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REVIEW ARTICLE

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Nutritional modulation of gut microbiota in inflammatory bowel disease: a systematic review

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Abstract

Introduction: Inflammatory bowel diseases (IBD) have shown an increase in incidence worldwide. The pathogenesis of IBD is that genetically susceptible individuals develop intolerance to dysregulated gut microbiota (dysbiosis) and chronic inflammation develops as a result of poor dietary triggers. 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:** It was to carry out a systematic review of the main interactions between nutrology, gut microbiota, and inflammatory bowel disease, to elucidate the main clinical outcomes of the disease after nutrological treatment, analyzing the main macro and micronutrients. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to October 2023 in the Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** 144 articles were found. A total of 39 articles were evaluated in full and 30 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 27 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=59.9%>50%. With nutritional treatment, several micronutrients have the potential to modulate intestinal inflammation. Immunonutrition has demonstrated its importance through vitamins A, C, E, and D, folic acid, beta-carotene, and trace elements such as zinc, selenium, manganese, and iron. The Specific Carbohydrate Diet, fermentable oligosaccharides, disaccharides, monosaccharides, and polyol diet, and the Mediterranean diet also appear to show strong anti-inflammatory properties and promise to improve symptoms of inflammatory bowel disease. Diet modulation can control IBD by reducing persistent intestinal symptoms, balancing the gut microbiota, and reducing markers of inflammation. Dietary therapy can improve the quality of life of IBD patients.

Keywords: Inflammatory bowel diseases. Gut microbiota. Nutrology. Macronutrients. Micronutrients.

Introduction

Inflammatory bowel diseases (IBD) have shown an increase in incidence worldwide **[1]**. The main proven

risk factor for both IBD is a positive family history in 25% of patients. Crohn's disease (CD) can affect individuals aged 15 to 40 and 50 to 80 years old, has a higher percentage in women, and has increased by around 15 times in recent decades **[2]**.

Regarding ulcerative colitis (UC), the disease can start at any age **[3]**. The peak incidence appears to occur between the ages of 20 and 40, and many studies show a second peak in 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, United Kingdom, and Australia have 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 (dysbiosis) and chronic inflammation develops as a result of poor dietary triggers **[4-6]**. Thus, 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 **[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 to date 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 aspect, the diet participates in the regulation of intestinal inflammation, modifying and modulating the gut microbiota **[10,11]**. In this sense, the evolution of epigenetics has offered new explanations about the mechanisms by which environmental changes induce the expression of pathological genes and determine the cellular 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 gut microbiota and mucosal immunoregulation **[12-17]**. In this context, metabolism encompasses the interactions between diet, the microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to maintain 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 cellular state by modulating signaling pathway activity. One example is through the mechanistic target of rapamycin (mTOR) signaling pathway and, in particular, 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 mTORC1 recruitment to the lysosome where it can be activated by Rheb GTPase **[18]**.

Another way that nutrients are sensed to impact cellular state is through AMP-activated 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 glucose-rich diets regulate the balance of self-renewal by ISC **[18]**.

Thus, all these epigenetic and nutritional mechanisms are of paramount importance, as around 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 aspect, diet also plays a decisive role in modulating the composition of the microbiome **[13]** and influencing the inflammatory response **[17]**. Therefore, a balanced diet low in fat and fiber can be important in preventing dysbiosis and preserving the immune system **[21]**.

In this sense, gut microbiota is fundamental for the activation of the immune system, with emphasis on *Lactobacillus acidophilus, Lactobacillus bulgaricus*, and *Lactobacillus casei*, increasing IgA to remove antigens through a non-inflammatory pathway and increasing T and B lymphocytes. 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 **[22-24]**.

Added to this, *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. Therefore, to increase the numbers of these bacteria it is necessary to eat foods rich in fiber, and increase the consumption of fruits, vegetables, legumes, whole grains and 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 **[23]**.

The gut's adaptive immune system is also rapidly activated following exposure to commensal bacteria, with an increase in the expression of major histocompatibility complex class II molecules and an increase in T cells **[1]**. T cells can generate subpopulations whose immune response is pro-inflammatory or anti-inflammatory. Th1 and Th17 cells – T helper cells are pro-inflammatory, while Treg cells (CD4+ CD25+ phenotype) and Th2 cells are anti-inflammatory **[8]**.

In this sense, the Gram-negative bacterium *Bacteroides fragilis* induces the differentiation of CD4+ T cells into Treg cells, leading to the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta (TGFβ), abrogating the Th17 pro-inflammatory response **[8]**. The differentiation of Treg cells depends on the recognition by CD4+ T cells of the polysaccharide presented by CD. In turn, filamentous segmented bacteria, after contact with antigen-presenting cells, have been shown to induce pro-inflammatory cells, such as Th17 cells **[8]**.

Therefore, the present study aimed to carry out a systematic review of the main interactions between nutrology, gut microbiota, and inflammatory bowel disease, to elucidate the main clinical outcomes of the disease after nutrological treatment, analyzing the main macro and micronutrients.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/24/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/24/2023.

Data Sources and Research Strategy

The literary search process was carried out from August to October 2023 and developed based on Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: *"Inflammatory bowel diseases. Gut microbiota. Nutrology. Macronutrients. Micronutrients"*, and using the Boolean "and" between the terms MeSH and "or" between historical discoveries.

Study Quality and Risk of Bias

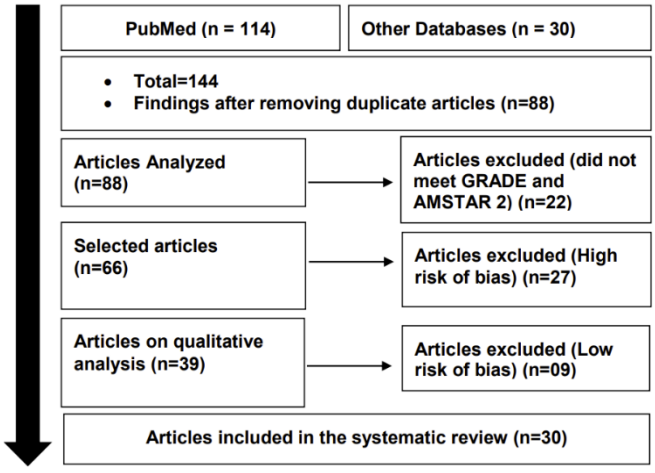
Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The 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 by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

Results and Discussion

Summary of Findings

A total of 144 articles were found that were subjected to eligibility analysis, with 30 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, 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=59.9%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 27 studies with a high risk of bias and 22 studies that did not meet GRADE and AMSTAR-2.

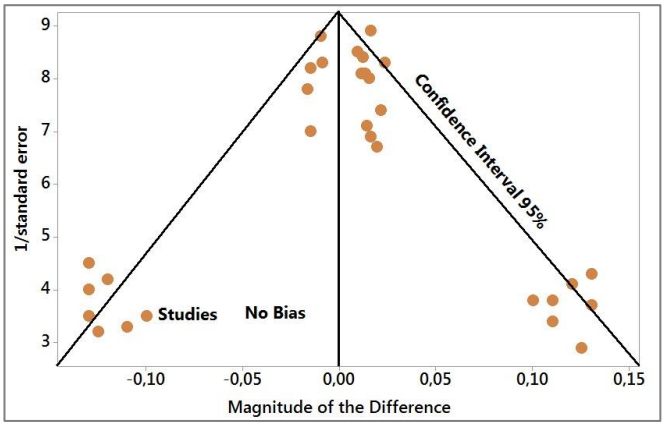
Figure 1. Flowchart showing the article selection process.



Source: Own Authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly 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 a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no 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=30 studies).



Source: Own Authorship.

Main Outcomes - Nutrology, Gut Microbiota and IBD

The present study found important randomized controlled clinical studies and other clinical studies in the last ten years that highlighted the important role of dietary modulation in controlling IBD **[25-29]**. In this sense, these studies showed important reductions in persistent intestinal symptoms, improvement in the gut microbiota, reduction in circulating markers of inflammation, and improvement in quality of life.

In this setting, the history of nutritional therapy for IBD began with initial observations in adults hospitalized with a severe CD that improved with exclusive enteral nutrition (EEN). Since the initial report of SEN in the late 1970s, there have been more than 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 **[29,30]**.

Many studies have evaluated the ability of diet to modulate the gut microbiota 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. Butyrate, a short-chain fatty acid, is essential for colon health and the main source of energy for colonocytes **[24]**.

In this sense, short-chain fatty acids also promote immunological tolerance by promoting the development of regulatory T cells **[1]**. 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 wild-type mice and promote colitis in genetically predisposed IL-10 knockout mice. 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 **[25]**.

Furthermore, clinical trials and data reports on the results of dietary therapies in IBD are well described, according to the results obtained in the present study. Importantly, many of these trials are smaller in size, considered to produce a lower degree of evidence, and some are limited by a lack of long-term results **[26,27]**.

Additionally, intervention diets involved the complete exclusion or significant limitation of one or more food groups. The main examples include diets with low carbohydrates, microparticles, low calcium, red and processed meats, low disaccharides, grains, saturated fats, symptom-guided diets, highly restricted organic diets, dairy-free, anti-inflammatory diets, and carrageenan-free diets. The different studies analyzed various outcomes, including remission induction, clinical relapse, surrogate biomarkers of inflammation, endoscopic improvement, quality of life, and need for surgery **[29,30]**.

In this regard, the most rigorously studied dietary intervention in IBD is EEN, a formula-based therapy for CD. Numerous studies in children and adolescents have demonstrated the ability of EEN to induce remission of active CD in 80-85% of patients **[14]**. EEN is equivalent to corticosteroid therapy in inducing clinical remission and superior in achieving endoscopic mucosal healing. Still, EEN is a first-line therapy for CD pediatricians worldwide, and the treatment protocol typically involves the administration of the formula to provide 100% of caloric needs and the exclusion of food for 6–8 weeks **[16]**.

In this sense, however, the exact mechanism by which EEN exerts its effect is unknown. Hypothetical mechanisms include limiting antigen exposure, and antigenic monotony, improving nutritional status and nutrient delivery, altering the gut microbiota and

immune response, and avoiding deleterious effects [17]. As EEN and exclusion diets are extremely different interventions, the mechanism by which they affect the disease is likely equally different. Despite disease improvement, studies examining fecal metagenomics in children with CD have found that EEN appears to decrease gut microbiota diversity and promote a more "dysbiotic" state when compared to healthy controls [18].

Furthermore, the functional capacity of the gut microbiota was also decreased with EEN, as were the genes encoding proteins involved in the biosynthesis of B vitamins. In studies that evaluated changes in the gut microbiota in IBD patients treated with conventional medical therapies, the dysbiosis improved with therapy [18,19]. Therefore, the relationship between the beneficial effects of SEN and changes in the gut microbiota needs further characterization and may result from changes in the beneficial or harmful metabolites produced by the bacteria [18].

In this scenario, EEN 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 have been found useful in both CD and UC [20]. In this sense, one of the most studied exclusion diets is the specific carbohydrate diet. This diet removes all grains, sweeteners (except honey), processed foods, and all dairy products except hard cheeses and yogurts fermented for more than 24 hours. Clinical and laboratory improvements have been reported in pediatric and adult IBD patients. As a corollary to this, a study over 12 weeks in children and adolescents used capsule endoscopy and demonstrated mucosal healing. Specific carbohydrate diet therapy has been shown to result in significant changes in the composition of the gut microbiota [15,16].

The Crohn's Disease Exclusion Diet (DEDC) 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 (a formula that provides approximately 50% of daily calorie intake) and DEDC showed success in achieving the induction of clinical remission [22].

Also, the Anti-Inflammatory Diet for IBD (IBD-AID) is a whole foods-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 IBD patients on IBD-AID for at least 4 weeks, all demonstrated improved clinical symptoms. 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 [13].

The worsening of dysbiosis and decreased butyrate production is demonstrated with EEN therapy and is counterintuitive, as is the lack of any fiber content in formulas commonly used for EEN. It may be the case that EEN acts through a unique mechanism of action to impact inflammation in IBD compared to the action of restricted diets. As the gut microbiota can drive inflammation and respond to underlying inflammation, further elucidation of the complex interplay between diet, microbiome, and host will help guide future therapy [1,5].

In this context, with the paradoxical findings seen in EEN versus restricted 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 demonstrated 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. Higher meat intake was associated with an increased risk of UC relapse in adults and a decreased rate of achieving CD remission in children on partial enteral nutritional therapy [6].

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 gut microbiota that trigger and perpetuate the cycle of inflammation in IBD [6,7]. 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 greater detail and will help guide toward more targeted diets.

Conclusion

With nutritional treatment, several micronutrients have the potential to modulate intestinal inflammation. Immunonutrition has demonstrated its importance through vitamins A, C, E, and D, folic acid, beta-

carotene, and trace elements such as zinc, selenium, manganese, and iron. The Specific Carbohydrate Diet, fermentable oligosaccharides, disaccharides, monosaccharides, and polyol diet, and the Mediterranean diet also appear to show strong anti-inflammatory properties and promise to improve symptoms of inflammatory bowel disease. Diet modulation can control IBD by reducing persistent intestinal symptoms, balancing the gut microbiota, and reducing markers of inflammation. Dietary therapy can improve the quality of life of IBD patients.

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