



Nutrological management of the gut microbiota for regulation of symptoms and improvement of quality of life of patients with inflammatory bowel diseases: a systematic review

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Abstract

Introduction: The major predictor for inflammatory bowel disease (IBD) is a positive family history. Endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate by controlling chromatin accessibility and gene expression patterns. **Objective:** It was to highlight the main interactions between nutrition and intestinal microbiota in the treatment of inflammatory bowel diseases. **Methods:** The present study followed the international systematic review model (PRISMA). This study was carried out from September to October 2024. It included randomized controlled, prospective, and retrospective studies published from 2013 to 2024. The Cohen test was performed to calculate the Effect Size and the inverse error standard (precision or sample size) for the risk of bias (Funnel Plot). **Results and Conclusion:** A total of 30 articles were found, and 17 clinical studies on the modulation of diet to control IBD were included in this study. These studies

have shown reductions in persistent gut symptoms, improved gut microbiota, reduced markers of inflammation, and improved quality of life. Diet has an important role in controlling and even remitting IBD. The studies were homogeneous in results, with $X^2 = 85.5\%$, which increases the reliability of clinical results on the importance of diet in modulating IBD.

Keywords: Inflammatory bowel disease. Crohn's disease. Ulcerative colitis. Gut microbiota. Nutrients.

Introduction

The main risk factor for inflammatory bowel diseases (IBD) is a positive family history [1-3]. 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 focuses largely 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 respect, 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 major mutations (R 702W, G908 R and 1007 frameshift) have been described and linked to the disease phenotype, the gut microbiota, and mucosal immunoregulation [12-17].

In this context, metabolism encompasses the interactions between diet, microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to maintain life. Endogenous metabolites as well as dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter the cell's fate, controlling chromatin accessibility and downstream gene expression patterns [18].

Beyond 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, 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-adenosylmethionine, 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 nutrients are detected 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 and kynurenine [18]. Also, dietary manipulations and metabolites can affect tissue stem cells and direct cell

fate decisions, as highlighted in the small intestine by intestinal stem cells (ISCs). In this case, the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed. Also, ketogenic or high-glucose diet sources regulate the balance of self-renewal by ISCs [18].

Thus, all these epigenetic and nutritional 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 outpatients and 85.0% of hospitalized patients with predominant malnutrition [19,20]. In this respect, diet also plays a decisive role in modulating the composition of the microbiome [13] and influencing the inflammatory response [17]. Thus, 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 for the removal of antigens by a non-inflammatory pathway and increasing T and B lymphocytes. Lactobacilli and 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 vitamin synthesis [22-24].

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]. 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 (TGF β), abolishing the pro-inflammatory response of Th17 [8].

Therefore, the present study carried out a systematic review followed by a meta-analysis on the main interactions between nutrition, lifestyle change, gut microbiota, and inflammatory bowel diseases, in order to highlight the main clinical outcomes.

Methods

Study Design

This study followed an international model for systematic review, adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Available at: <http://www.prismastatement.org/?AspxAutoDetectCookieSupport=1>. Accessed on: 09/05/2024. The methodological quality standards of AMSTAR-2 (Assessing the methodological

quality of systematic reviews) were also followed. Available at: <https://amstar.ca/>. Accessed on: 09/05/2024.

Data Sources and Search Strategy

The literature search process was conducted from September to October 2024 and developed using Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The PICOS search strategy model was applied. The following descriptors were used (DeCS/MeSH Terms): "*Inflammatory bowel disease. Crohn's disease. Ulcerative colitis. Gut microbiota. Nutrients*"; and using the Boolean operator "and" between MeSH terms and "or" between historical findings.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low regarding the risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident highlight was for systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. Low quality 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 (Sample size versus Effect size), using Cohen's d test.

Results and Discussion

Summary of Findings

After a detailed literature search, this study selected 17 out of a total of 30 studies for systematic analysis, including 11 randomized controlled clinical trials and 6 prospective studies from the last ten years, showing a high quality of scientific evidence in the studies addressed, with a level of evidence IA, according to GRADE criteria. Furthermore, the analyzed studies showed high homogeneity in the results (high association = >50%), presenting 85.5% in relation to the R-sq (I^2) value.

Most of the studies listed in this study followed a randomized controlled design and were homogeneous in relation to symptom reduction, reduction of inflammatory bowel syndrome (IBS), improvement in quality of life (QoL), and improvement in the gut microbiota, highlighting the important influence of dietary interventions on inflammation and clinical outcomes of IBD. Only 4 studies presented the results of changes in the gut microbiota with dietary interventions. There was a prevalence of symptom

reduction (88.24%), IBS reduction (88.24%), QoL improvement (88.24%), and gut microbiota improvement (80%), highlighting the significant influence of dietary interventions on the clinical outcomes of IBD.

Using the Chi-Square test, it is possible to observe the differences between the observed and expected data, analyzing which variables presented the greatest differences, which may indicate dependence or association between them. In addition, the contributions to the Chi-Square statistic (Pearson and Likelihood Ratio) can be compared to analyze which variables presented the highest values. As a result, there was a significant dependence between the variables Symptom Reduction vs. QoL Increase, with contributions to the Chi-Square of 14.336, and with Pearson's test equal to 17.000 and Likelihood Ratio equal to 12.315, with $p=0.019<0.05$.

Also, using the Chi-Square test, the correlation between the variables Reduction of Symptoms vs. Improvement of Gut Microbiota (Improvement_GM) was performed using the Chi-Square method (X^2). As a result, there was a significant dependence between the variables Reduction of Symptoms vs. Improvement_GM, with contributions to the Chi-Square of 19.0627 and with a Pearson test equal to 21.000 and a Likelihood Ratio equal to 18.415, with $p=0.011<0.05$.

In light of these results, the present study found important randomized controlled clinical trials and other clinical studies in the last ten years that highlighted the important role of dietary modulation in the control of IBD [25]. In this sense, these studies showed significant reductions in persistent intestinal symptoms, improvement in gut microbiota, reduction in circulating markers of inflammation, and improvement in quality of life. In this context, 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 energy source for colonocytes [26].

In addition, short-chain fatty acids also promote immune tolerance by promoting the development of regulatory T cells. Dietary additives are commonly consumed by patients with IBD, and specific dietary emulsifiers (carboxymethylcellulose and polysorbate 80) have been shown to induce low-grade inflammation and metabolic syndrome in 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 [27].

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 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 CDED showed success in achieving the induction of clinical remission [28].

Furthermore, certain food additives may promote the pathogenesis of CD, but to date, the assessment of exposure to food additives in humans has been limited. Thus, a study quantified exposures to food additives in children with CD. The children were followed for 24 months with assessment of disease characteristics, food intake, and body composition. At the beginning of the study, participants completed three 24-hour dietary recalls. Foods were categorized, and the ingredient list for each item was assessed for the presence of selected food additives, such as polysorbate-80, carboxymethylcellulose, xanthan gum, soy lecithin, titanium dioxide, carrageenan, maltodextrin, and aluminosilicates. At the beginning of the study, 138 participants, with a mean age of 14.2 ± 2.8 years, 95% with inactive or mild disease, were enrolled. A total of 1325 unique foods were recorded. The mean exposure per day for 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 course of the disease needs further study [29].

Finally, the anti-inflammatory diet for IBD (IBD-AID) is based on whole foods 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 any medical therapy or surgery,

patients maintained a higher rate of clinical remission over 2 years [30].

Conclusion

It was concluded that 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. Enteral nutrition in pediatric Crohn's disease appears to be the only nutritional intervention currently recommended as first-line therapy. 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 the symptoms of inflammatory bowel disease. Dietary modulation can control inflammatory bowel diseases by reducing persistent intestinal symptoms, balancing the gut microbiota, and reducing markers of inflammation. Dietary therapy can improve the quality of life of patients with inflammatory bowel disease.

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