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REVIEW ARTICLE

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Evidence from clinical studies of the nutrological modulation of the gut microbiota in inflammatory bowel diseases: a systematic review

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Abstract

Introduction: The main risk factor for inflammatory bowel disease (IBD) is a positive family history in 10-25% of patients. Crohn's disease (CD) can affect individuals from 15 to 40 years old and from 50 to 80 years old, more frequently in women. Ulcerative colitis (UC) can start at any age. The pathogenesis of IBD is linked to genetically susceptible individuals, dysregulated gut microbiota (dysbiosis), chronic inflammation, and poor dietary patterns. Diet plays an important role in modulating the gut microbiota and can be applied as a therapeutic tool to improve the course of the disease. **Objective:** To carry out a systematic review of the main interactions between dietary therapy, gut microbiota, and inflammatory bowel disease, to elucidate the main clinical outcomes after nutrological treatment. **Methods:** The present study followed the international model of systematic review (PRISMA). Clinical studies were included, involving randomized controlled, prospective, and retrospective studies published from 2010 to 2022. **Results:** It was founded 87 studies on diet modulation in the control of IBD. These studies showed reductions in persistent intestinal symptoms, improvement of gut microbiota, reduction of inflammation markers, and improvement in quality of life, with $p<0.05$ (95% CI). The studies were homogeneous (X^2 = 98.9%), which increases the reliability of the clinical results on the dietary importance in the modulation of IBD. Conclusion: The important role of diet modulation in the control and even in the remission of IBD was evidenced.

Keywords: Inflammatory bowel disease. Diet therapy. Nutrological treatment. Gut microbiota. Quality of life.

Introduction

Inflammatory bowel diseases (IBD) have increased in incidence worldwide **[1]**. The main proven risk factor for both IBD is a positive family history in 10-25% of patients. Crohn's disease (CD) can affect individuals from 15 to 40 years old and from 50 to 80 years old, it has a higher percentage in women and has increased by around 15 times in recent decades. The incidence reaches around 5:100,000 per year in the US and Europe, and the prevalence reaches around 50:100,000 **[1]**. A study in the city of São Paulo in Brazil reported a prevalence of 14.8 cases of CD per 100,000 inhabitants **[2]**.

As for ulcerative colitis (UC), the disease can start at any age **[3]**. The peak of incidence seems to occur between 20 and 40 years of age, and many studies show a second peak of incidence in the elderly. Most studies show a slight predominance in males, although some recent studies have shown the opposite **[3]**. Latin America has a low prevalence. The United States, the United Kingdom, and Australia have a high prevalence **[1]**. There are no Brazilian data on its prevalence or incidence. An estimate is suggested in a population study in the state of São Paulo, which identified an incidence of 3.8 to 6.7 per 100,000 inhabitants/year in the last two decades **[3]**.

The pathogenesis of IBD is that genetically susceptible individuals develop intolerance to dysregulated gut microbiota (GM) (dysbiosis) and chronic inflammation develops as a result of poor dietary triggers **[4-6]**. Thus, diet plays an important role in the modulation of the GM, and can be applied as a therapeutic tool to improve the course of the disease **[7]**. Thus, current research in the field of IBD largely focuses on establishing the role of causal variants in

gene expression [8].

Despite this, genetic risk loci identified so far explain only a small part of the genetic variation in disease risk and more factors need to be taken into account to understand this multifactorial pathology [9]. In this regard, the diet participates in the regulation of intestinal inflammation, modifying and modulating the GM [10,11]. In this sense, the evolution of epigenetics offered new explanations about the mechanisms by which environmental changes induce the expression of pathological genes and determine the cell phenotype as a function of IBD.

Furthermore, the evolution and clinical manifestation of IBD are related to the interaction between genetic factors, with emphasis on mutations in the NOD2 gene (or CARD15), and also three other main mutations (R 702W, G908 R, and 1007 frameshift) have been described and linked to the phenotype of the disease, the GM and the immunoregulation of the mucosa [12-17]. In this context, metabolism encompasses the interactions between diet, the microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to sustain life. Endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications to DNA and histone proteins alter cell fate by controlling chromatin accessibility and downstream gene expression patterns [18].

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact the cellular state by modulating signaling pathway activity. One example is through the mechanistic targeting of the rapamycin (mTOR) signaling pathway and, in particular, the mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present. Depletion of specific nutrients including arginine, leucine, and S-adenosyl methionine prevents growth factor-induced mTORC1 activation by blocking Rag GTPase-mediated recruitment of mTORC1 to the lysosome where it can be activated by Rheb GTPase [18].

Another way that nutrients are sensed to impact cellular status is through AMPactivated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance and in the process regulates cell growth. and autophagy. Furthermore, transcription factors can be directly regulated by metabolites such as tryptophan kynurenine [18]. Furthermore, dietary manipulations and metabolites can affect tissue stem cells and direct cell fate decisions, as highlighted in the small intestine by intestinal stem cells (ISC). In this case, the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed. Also, sources of ketogenic or high-glucose diets regulate the balance of self-renewal by CTI [18].

Thus, all these epigenetic and nutrological mechanisms are of paramount importance, as approximately 70.0 to 80.0% of patients lose weight with IBD, leading to some degree of nutritional impairment, and around 23.0% of patients outpatients and 85.0% of those hospitalized with a predominance of malnutrition [19,20]. In this regard, diet also plays a decisive role in modulating the composition of the microbiome [13] and influences the inflammatory response [17]. Thus, a balanced diet low in fat and fiber may be important in preventing dysbiosis and preserving the immune system [21-24].

In this sense, GM is essential for activating the immune system, with emphasis on *Lactobacillus acidophilus, Lactobacillus bulgaricus*, and *Lactobacillus casei*, increasing IgA to remove antigens through a non-inflammatory path and increasing T and B lymphocytes [25-27]. Bifidobacteria inhibit the growth of exogenous and/or harmful bacteria, stimulate immune functions, aid in the digestion and/or absorption of food ingredients and minerals, and contribute to the synthesis of vitamins [28-30].

Also, *Faecalibacterium prausnitzii* is one of the most prevalent intestinal bacterial species in healthy adults, being beneficial and producing butyrate [1]. The reduction of this bacteria in the intestine can contribute to the onset or worsening of IBD. Thus, to increase the numbers of these bacteria, it is necessary to eat foods rich in fiber and increase the consumption of fruits, vegetables, whole grains, cereals, seeds, and nuts [1,4].

Therefore, short-chain fatty acids such as butyrate, propionate, and acetate serve as an energy source for intestinal epithelial cells and induce protective regulatory immune responses [31-38]. The adaptive immune system of the intestine is also rapidly activated after exposure to commensal bacteria, with an increase in the expression of class II molecules of the major histocompatibility complex and an increase in T cells [1,39-44]. T cells can generate subpopulations whose immune response is either pro-inflammatory or antiinflammatory. Th1 and Th17 cells – helper T cells, are pro-inflammatory, while Treg cells (CD4+ CD25+ phenotype) and Th2 are anti-inflammatory [8].

In this context, the Gram-negative bacterium *Bacteroides fragilis* induces the differentiation of CD4+ T cells into Treg cells, leading to the production of antiinflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta (TGFβ), nullifying the Th17 pro-inflammatory response [8]. The

differentiation of Treg cells depends on the recognition by T CD4+ cells of the polysaccharide presented by CD. In turn, segmented filamentous bacteria, after contact with antigen-presenting cells, have been shown to induce pro-inflammatory cells, such as Th17 cells **[8]**.

Therefore, the present study carried out a systematic review of the main interactions between dietary therapy, gut microbiota, and inflammatory bowel disease, to elucidate the main clinical outcomes of the disease after nutrological treatment.

Methods

Study Design

The present study followed a concise systematic review model, following the systematic review rules - PRISMA (Transparent reporting of systematic review and metaanalysis: //www.prisma-statement.org/).

Search Strategy and Search Sources

The literary search process was carried out from September to October 2022 and was developed based on Scopus, PubMed, Science Direct, Scielo, and Google Scholar, with studies published from 2010 to 2022. The descriptors (MeSH Terms) were used: *Inflammatory bowel disease. Diet therapy. Nutrological treatment. Gut microbiota. Quality of life*, and using Boolean "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was rated as high, moderate, low, or very low for risk of bias, clarity of comparisons, accuracy, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analysis of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument through the analysis of the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

As a corollary of the literary search system, a total of 130 articles were found that were submitted to the eligibility analysis and, then, 87 of the 93 final studies were selected to compose the results of this systematic review. The listed studies showed medium to high quality (Figure 1), considering in the first instance the level of scientific evidence of studies in types of study such as meta-analysis, consensus, randomized clinical trial, prospective and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X 2=98.9%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 7 studies with a high risk of bias and 10 studies that did not meet GRADE.

Figure 1. Flowchart showing the article selection process.

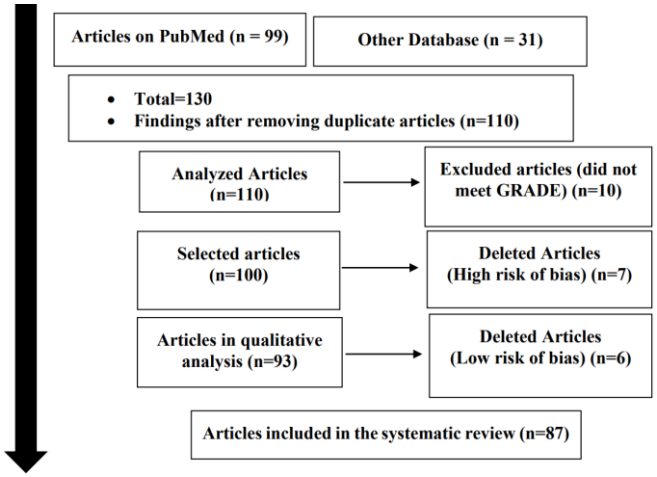
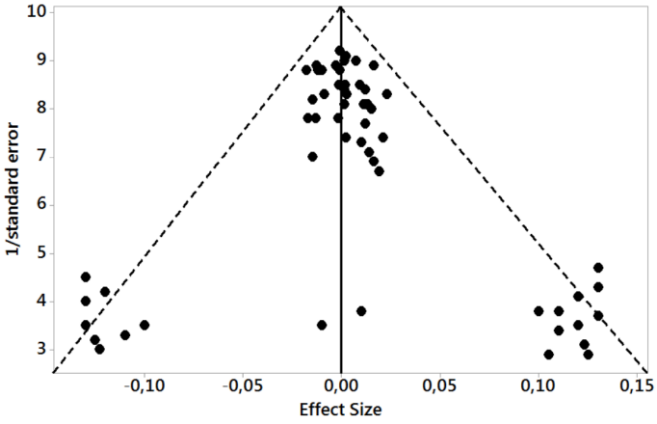


Figure 2 presents the results of the risk of bias of the studies through the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was indirectly determined by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with small sample sizes (lower precision) that are shown at the bottom of the graph (studies shown in red color) and in studies with large sample sizes that are presented at the top (studies shown in blue color).

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=87 studies).



Source: Own authorship.

Clinical Findings

The history of nutritional therapy for IBD begins with early observations in hospitalized adults with severe CD who improved with exclusive enteral nutrition (EEN) **[45-51]**. Since the initial report of EEN in the late 1970s, there have been over 200 publications on EEN with multiple meta-analyses showing that the use of EEN in children with CD is as effective as corticosteroids in inducing remission of active inflammation **[52- 55]**.

In this context, many studies have evaluated the ability of the diet to modulate GM and influence epithelial barrier function. Low-fiber diets have been associated with IBD with a postulated mechanism of reduced production of short-chain fatty acids by commensal bacteria whose preferred energy source is fiber **[56]**. Butyrate, a short-chain fatty acid, is essential for colon health and the main source of energy for colonocytes **[57]**.

In this sense, short-chain fatty acids also promote immune tolerance by promoting the development of regulatory T cells **[58,59]**. Food additives are commonly consumed by IBD patients, and specific dietary emulsifiers (carboxymethylcellulose and polysorbate 80) have been shown to induce low-grade inflammation and metabolic syndrome in the wild in type mice and promote colitis in genetically predisposed IL-10 knockout mice **[60,61]**. Emulsifiers can alter the host microbiota, resulting in increased inflammatory potential with an increase in the number of mucolytic bacteria and erosion of the protective mucosal layer.

Furthermore, clinical trials and data reports on the results of dietary therapies in IBD are well described **[61-63]**, as per the results found in the present study. Importantly, many of these trials are smaller in size, considered to produce a lower grade of evidence, and some are limited by a lack of long-term results. In a recently published Cochrane review, Limketkai et al. analyzed 18 randomized controlled trials, comprising 1878 participants, published between 1965 and 2018 **[61]**.

Additionally, intervention diets involved complete exclusion or significant limitation of one or more food groups. As main examples are listed the diets included low carbohydrate content, microparticles, low calcium, red and processed meats, low disaccharides, grains, saturated fats, symptom-guided diets, highly restricted organic diet, without milk, antiinflammatory diet, and free diet. of carrageenan. The different studies analyzed various outcomes, including remission induction, clinical relapse, surrogate inflammation biomarkers, endoscopic improvement, quality of life, and need for surgery **[64-66]**.

In this regard, the most rigorously studied dietary interventions in IBD are ENE, a formula-based therapy for CD. Numerous studies in children and adolescents have demonstrated the ability of NEE to induce remission of active CD in 80-85% of patients **[67,68]**. NEE is equivalent to corticosteroid therapy in inducing clinical remission and superior in achieving endoscopic mucosal healing **[67,69]**. Furthermore, NEE is a first-line therapy for CD pediatricians worldwide, and the treatment protocol typically involves the administration of formula to provide 100% of caloric requirements and the exclusion of food for 6–8 weeks **[69]**.

In this regard, however, the exact mechanism by which NEE exerts its effect is unknown. Hypothetical mechanisms include limiting antigen exposure, and antigenic monotony, improving nutritional status and nutrient delivery, altering GM and immune response, and preventing deleterious effects **[70]**. As EEN and exclusion diets are extremely different interventions, the mechanism by which they affect disease is likely similarly different. Despite disease improvement, studies examining fecal metagenomics in children with CD have found that EEN appears to decrease GM diversity and promote a more "dysbiotic" state when compared to healthy controls **[71]**.

Furthermore, the functional capacity of the GM also decreased with NEE, as did the genes encoding proteins involved in the biosynthesis of B vitamins **[71]**. In studies that assessed changes in GM in patients with IBD treated with conventional medical therapies, dysbiosis improved with therapy **[72]**. Therefore, the relationship between the beneficial effects of NEE and changes in the GM needs further characterization and may result from changes in beneficial or harmful metabolites produced by the bacteria.

In this scenario, NEE can drive CD into remission, but NEE is difficult to maintain as long-term maintenance therapy and is not effective for UC. Exclusion diets, however, are practical as long-term therapy and be useful in both CD and UC cases **[73,74]**.

In this sense, one of the most studied exclusion diets is the specific carbohydrate (EC) diet. This diet removes all grains, sweeteners (except honey), processed foods, and all milk products except hard cheeses and yogurts fermented for more than 24 hours. Clinical and laboratory improvements have been reported in pediatric and adult patients with IBD **[73-76]**. As a corollary to this, a study over 12 weeks in children and adolescents used capsule endoscopy and demonstrated mucosal healing **[77]**. EC therapy has been shown to result in significant changes in the composition of the GM **[73]**. Furthermore, a survey of 417 respondents found that patients reported

significant improvement in symptoms [74].

The Crohn's Disease Exclusion Diet (CDED) is based on the hypothesis that components of the Western diet promote a pro-inflammatory microbiome and can disrupt the mucosal barrier. The diet focuses on excluding gluten, dairy, gluten-free baked goods, animal fat, emulsifiers, and all canned goods or processed foods. As an example, a prospective cohort of pediatric and adult participants with mild to moderate CD was treated with partial enteral nutrition (formula providing approximately 50% of daily calorie intake) and CDED was successful in achieving clinical remission induction [65].

In addition, certain food additives may promote the pathogenesis of CD, but to date, the evaluation of exposure to food additives in humans has been limited. Thus, one study quantified exposures to food additives in children with CD. The children were followed up for 24 months with an assessment of disease characteristics, food intake, and body composition. At baseline, participants completed three 24-hour dietary recalls. Foods were categorized and the list of ingredients for each item was evaluated for the presence of selected food additives, such as polysorbate-80, carboxymethylcellulose, xanthan gum, soy lecithin, titanium dioxide, carrageenan, maltodextrin, aluminosilicates. At baseline, 138 participants, mean age of 14.2 ± 2.8 years, 95% with inactive or mild disease, were enrolled. A total of 1325 unique foods were recorded. Mean daily exposure to xanthan gum was 0.96 ± 0.72, carrageenan 0.58 ± 0.63, maltodextrin 0.95 ± 0.77, and soy lecithin 0.90 ± 0.74. For the 8 food additives examined, participants were exposed to a mean (SD) of 3.6 ± 2.1 total additives per recall day and a mean (SD) of 2.4 ± 1.0 different additives per day. Therefore, children with CD frequently consume food additives, and the impact on the disease course needs further study [78].

Also, the Anti-Inflammatory IBD Diet (IBD-AID) is a whole-food-based diet that restricts the intake of complex carbohydrates such as refined sugar, gluten-based grains, and certain dietary starches, but also incorporates the intake of prebiotics and probiotics. The diet also incorporates phases of food textures. As an example, in a small retrospective case series of patients with IBD on IBD-AID for at least 4 weeks, all demonstrated improved clinical symptoms [79]. In a study of a semi-vegetarian diet in patients with CD remission induced by either medical therapy or surgery, patients maintained a higher rate of clinical remission over 2 years [80].

Furthermore, worsening dysbiosis and decreased butyrate production are demonstrated with EEN therapy and are counterintuitive, as is the lack of any fiber content in commonly used formulas for EEN [81,82]. It may be the case that NEE acts through a unique mechanism of action to impact inflammation in IBD compared to the action of restricted diets. As the GM can drive inflammation and respond to underlying inflammation, further elucidation of the complex diet, microbiome, and host interaction will help guide future therapy.

In this context, with the paradoxical findings seen in EEN versus food restriction diets, changes may occur during the transition from one diet to another, providing a better understanding of the mechanisms. As an example, epidemiological studies have shown an increased risk of developing IBD with increased intake of total fat, polyunsaturated fatty acids, omega-6 fatty acids, and meat, while fruit, vegetable, and fiber intake have been shown to have protective effects [83]. Higher meat intake was associated with an increased risk of UC relapse in adults and a decrease in the rate of achieving CD remission in children on partial enteral nutritional therapy [84,85].

Even though a variety of exclusion diets have shown efficacy in treating inflammation in small case series reports, additional studies are needed to better substantiate these findings. Although these studies suggest that specific food components may be deleterious, it may be the complex interactions of food components within the food matrix with the GM that trigger and perpetuate the cycle of inflammation in IBD [86,87]. Despite these important clinical findings, the mechanism by which dietary interventions influence IBD remains unknown. Studies involving the microbiome, metabolome, and proteome are beginning to shed more detail and will help guide toward more targeted diets.

Conclusion

It was concluded that there are important randomized controlled clinical studies in the last ten years that have shown the role of diet modulation in the control and even in the remission of inflammatory bowel diseases, revealing important reductions in persistent bowel symptoms, in the balance of the gut microbiota, in the reduction of inflammation markers and improvement in quality of life.

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Ethical Approval

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Informed consent
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Data sharing statement
No additional data are available.

Conflict of interest
The authors declare no conflict of interest.

Similarity check
It was applied by Ithenticate@.

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