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Clinical evidence on nutrological management and 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. Crohn's disease (CD) can affect individuals aged 15 to 40 and 50 to 80 years, with a higher percentage in women. Ulcerative colitis (UC) can start at any age. 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. **Objective:** It was to highlight the main interactions between nutrition and gut 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 July to September 2024. It included randomized controlled, prospective, and retrospective studies published from 2013 to 2023. 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 = 82.5%, which increases the reliability of clinical results on the importance of diet in modulating IBD.

Keywords: Nutrology. Inflammatory bowel disease. Diet therapy. Gut microbiota. Lifestyle.

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 aged 15 to 40 and 50 to 80 years, with a higher incidence in women and an increase of approximately 15 times in recent

decades. The incidence reaches approximately 5:100,000 per year in the USA and Europe, and the prevalence reaches approximately 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]**. Regarding Ulcerative Colitis (UC), the disease can begin at any age **[3]**.

The peak incidence appears 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 the 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 regard, 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 in the 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) that have been described and linked to the phenotype of the disease, the gut microbiota and the immunoregulation of the mucosa **[12-17]**.

In this context, metabolism encompasses the interactions between diet, the microbiome, and the 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 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 recruitment of mTORC1 to the lysosome where it can be activated by the Rheb GTPase **[18]**.

Another way that nutrients are sensed to impact cellular state 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]**.

Dietary manipulations and metabolites can affect tissue stem cells and direct cell fate decisions, as highlighted in the small intestine by intestinal stem cells (ISTCs). In this case, the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed. Also, ketogenic or high-glucose diets regulate the balance of self-renewal by ISTCs **[18]**. Thus, all these epigenetic and nutrological mechanisms are of utmost importance, since 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 have predominant malnutrition **[19,20]**.

In this regard, 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, the gut microbiota is essential 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 the synthesis of vitamins **[22-24]**.

In addition, *Faecalibacterium prausnitzii* is one of

the most prevalent intestinal bacterial species in healthy adults, being beneficial and a producer of 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 this bacteria it is necessary to eat foods rich in fiber, 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]**.

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), nullifying the pro-inflammatory response of Th17 **[8]**. The differentiation of Treg cells depends on the recognition by CD4+ T 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 on the main interactions between nutrology, lifestyle changes, gut microbiota and inflammatory bowel diseases, in order to highlight the main clinical outcomes.

METHODS

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 08/07/2024. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 08/07/2024.

Data Sources and Search Strategy

The literature search process was carried out from July to September 2024 and developed based on 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 health science descriptors (DeCS/MeSH Terms) were used: "Inflammatory bowel disease. Crohn's disease. Ulcerative colitis. Gut microbiota. Nutrients", and using the Boolean "and" between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

The 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 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 Cohen's test (d).

Results and Discussion

Summary of Findings

After the detailed literature search process, this study selected 17 of the total 30 studies for systematic analysis (Table 1), 11 of which were randomized controlled clinical trials and 6 prospective studies in the last ten years, showing high-quality scientific evidence in the studies addressed, with evidence level IA, according to the GRADE criteria. Furthermore, the studies analyzed showed high homogeneity in the results (high association = >50%), with 82.5% to the R-sq value (I^2).

Most of the studies listed in this study followed a randomized and controlled model and were homogeneous to symptom reduction, reduction of inflammatory bowel syndrome (IBS), improvement in quality of life (QoL), and improvement of the gut microbiota, evidencing an important influence of dietary interventions on inflammation and clinical outcomes of IBD (Table 1).

Table 1. The main outcomes of each study listed symptom reduction, reduction of inflammatory bowel syndrome (IBS), improvement in quality of life (QoL), and improvement of gut microbiota. Most studies presented p<0.001 to the control group of each study, that is, they presented a statistically significant difference.

Authors /Data	Reduction of symptoms*	IBS Reduction	Increased QoL	Improvement of the Gut Microbiota
Cox et al. 2020	1	1	1	1
Cox et al. 2017	1	1	1	**(-)
Pedersen et al. 2017	1	1	1	(-)
Bodini et al. 2019	1	1	1	(-)
Papada et al. 2019	0	0	0	(-)
Jian et al., 2018	1	1	1	(-)
Albenberg et al. 2019	1	1	1	(-)
Svolos et al.,2018	1	1	1	1
Levine et al. 2019	1	1	1	1
Racine et al. 2016	0	0	0	0
Braly et al., 2017	1	1	1	1
Machado et al., 2015	1	1	1	(-)

Brotherton et al., 2014	1	1	1	(-)
Sökülmez et al., 2014	1	1	1	(-)
Kyaw et al., 2014	1	1	1	(-)
Hanai et al., 2012	1	1	1	(-)
Kang et al., 2015	1	1	1	(-)

* Code 1 means "yes" answer and code 0 means "no" answer in terms of statistical denotation. **(-) not reported in the studies.

Only 4 studies presented the results of changes in the gut microbiota with dietary interventions (Table 1). There was a prevalence of symptom reduction (88.24%), IBS reduction (88.24%), improvement in QoL (88.24%), and improvement in the gut microbiota (80%), evidencing an important influence of dietary interventions on the clinical results 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, it is possible to compare the contributions to the Chi-Square statistic (Pearson and Likelihood Ratio) to analyze which variables presented the highest values. As a result, there was a significant dependence between the variables Symptom Reduction (1) vs. Increased QoL (1), with contributions to the Chi-Square of 14.336, and with Pearson's test equal to 17.000 and Likelihood Ratio (likelihood) 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_MI) was performed using the Chi-Square (X2) method. As a result, there was a significant dependence between the variables Reduction of Symptoms (1) vs. Improvement_MI (1), with contributions to the Chi-Square of 19.0627 and with Pearson's test equal to 21.000 and Likelihood Ratio (likelihood) equal to 18.415, with $p=0.011<0.05$.

Given these results, the present study found important randomized controlled clinical trials and other clinical studies in the last ten years that demonstrated 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 of the gut microbiota, reduction of circulating markers of inflammation, and improvement in quality of life.

In this context, many studies have evaluated the ability of the 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. Food additives are commonly consumed by IBD patients and specific dietary emulsifiers (carboxymethyl cellulose 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 may disrupt the mucosal barrier. The diet focuses on the exclusion of 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 (formula providing approximately 50% of daily calorie intake) and CDED was successful in achieving induction of clinical remission **[28]**.

Also, certain food additives may promote the pathogenesis of CD, but to date, assessment of food additive exposure in humans has been limited. Thus, one study quantified food additive exposures in children with CD. Children were followed for 24 months with an assessment of disease characteristics, dietary intake, and body composition. At baseline, 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, carboxymethyl cellulose, xanthan gum, soy lecithin, titanium dioxide, carrageenan, maltodextrin, and 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. 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 disease course needs further study **[29]**.

Finally, 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 starches from the diet, but also incorporates the intake of prebiotics and probiotics.

The diet also incorporates phases of food textures. For example, in a small retrospective case series of IBD patients on IBD-AID for at least 4 weeks, all demonstrated improvement in clinical symptoms. In a study of a semi-vegetarian diet in patients with remission of CD induced by either medical therapy or surgery, patients maintained a higher rate of clinical remission over 2 years **[30]**.

Conclusion

It was concluded that with nutritional treatment, several micronutrients have the potential to modulate intestinal inflammation. Immunonutrition is important 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 show promise for improving symptoms of inflammatory bowel disease. Dietary modulation may control inflammatory bowel disease by reducing persistent intestinal symptoms, balancing the gut microbiota, and reducing markers of inflammation. Dietary therapy may improve the quality of life of patients with inflammatory bowel disease.

CRediT

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