors are at least as important as genetic susceptibility in the development of this disease. Diet and the host microbiota are among the factors that may play crucial, albeit not well-defined, roles [3]. The major constituents of a standard Western diet could potentially contribute to or protect against intestinal inflammation through several mechanisms, including the effects of insulin resistance and short-chain fatty acids like butyrate, alteration of intestinal permeability,

the anti-inflammatory role of polyunsaturated fatty acids, and the influence of sulfur compounds from protein on host microbiota [22].

Over the past two decades, numerous drugs have emerged for the treatment of IBD, and a “top-down” therapeutic approach is now preferred to achieve sustained clinical remission and resection-free survival for patients with IBD [23]. However, many patients exhibit resistance to current therapies such as immunosuppressants, biologics, and corticosteroids, or experience an initial response that is not sustained. The efficacy of therapeutic agents also varies depending on whether they are administered to naive patients with newly diagnosed IBD or patients who have failed or lost response to other treatments.

Although treatments have been shown to achieve mucosal healing, improve quality of life, and avoid complications, they are associated with significant toxic effects such as infections and malignancy risks. Despite available therapeutic options, achieving sustained remission remains a clinical challenge. Furthermore, the cost of treatment, particularly in the context of a ‘top-down’ approach, may impede patients’ access to therapy in many countries where centralized funding is not available [24].

In recent decades, the public has become increasingly interested in the role of dietary structure in the pathogenesis of IBD. It is commonly believed that the composition of the diet can contribute to the development of intestinal inflammation. The nutritional status of patients with IBD is a crucial clinical concern, as it is well-established that nutritional deficiencies are associated with disease activity, location, and extent.

To the best of our knowledge, this is the first scoping review which makes a comprehensive analysis regarding the effect of the diet on the improvement of inflammation, objectified by ESR, CRP or FC. Even if various diets seem to improve the patient’s clinical condition, in terms of inflammatory markers, no significant and constant improvement was observed in all diets.

Enteral nutrition involves delivering liquid formula into the gastrointestinal tract through a feeding tube or oral consumption to provide nutrition. Initially designed for individuals unable to consume enough calories orally, specialized EN formulas now cater to specific diseases. These formulas vary in macronutrient and micronutrient composition, caloric density, and osmolarity. They are classified as standard, peptide-based, immune-modulating, disease-specific, or food-based, mainly based on their protein content [25]. The studies included in this review demonstrate the potential of EN as a valuable therapeutic intervention for CD.

Evidence from animal models and limited human studies suggests that protein intake and amino acid supplementation can modulate inflammatory responses. By providing the necessary building blocks for tissue repair and immune function, adequate protein intake may help reduce systemic inflammation in IBD patients. The specific mechanisms and optimal protein requirements for mitigating systemic inflammation in IBD are still not fully understood [26]. However, in the present analysis, Machado and Zhao’s studies [9, 18] did not show an improvement in the inflammatory status of the patients after supplementing the protein diet.

While omega-3 fatty acids have shown anti-inflammatory properties and have been beneficial in treating other inflammatory disorders, such as rheumatoid arthritis and IgA nephropathy, the results of clinical trials specifically evaluating their impact on inflammation in IBD have been inconsistent. Some studies such as the EPIC trials did not find a significant benefit in reducing relapse rates in patients with quiescent CD [27]. These findings suggest that the use of omega-3 fatty acid supplementation alone may not be sufficient in managing inflammation in IBD.

Dietary fiber is made up of carbohydrates that cannot be digested by human digestive tract enzymes and are naturally present in plants. Consumption of dietary fiber may provide a protective function [28]. Prebiotic non-digestible carbohydrates are fermented in the colon (circumventing small intestinal absorption) and aid in the maintenance of epithelial integrity, increased levels of Bacteroidetes/Firmicutes, Bifidobacteria, and Clostridium cluster IV, increased production of short-chain fatty acids such as butyrate, acetate, and propionate, and reduced levels of enteric pathogens [29]. The studies included in this review examining the relationship between fiber intake and systemic inflammation levels, as measured by CRP and ESR, have yielded conflicting results, possibly due to variations in study populations, types and amounts of fiber, and intervention durations. Genetic and environmental factors may also influence dietary response. Although segmental colitis associated with diverticulosis is considered a 'bridge' between a classical IBD and diverticular disease and is characterized by a chronic inflammation engaging the interdiverticular mucosa of the colonic segment involved [30], there is no data in the literature regarding the role of diet in improving symptoms or inflammatory markers in diverticular disease. Instead, several guidelines [31-35] recommend high diet fiber or fiber supplementation for symptomatic relief in symptomatic uncomplicated diverticular disease patients (evidence 1b) and for preventing recurrent episodes or persistent symptoms in patients with acute diverticulitis (evidence level 3), although the therapeutic benefit of this diet is conflicting. In a systematic review and a meta-analysis, Eberhardt et al. [36] concluded with a low level of evidence that high dietary fiber intake (>29 g/day) could be useful in the treatment of symptomatic uncomplicated diverticular disease, but there were few limitations, such as variations in study designs and therapeutic regimens [36]. In a previous systematic review, Carabotti et al. [37] could not demonstrate the efficacy of fiber treatment in symptomatic uncomplicated diverticular disease patients due to the very low quality of the studies [37].

Restrictive diets such as the low FODMAP, SCD, and exclusion diet have been studied and may help manage symptoms in patients with quiescent IBD. Gibson [38] reported significant improvement in overall abdominal symptoms, pain, bloating, and diarrhea in IBD patients who followed a low FODMAP diet. However, the absence of control groups in some studies raises concerns about the potential for a placebo effect. Overall, the studies suggest that a low FODMAP diet may not have a significant effect on inflammatory markers in patients with IBD.

Our scoping review has several limitations which should be mentioned. For some of the studies included here, there

was limited availability of data, such as incomplete reporting, that can limit the precision of the results. Also, some of the studies evaluated the effect of diet in IBD patients without differentiation of the results according to the type. Hence, evaluating the dietary interventions according to the types of IBD remains to be assessed in future studies in more comprehensive analyses.

This study also has several strengths, including a thorough and systematic search using multiple databases, critical appraisal of primary studies to assess bias and evidence quality, and adherence to standardized methods and reporting guidelines. The topic of this review is clinically significant given the global prevalence and impact of IBD. The comprehensive search strategy encompassed diverse populations, enhancing the generalizability of the findings. This scoping review is the first to examine the effects of various diets on inflammatory markers including CRP, ESR, FC, and disease severity scores in IBD patients.

CONCLUSIONS

Diet plays a significant role in the management of IBD by influencing the inflammatory response. Among the dietary interventions presented in this study, enteral nutrition had the most promising results, improving the inflammatory status of the patients. Restrictive diets were effective in managing symptoms and clinical remission but were associated with inconclusive effects on inflammatory markers. Supplementing the diet with fatty acids, omega 3 or proteins did not concretely improve the patients' condition or inflammation. The differences in genetic background and the multiple risk factors to which each individual is exposed suggest that there is no universal diet that can be applicable to all patients. Hence, a personalized diet could be more useful. More research is required to determine the optimal dietary approach for managing IBD and associated symptoms.

Conflicts of interest: None to declare.

Authors' contribution: C.M.S. and A.I. created the idea of the manuscript. C.M.S. and C.S. independently applied the search strategy and performed the study selection. C.M.S. and C.S. performed the risk of bias assessment. C.M.S., C.S. and A.I. performed the data extraction. C.M.S. and C.S. drafted the manuscript. A.I. and D.L.D. contributed to the writing of the manuscript. A.I. and D.L.D. made substantial contributions to the conception and critically revised the manuscript for important intellectual content. All authors revised the final manuscript and approved the final version.

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