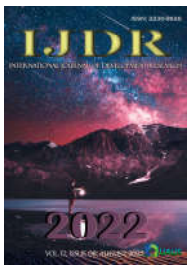
ISSN: 2230-9926

Available online at http://www.journalijdr.com

IJDR

International Journal of Development Research
Vol. 12, Issue, 08, pp. 58438-58448, August, 2022
https://doi.org/10.37118/ijdr.25155.08.2022



RESEARCH ARTICLE **OPEN ACCESS**

INTERACTIONS BETWEEN DIETARY THERAPY AND GUT MICROBIOTA IN INFLAMMATORY BOWEL DISEASE: A SYSTEMATIC REVIEW AND META-ANALYSIS

Aline Damasceno de Avance[1], Idiberto José Zotarelli Filho[2*], Marilda Aparecida Milanez Morgado de Abreu[1], Hermann Bremer Neto[1] and Rogéria Keller[1]

[1]Unoeste – University of Western Sao Paulo, Master's Program in Health Sciences, Presidente Prudente, Sao Paulo, Brazil; [2]Faceres – Faculty of Medicine of Sao Jose do Rio Preto, Sao Paulo, Brazil

ARTICLE INFO

Article History:
Received 20th June, 2022
Received in revised form
16th July, 2022
Accepted 15th July, 2022
Published online 30th August, 2022

Key Words:

Inflammatory bowel disease. Functional Nutrition. Dietary therapy. Nutritional treatment. Gut microbiota. Quality of life.

Corresponding author:
Idiberto José Zotarelli Filho

ABSTRACT

Background: The main risk factor for inflammatory bowel disease (IBD) is a positive family history of 10-25% of patients. Crohn's disease (CD) can affect individuals aged 15 to 40 years and aged 50 to 80 years, more frequently in women. Ulcerative colitis (UC) can start at any age. The pathogenesis of IBD is linked to genetically susceptible individuals, deregulated gut microbiota (GM) (dysbiosis), chronic inflammation, and poor eating patterns. Diet plays an important role in modulating the GM and can be applied as a therapeutic tool to improve the course of the disease. **Objective:** To carry out a systematic review and meta-analysis on the main interactions between dietary therapy, gut microbiota, and inflammatory bowel disease, to elucidate the main clinical outcomes after nutritional treatment. **Methods:** This study followed the international model of systematic review and meta-analysis (PRISMA). Clinical studies were included, involving randomized controlled, prospective, and retrospective studies published from 2010 to 2020. **Results:** It was found 17 randomized controlled clinical studies and other clinical studies on the modulation of diet in the control of IBD. These studies showed reductions in persistent bowel symptoms, improved gut microbiota, reduced markers of inflammation, and improved quality of life, with $p<0.05$ (95% CI). The studies were homogeneous ($I^2 = 98.95\%$), which increases the reliability of the clinical results about 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.

Citation: ***Aline Damasceno de Avance, Idiberto José Zotarelli Filho, Marilda Aparecida Milanez Morgado de Abreu et al .*** "Interactions between dietary therapy and gut microbiota in inflammatory bowel disease: a systematic review and meta-analysis*", International Journal of Development Research*, 12, (08), 58438-58448.

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 aged 15 to 40 years and aged 50 to 80 years, it has a higher percentage in women and has increased around 15 times in recent decades. The incidence is around 5:100,000 per year in the US and Europe, and the prevalence is around 50:100,000 (1). A study in the city of Sao Paulo in Brazil reported a prevalence of 14.8 cases of CD per 100,000 inhabitants (2). In relation to 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 of males, although some recent studies have shown the opposite (3). Latin America has a low prevalence. The United States, 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 Sao 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 unregulated 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 is largely focused on establishing the role of causal variants in gene expression (8). Despite this, the genetic risk locus identified so far explains 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 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, especially mutations in the NOD2 (or CARD15) gene, and also three other main mutations (R 702W, G908 R, and 1007 frameshift) were described and linked to the phenotype of the disease, the intestinal microbiota, and mucosal immunoregulation (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 sustain life. Endogenous metabolites and nutrients in the diet can directly influence epigenetic enzymes. Epigenetic modifications in DNA and histone proteins alter cell fate, 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 the activity of the signaling pathway. One example is via the mechanistic target signaling pathway of rapamycin (mTOR) and, in particular, the mTOR 1 complex (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 activation of mTORC1 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 the 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). Also, dietary manipulations and metabolites can affect tissue stem cells and drive 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, di*et al*so plays a decisive role in modulating the composition of the microbiome (13) and influencing the inflammatory response (17). Thus, a balanced diet with low fat and fiber content can be important in preventing dysbiosis and preserving the immune system (21). In this sense, GM 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. Lactobacilli and Bifidobacteria inhibit the growth of exogenous and/or harmful bacteria, stimulate immune functions, aid in digestion and/or absorption of food ingredients and minerals, and contribute to vitamin synthesis (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 appearance or worsening of IBD. Thus, to increase the numbers of these 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 a source of energy for intestinal epithelial cells and induce protective regulatory immune responses (23). The adaptive immune system of the GM 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). 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 (with CD4+ CD25+ phenotype) and Th2 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)), canceling 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 aimed to carry out a systematic review and meta-analysis on the main interactions between dietary therapy, GM, and inflammatory bowel disease, to elucidate the main clinical outcomes of the disease after nutritional treatment, analyzing the main macro and micronutrients, the effects of nutritional treatment on immunonutrition, enteral nutrition in pediatric Crohn's disease, the specific carbohydrate diet, fermentable oligosaccharides, disaccharides, monosaccharides, and polyol diet and the Mediterranean diet, and the clinical outcomes of the nutritional action on the activation of Lgr5+ crypt base cells that act as intestinal stem cells in the regeneration process.

METHODS

Study Design: This study followed the international model of systematic review and meta-analysis, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis) (31). Table 1 shows the main variables of the present study that were addressed according to the classification of the acronym PICOS (P=Patients; I=Intervention; C=Control; O=Outcomes; S=Study Design).

Table 1. PICOS framework (Patients; Intervention; Control; Outcomes and Study Design)

Patients	Patients with inflammatory bowel disease
Intervention	Nutrological treatment
Control	Pharmacological treatment only
Outcomes	Improvement of the inflammatory condition
Study Design	Randomized Controlled Studies; Prospectives; Retrospectives (observational/epidemiological)

Study eligibility criteria: Inclusion criteria were clinical studies, involving randomized controlled, prospective, and retrospective (observational/epidemiological) studies published from 2010 to 2020 on the main clinical outcomes of the nutritional treatment of inflammatory bowel diseases. The main characteristics of the studies analyzed in this meta-analysis included patients of all age groups and patients with inflammatory bowel disease, with or without the use of drugs, including treatment of biologicals or biosimilars, who received adequate nutritional treatment. Exclusion criteria for this study were case report studies, editorials, letters to the editor, review studies, and meta-analysis.

Figure 1. Example of the search structure in PubMed, the similar search strategy was used in other databases

PubMed	Inflammatory bowel disease **OR** Functional Nutrition **OR** Diet therapy **OR** Nutrological treatment **OR** Gut microbiota **OR** Quality of life
	AND
PubMed	Randomized controlled trial **OR**Prospective study**OR**Retrospective study **OR**Observational/Epidemiological studies
	NOT
PubMed	**OR** Case reports **OR** Editorials **OR**Letters to the editor **OR** Review study **OR** Meta-analysis

Bias Risk: The quality of scientific evidence in the studied studies was classified as high, moderate, low, or very low, according to the risk of bias in the body of evidence, clarity of comparisons, precision, and consistency in treatment effects, according to the criteria of the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (32). High quality of evidence was attributed to well-designed randomized controlled trials with consistent results. The quality of evidence was downgraded to moderate if 1 of the 4 evidence quality criteria is not met and lower if 2 or more are not met.

Low quality of evidence was attributed to studies with inconclusive results. The Cochrane Instrument was adopted to assess the risk of bias of the included studies (33).

Data Sources and Research Strategy: The search strategies for this systematic review and meta-analysis were based on the keywords (MeSH Terms) "Inflammatory bowel disease. Functional Nutrition. Dietary therapy. Nutritional treatment. Gut microbiota. Quality of life". The survey was conducted in November 2020 and developed in the databases of Scopus, Web of Science, PubMed/Medline, Embase, Science Direct, Ovid, Lilacs, Scielo, Cochrane Library, and EBSCO, including the National Institutes of Health RePORTER database Grant and Clinical Trials Records. In addition, a combination of keywords with the Boolean "OR", AND and the operator "NOT" were used to target the scientific articles of interest. Title and abstracts were examined under all conditions. Figure 1 shows the example of the search structure in PubMed. Similar search strategies were used in other databases.

Statistical Analysis: For data analysis, a database was built in a Microsoft Excel spreadsheet that was exported to the statistical program Minitab 18® (version 18, Minitab, LLC, State College, Pennsylvania, USA) (Minitab®) and also to OriginPro® 9 (DPR Group, Inc., Northampton, Massachusetts, USA) (Moberly, Bernards, Waynant, 2018). A common descriptive statistical analysis was performed, obtaining the values of total N, mean, standard deviation, confidence interval (CI), and percentage (frequency) for all variables. The R-sq (I^2) value was analyzed to discover the imprecision or heterogeneity of the analyses, adopting the codes of low association = <25%, medium association 25%<X<50%, and high association =>50%. Analyzes followed Pearson's chi-square test, with $p<0.05$ with statistical significance of association, with a confidence interval (CI) of 95%. Predictive Binary Logistic Regression analysis was also applied, adopting a reference group, with $p<0.05$ with statistical significance.

RESULTS

Summary of findings: The total of initial articles was 107. After the detailed literary search process and the use of search filters (PICOS) and MeSH Terms, as highlighted in Table 1 and Figure 1,

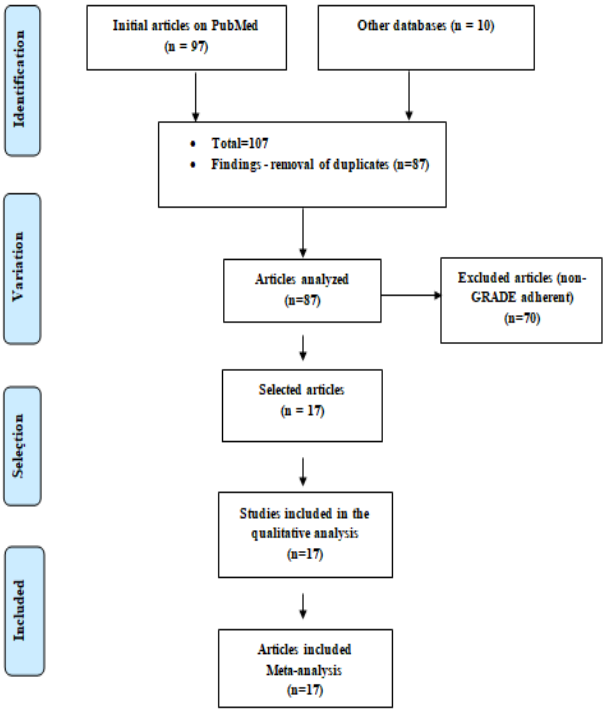


Figure 2. The selection process of scientific articles

respectively, the present study found seventeen (17) studies, being 11 randomized controlled clinical studies and 6 prospective studies in the last ten years, out of a total of 87 studies evaluated, showing a high quality of scientific evidence in the studied studies, with evidence level IA, according to the GRADE criteria. Still, the analyzed studies showed high homogeneity in the results (high association = >50%), presenting 98.95% to the R-sq value (I^2). Studies have shown the important role of diet modulation in the control and even remission of IBD. In this sense, they showed important reductions in persistent intestinal symptoms, improved GM, reduced inflammation markers, and improved quality of life. Figure 2 represents the flowchart of the selection and eligibility process for each study that entered the systematic review and meta-analysis.

Major Findings of Clinical Studies of the Last 10 Years - Meta-Analysis: The description of the results of each study (total of 17) followed the order presented in Tables 2 and 3. Most of the studies listed in this study followed a randomized and controlled model and were homogeneous in terms of symptom reduction, reduction of inflammatory bowel syndrome (IBS), improved quality of life (QoL), and improved GM, showing the important influence of dietary interventions on inflammation and the clinical outcomes of IBD, as shown in Tables 2 and 3. Only 4 studies presented the results of changes in the GM with dietary interventions (Table 3). Figure 3 graphically shows the prevalence of symptom reduction (88.24%), IBS reduction (88.24%), QoL improvement (88.24%), and GUT improvement (80%), showing an important influence of dietary interventions in the clinical outcomes of IBD. This Figure also shows the values of the mean and standard deviation to values from zero (0) to one (1), to express in decimal places that all mean values approximate the value of one (1). Table 4 shows the correlation between the Reduction of Symptoms vs. Improvement of QoL by the Chi-Square method (X^2). It is possible to observe the differences between the observed and expected data, analyzing which variables showed the greatest differences, which may indicate dependence or association between them. Furthermore, it is possible to compare the contributions to the Chi-Square statistics (Pearson and Likelihood Ratio) to analyze which variables had the highest values. As a result, there was an important dependence between the Reduction of Symptoms (1) vs. Improvement of 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 $p=0.019<0.05$. Still, the results obtained to the correlation between the variables Reduction SII vs. QoL increase by the Chi-Square method (X^2) are identical to those presented in Table 4. Table 5 shows the correlation between the Reduction of Symptoms vs. Improvement of GM (Improvement_MI) by the Chi-Square method (X^2). As a result, there was an important dependence between the Reduction of Symptoms (1) vs. Improvement_GM (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 $p=0.011<0.05$. Still, the results obtained to the correlation between the variables Reduction IBS vs. Improvement_GM by the Chi-Square method (X^2) are identical to those presented in Table 5. In Figure 4, through the predictive binary logistic regression analysis, it was observed that as the Reduction of Symptoms increases (from 0 to 1), there is also an increase in quality of life (Improvement of QoL), from 0 a 1, with $p=0.02<0.05$ in the 95% CI. Still, the results obtained to the regression analysis between the variables Reduction IBS vs. Improvement of QoL are identical to the one shown in this Figure. In Figure 5, it was observed that as the Reduction of Symptoms increases (from 0 to 1), there is also an increase in the Improvement of GM (Improvement_GM), from 0 to 1, with $p=0.01< 0.05$ at 95% CI. Still, the results obtained from the regression analysis between the variables Reduction IBS vs. Improvement_GM are identical to the one shown in this Figure.

DISCUSSION

The present study found important randomized controlled clinical studies and other clinical studies in the last ten years that showed the important role of diet modulation in the control of IBD (34-50).

Table 2. Major characteristics and general results of clinical studies in the last ten years that showed the important nutritional role of diet in the control and/or remission of IBD

AUTHORS / DATA	TYPE OF STUDY	N	IBD	DIET	MAJOR RESULTS (Improvement)	FOLLOW UP (months)
Cox *et al.*2020 [34]	RCT*	52	CD/ UC	↓ FODMAP**	- Persistent bowel symptoms - Gut microbiota - Circulating inflammation markers	1
Cox *et al.*2017 [35]	RCT	29	CD/UC	↓ FODMAP	- Persistent bowel symptoms - Gut microbiota - Circulating inflammation markers	1
Pedersen *et al.* 2017 [36]	RCT	89	CD/UC	↓ FODMAP	- Persistent bowel symptoms - Gut microbiota - Circulating inflammation markers	1.5
Bodini *et al.* 2019 [37]	RCT	55	CD/UC	↓ FODMAP	- Persistent bowel symptoms - Gut microbiota - Circulating inflammation markers	1.5
Papada *et al.* 2019 [38]	RCT	68	CD/UC	Mastiha (2.8g/day)	- Increased serum IL-6, fecal calprotectin and fecal lactoferrin in the placebo group - Attenuation in the increase of free amino acids levels in the Mastiha group	6
Jian *et al.*, 2018 [39]	Prospective controlled	97	UC	immunoglobulin G (IgG) guided exclusion diet	- Extraintestinal manifestations decreased from 7 to 2 in the intervention group - Higher mean body mass index and albumin in the intervention group	6
Albenberg *et al.* 2019 [40]	RCT	214	CD	↓ Red meat	Moderate to severe relapse occurred in 62% of participants in the group with higher meat consumption and 42% of participants in the low consumption group.	20
Svolos *et al.*,2018 [41]	RCT	25	CD	NEE vs. CD-TREAT***	In children who received CD-TREAT, 4 (80%) had a clinical response and 3 (60%) went into remission, with concurrent significant reductions in fecal calprotectin	2
Levine *et al.* 2019 [42]	Prospective controlled	74	CD	NEE vs. CDED plus PEN****	Children who received CDED plus PEN, corticosteroid-free remission was associated with sustained reductions in inflammation, based on serum C-reactive protein level, fecal calprotectin level and fecal Proteobacteria	3
Racine *et al.* 2016 [43]	Prospective controlled	256 (UC) 117 (CD) 4(controle por caso)	CD/ UC	High sugar content and soft drinks reduction of vegetables	Sugar and soft drink consumers were at greater risk of UC if they had low vegetable consumption	24
Braly *et al.*, 2017 [44]	Prospective controlled	8	CD/UC	Specific carbohydrates	Six of the 8 subjects gained weight, 1 subject lost weight and 1 did not change weight. Energy intake was significantly greater than 100% of the recommended daily intake (RDI)/adequate intake for 64% of completed daily intakes	3
Machado *et al.*, 2015 [45]	Prospective controlled	68	CD	Whey and Soy Proteins	Supplementation with whey and soy proteins alters body composition by reducing body fat and contributing to inflammation control	4
Brotherton *et al.*, 2014 [46]	RCT	7	CD	Cereal fibers (wheat)	It did not cause adverse effects, and participants reported improvements in health-related quality of life (p=0.028) and gastrointestinal function (p=0.008) compared to the control group.	1
Sökülmez *et al.*, 2014 [47]	RCT	38	CD/UC	Regulated hospital diets (macronutrients and fiber)	Consumption levels of macronutrients and water-soluble fiber improved persistent bowel symptoms with statistical significance	1
Kyaw *et al.*, 2014 [48]	RCT	112	UC	Dietary guidelines in the form of an educational booklet that has been recommended for use for 4-6 weeks during the disease outbreak, that patients eat sparingly and frequently (four to six times a day), drink adequate fluids, decrease excessive fat intake, decrease in simple carbohydrates and decrease in fiber-rich foods during the crisis.	- There was a mean increase in the Inflammatory Bowel Disease Questionnaire score in the intervention group compared to a decrease in score in the control group. - A total of 69% of patients in the intervention group found dietary advice significantly helpful	6
Hanai *et al.*, 2012 [49]	RCT	95	CD	Elemental (≥900 kcal/day) and 6-mercaptopurine	- No significant differences were found between 6-mercaptopurine and Elental. - In the 6-mercaptopurine group, 2 patients had liver damage and one developed alopecia. -Elental should be useful for long-term maintenance therapy in Crohn's disease	24
Kang *et al.*, 2015 [50]	Prospective controlled	78	CD	Short-term PEN (n=17) (1 month)	- Nutritional status improved substantially after 1 year of treatment in the severe CD group. - The <13 years group showed better improvement in nutritional status than the ≥13 years group	12

*RCT - randomized controlled trial. ** FODMAP -Fermentable Oligo-, Di-, Mono-saccharides, and Polyols *** Individualized food-based diet (CD-TREAT), with similar composition to EEN ****CD exclusion diet (CDED), partial enteral nutrition (PEN)

Table 3. The main outcomes of each study were listed as reduction of symptoms, reduction of inflammatory bowel syndrome (IBS), improvement of 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	Improvement of QoL	Improvement of gut Microbiota
Cox et al.2020 (34)	1	1	1	1
Cox et al.2017 (35)	1	1	1	**(-)
Pedersen et al. 2017 (36)	1	1	1	(-)
Bodini et al. 2019 (37)	1	1	1	(-)
Papada et al. 2019 (38)	0	0	0	(-)
Jian et al., 2018 (39)	1	1	1	(-)
Albenberg et al. 2019 (40)	1	1	1	(-)
Svolos et al.,2018 (41)	1	1	1	1
Levine et al. 2019 (42)	1	1	1	1
Racine et al. 2016 (43)	0	0	0	0
Braly et al., 2017 (44)	1	1	1	1
Machado et al., 2015 (45)	1	1	1	(-)
Brotherton et al., 2014 (46)	1	1	1	(-)
Sökülmez et al., 2014 (47)	1	1	1	(-)
Kyaw et al., 2014 (48)	1	1	1	(-)
Hanai et al., 2012 (49)	1	1	1	(-)
Kang et al., 2015 (50)	1	1	1	(-)

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

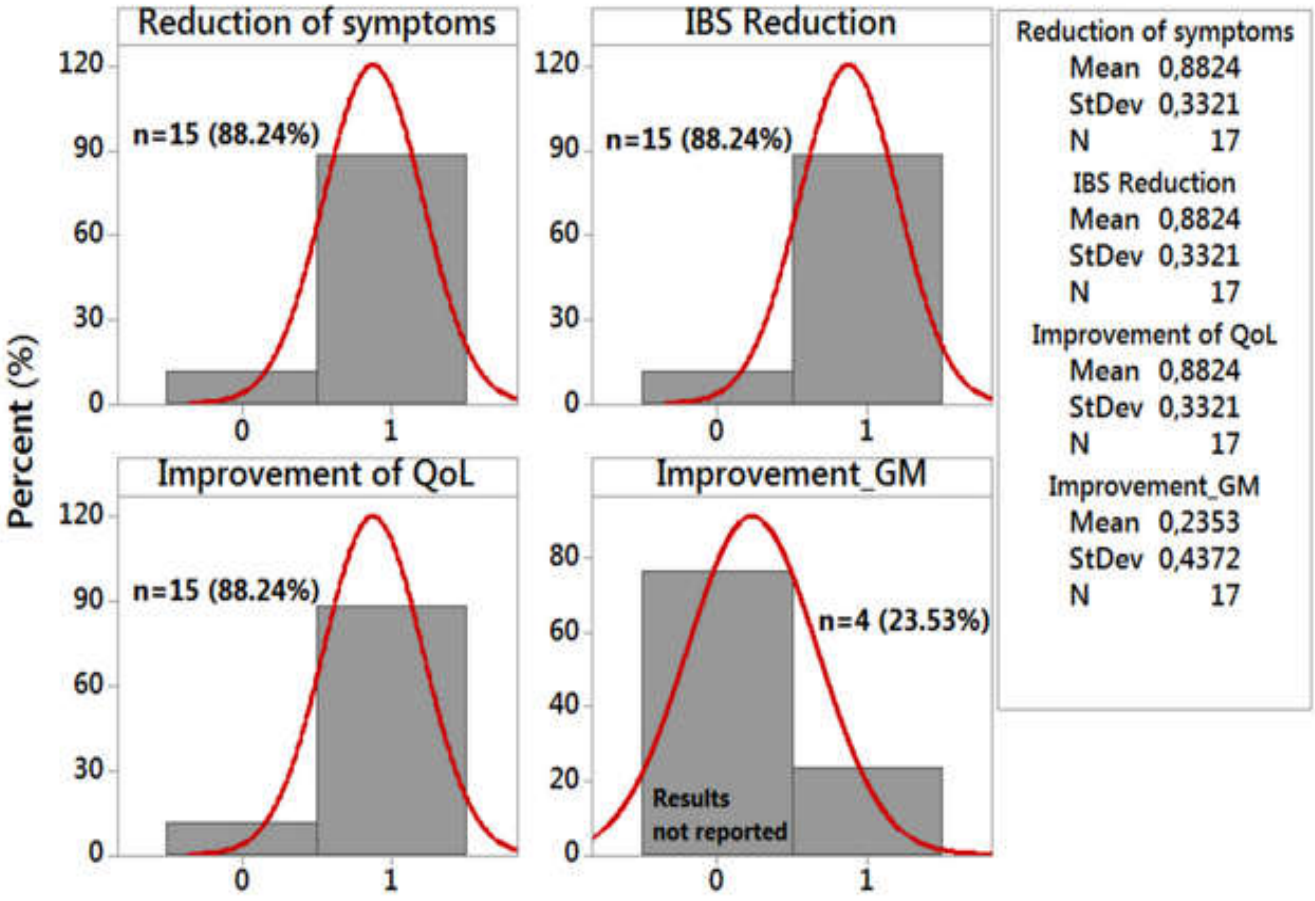


Table 4. Shows the correlation between the Reduction of Symptoms vs. Improvement of QoL by the Chi-Square method (X^2). It is possible to observe the differences between the observed and expected data, analyzing which variables showed the greatest differences, which may indicate dependence or association between them. Furthermore, it is possible to compare the contributions to the Chi-Square statistics (Pearson and Likelihood Ratio) to analyze which variables had the highest values. As a result, there was an important dependence between the Reduction of Symptoms (1) vs. Improvement of 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. Still, the results obtained to the correlation between the variables Reduction SII vs. QoL increase by the Chi-Square method (X^2) are identical to those presented in Table 4.

Table 4. Correlation between the Reduction of Symptoms vs. QoL increase by the Chi-Square method (X^2), with p<0.05 with a statistically significant association, at 95% CI. Code 1 means "yes" answer, and code 0 means "no" answer in terms of statistical denotation

Variables	Improvement of QoL (0)	Improvement of QoL (1)	Total
Reduction of Symptoms (0) (observed)	2	0	2
(expected)	0.235	1.765	
Contributed to Chi-square	13.235	1.765	
Reduction of Symptoms (1) (observed)	0	15	15
(expected)	1.765	0.154	
Contributed to Chi-square	1.765	14.336	
Total	2	15	17
Chi-Square Test	Chi-Square	DF	p-value
Pearson	17.000	1	0.019
Likelihood Ratio	12.315	1	0.019

Table 5. Correlation between the Reduction of Symptoms vs. Improvement_GM by the Chi-Square method (X^2), with p<0.05 with a statistically significant association, at 95% CI. Code 1 means "yes" answer, and code 0 means "no" answer in terms of statistical denotation

Variables	Reduction of Symptoms (0)	Reduction of Symptoms (1)	Total
			13
Improvement_GM (0) (observed)	2	11	
(expected)	1.529	11.471	
Contributed to Chi-square	0.14480	0.01931	
Improvement_GM (1) (observed)	0	4	4
(expected)	0.471	0.2387	
Contributed to Chi-square	0.47059	19.0627	
Total			17
Chi-Square Test	Chi-Square	DF	p-value
Pearson	21.000	1	0.011
Likelihood Ratio	18.415	1	0.011

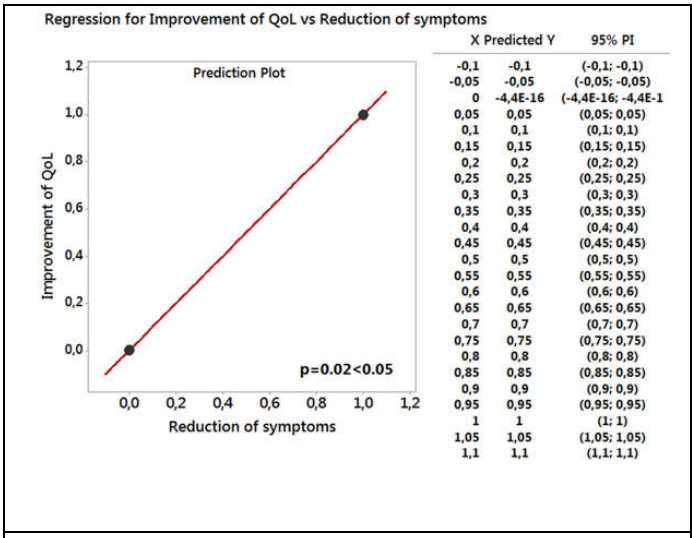


Figure 4. Predictive binary logistic regression analysis regarding symptom reduction and QoL improvement, with p<0.05 significant

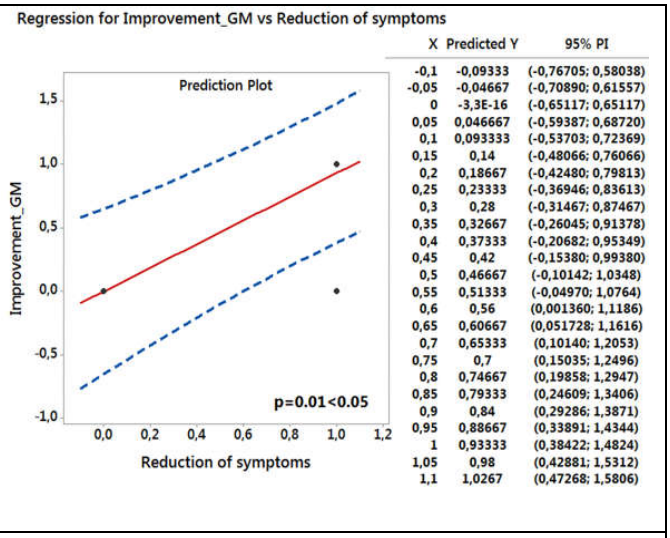


Figure 5. Predictive binary logistic regression analysis regarding symptom reduction and QoL increase, with p<0.05 significant

In this sense, these studies showed important reductions in persistent intestinal symptoms, improvement in GM, reduction in circulating markers of inflammation, and improvement in quality of life. In this study, the results of the meta-analysis showed that there was a prevalence of symptom reduction (88.24%), IBS reduction (88.24%), QoL improvement (88.24%), and GM improvement (80 %), showing an important influence of dietary interventions. Added to this, the Chi-Square method (X^2, Pearson and Likelihood Ratio) showed an important association between the variables Reduction of Symptoms and Increase QoL, IBS Reduction and Improvement of QoL, Reduction of Symptoms and Improvement_GM and between IBS Reduction and Improvement_MI, showing significantly, the dietary interventions presented in Table 2 can positively impact on the reduction of symptoms, reduction of IBS and change in the GM, which, together, improve the quality of life of patients with IBD. In this context, these findings were corroborated by the predictive binary logistic regression analysis, which showed that as the reduction in symptoms increases, there is also an increase in quality of life, with p<0.05. The same result was in relation to the regression analysis between the reduction in IBS and the increase in quality of life, as

well as between the reduction in symptoms and the increase in the improvement in the GM and between the reduction in IBS and the improvement in the GM. In this setting, the history of nutritional therapy for IBD began with initial observations in hospitalized adults with severe CD who improved with EEN (51-53). Since the initial EEN report in the late 1970s, there have been over 200 publications on SEN 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 (54 .55). In this context, many studies have evaluated the ability of diet to modulate the 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 energy source 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 patients with IBD and specific dietary emulsifiers (carboxymethylcellulose and polysorbate 80) have been shown to induce low-grade inflammation and metabolic syndrome in nature-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 being well described (61-63), 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 limited by a lack of long-term results. In a review recently published by Cochrane, Limketkai *et al*. analyzed 18 randomized controlled trials, comprising 1878 participants, published between 1965 and 2018 (61).

In addition, intervention diets involved complete exclusion or significant limitation of one or more food groups. The main examples are diets included with low carbohydrate content, microparticles, low calcium, red and processed meat, low disaccharides, grains, saturated fat, symptom-guided diets, highly restricted organic diet, no milk, anti-inflammatory diet, and free diet of carrageenan. Different studies looked at various outcomes, including induction of remission, clinical relapse, surrogate biomarkers of inflammation, endoscopic improvement, quality of life, and need for surgery (64-66). In this regard, the most rigorously studied dietary interventions in IBD are exclusive enteral nutrition (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 (67,68). EEN is equivalent to corticosteroid therapy in inducing clinical remission and superior in achieving endoscopic mucosal healing (67,69). In addition, EEN is first-line therapy for CD pediatricians worldwide, and the treatment protocol typically involves administering the formula to supply 100% of caloric requirements and excluding food for 6–8 weeks (69). In this sense, however, the exact mechanism by which EEN exerts its effect is unknown. Hypothetical mechanisms include limiting antigen exposure, antigenic monotony, improving nutritional status and nutrient delivery, altering intestinal microbiota and immune response, avoiding deleterious effects (70). As EEN and exclusion diets are extremely different interventions, it is likely that the mechanism by which they affect the disease is similarly different. Despite the improvement of the disease, studies examining fecal metagenomics in children with CD and 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 intestinal microbiota also decreased with EEN, as well as genes encoding proteins involved in the biosynthesis of B-complex vitamins (71). In studies evaluating 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 EEN and changes in the GM needs further characterization and may result from changes in beneficial or harmful metabolites produced by the bacteria. In this setting, EEN has the ability to drive CD into remission, but EEN 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 to be useful in both CD and UC cases (73,74). In this sense, one of the most studied exclusion diets is the specific carbohydrate (SC) 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 of this, a study of more than 12 weeks in children and adolescents used capsule endoscopy and demonstrated mucosal healing (77). SC therapy has been shown to result in significant changes in the composition of the GM (73). In addition, 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 may 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 DC was treated with partial enteral nutrition (a formula that provides approximately 50% of the daily caloric intake) and the CDED has shown success in achieving induction of clinical remission (65). Also, certain food additives can promote the pathogenesis of CD, but so far the assessment 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 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, and aluminosilicates. At baseline, 138 participants, mean age 14.2 ± 2.8 years, 95% with inactive or mild disease, were enrolled. A total of 1325 unique foods were registered. The average 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 often consume food additives, and the impact on the disease course needs further study (78).Besides, the anti-inflammatory diet for IBD (IBD-AID) is based on whole foods that restrict 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 di*et al*so 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, the worsening of dysbiosis and decreased production of butyrate is demonstrated with EEN therapy and is apparently counter-intuitive, as is the lack of any fiber content in commonly used formulas for EEN (81,82). It may be the case that EEN acts through a unique mechanism of action to impact inflammation in IBD compared to the action of restriction diets. As the GM can lead to inflammation and respond to underlying inflammation, further elucidation of the complex between 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 can 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 fruits, vegetables, and fiber intake have been shown to have protective effects (83). Higher meat intake was associated with an increased risk of relapse of UC in adults and a decreased rate of achieving CD remission in children on partial enteral nutrition therapy (84,85). Even though a variety of exclusion diets have shown efficacy in treating inflammation in small case

series reports, further studies are needed to better substantiate these findings. While 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 towards more targeted diets.

CONCLUSION

The present study analyzed the main interactions between dietary therapy, gut microbiota, and inflammatory bowel disease, elucidating the main clinical outcomes of the disease after nutritional treatment. As a corollary, important randomized controlled clinical studies were found in the last ten years that showed the important role of diet modulation in the control and even in the remission of IBD, revealing important reductions in persistent intestinal symptoms, in the balance of the gut microbiota, in reduction of inflammation markers and improved quality of life.

LIMITATIONS

Although these included studies may be superior because they are randomized controlled trials, additional studies on EEN and broader restricted diets may show a clearer impact on IBD. The mechanism by which dietary interventions influence IBD remains unknown, requiring the development of studies involving the microbiome, metabolome, and proteome. Therefore, the main areas requiring research are on the impact of dietary therapies with/without concomitant immunosuppression, the impact of long-term dietary therapies, mechanism of action for dietary therapies, exclusion diets - important dietary components, cost-benefit analysis of dietary interventions; and dietary approaches aimed at selectively modulating the microbiome.

FUTURE PERSPECTIVES

Dietary trials present challenges, but the ability to use nutrition to treat illness is an opportunity. It has long been accepted that dietary exposures are associated with the risk of developing IBD. Dietary intervention with EEN or even a change in fat and fiber consumption results in a tangible change in the gut microbiome (9). Efforts have been put into developing therapeutic approaches to selectively modulate the GM, including prebiotics, probiotics, antibiotics, and fecal transplantation, but persistent microbiome formation requires ongoing maintenance of these therapies (76). Dietary therapies that reshape food consumption patterns can alter exposure to harmful substances such as selected food additives, directly influence the gut microbiome, and also have a direct impact on the functioning of the host's immune system (86). The currently accepted dietary therapies are EEN in pediatric CD, dietary therapies for symptom control, and nutritional therapy to support malnutrition. Many individuals institute dietary changes based on a variety of sources of information and also as a reaction to the onset of IBD symptoms. Recommendations are of variable validity. Data on EEN therapy have led to its use as standard therapy for remission induction in pediatric CD (87). The limitation of EEN is the difficulty in sustaining the intervention. Food-based IBD trials may involve exclusion, supplementation, or dramatic changes in dietary pattern (62). So far, it seems unlikely that exclusion or targeted supplementation has a role in IBD therapy, but deeper changes in eating patterns have shown promise. While individual dietary components may be harmful (such as refined sugars, high fat and specific food additives), it may be that the effect of these components is balanced or attenuated by other components (eg fiber, antioxidants, bioactive molecules) (86,87). As such, future dietary trials in IBD should consider the global dietary pattern, while considering the role of individual dietary components. Currently, published trials for IBD exclusion diets generally include a description of the general principles of the diet, but do not characterize the variability within the proposed intervention and the impact this has on clinical outcomes. Challenges to be considered in IBD food-based dietary trials include issues with participant compliance, measuring compliance, and variability within a particular dietary intervention (9). While randomized controlled trials are the gold standard for generating evidence to guide clinical practice, the design of innovative studies and data from larger cohort studies, along with preclinical data, can also help to substantiate existing literature that supports dietary therapies in IBD. The paradigm of relying only on data from controlled trials is a challenge in the setting of dietary interventions that require profound changes in the usual diet, the need to maintain compliance, and the cost of implementing such trials (87). Also, as diet can be a primary or adjuvant therapy, the magnitude of effect considered significant may be different for dietary studies compared to drug studies. For example, if a dietary intervention results in a lack of endoscopic mucosal healing but significantly decreases the inflammatory burden measured by biochemical markers, this may suggest that the intervention has a promising role as an adjunct to conventional immunosuppressive therapy. As the mechanism by which dietary therapy affects IBD involves intestinal exposures, the microbiome and triggering of the mucosal immune system, the diet has the potential to be used in conjunction with medications to improve outcomes and durability and minimize the risks associated with immunosuppression (9). Recognition of the need for additional clinical trial data, inherent uncertainty of efficacy for all IBD therapies, and the potential benefit of dietary interventions will help guide progress towards a better understanding of the utility of dietary therapy for individuals with IBD.

Funding: This study had its own financing and did not have sponsorship or partnerships.

Disclosure Statement: Nothing to declare.

Conflict Of Interest: Nothing to declare.

Data Availability: The authors declare that data supporting the findings of this study are available within the article.

REFERENCES

1. Danilova NA, Abdulkhakov SR, Grigoryeva TV, Markelova MI, Vasilyev IY, Boulygina EA, Ardatskaya MD, Pavlenko AV, Tyakht AV, Odintsova AK, Abdulkhakov RA. Markers of dysbiosis in patients with ulcerative colitis and Crohn's disease. Ter Arkh. 2019 May 15;91(4):17-24. doi: 10.26442/00403660.2019.04.000211.
2. Ministério Da Saúde/Secretaria De Atenção À Saúde (Portaria Conjunta Nº 14, De 28 De Novembro De 2017). Aprova o Protocolo Clínico e Diretrizes Terapêuticas da Doença de Crohn). Acessado em fevereiro de 2021.
3. MINISTÉRIO DA SAÚDE/SECRETARIA DE ATENÇÃO À SAÚDE (CONITEC). Protocolo Clínico e Diretrizes Terapêuticas Retocolite Ulcerativa. Acessado em setembro de 2020.
4. Scaldaferri F, Correale C, Gasbarrini A, Danese S. Mucosal biomarkers in inflammatory bowel disease: Key pathogenic players or disease predictors? World J Gastroenterol. 2010 June 7; 16(21): 2616–2625.
5. Côté-Daigneault J, Bouin M, Lahaie R, Colombel JF, Poitras P. Biologics in inflammatory bowel disease: what are the data? United European Gastroenterol J. 2015;3(5):419-28.
6. Roda G, Chien Ng S, Kotze PG, *et al*. Crohn's disease (published correction appears in Nat Rev Dis Primers. 2020 Apr 6;6(1):26) (published correction appears in Nat Rev Dis Primers. 2020 May 20;6(1):42) (published correction appears in Nat Rev Dis Primers. 2020 Jun 19;6(1):51). Nat Rev Dis Primers. 2020;6(1):22. Published 2020 Apr 2. doi:10.1038/s41572-020-0156-2

7. Khanna S, Raffals LE. The Microbiome in Crohn's Disease: Role in Pathogenesis and Role of Microbiome Replacement Therapies. Gastroenterol Clin North Am. 2017 Sep;46(3):481-492. doi: 10.1016/j.gtc.2017.05.004. Epub 2017 Jul 19.
8. He Q, Gao Y, Jie Z, Yu X, Laursen JM, Xiao L, Li Y, Li L, Zhang F, Feng Q, Li X, Yu J, Liu C, Lan P, Yan T, Liu X, Xu X, Yang H, Wang J, Madsen L, Brix S, Wang J, Kristiansen K, Jia H. Two distinct metacommunities characterize the gut microbiota in Crohn's disease patients. Gigascience. 2017 Jul 1;6(7):1-11. doi: 10.1093/gigascience/gix050.
9. Green N, Miller T, Suskind D, Lee D. A Review of Dietary Therapy for IBD and a Vision for the Future. Nutrients. 2019 Apr 26;11(5). pii: E947. doi: 10.3390/nu11050947.
10. Benjamin JL, Hedin CR, Koutsoumpas A, Ng SC, McCarthy NE, Hart AL, *et al*. Randomised, double-blind, placebo-controlled trial of fructo-oligosaccharides in active Crohn's disease. Gut 2011;60:923-9.
11. Bernstein CN, Loftus EV Jr, Ng SC, Lakatos PL, Moum B; Epidemiology and Natural History Task Force of the International Organization for the Study of Inflammatory Bowel Disease (IOIBD). Hospitalisations and surgery in Crohn's disease. Gut 2012;61:622-9.
12. Hanauer SB, Sandborn W; Practice Parameters Committee of the American College of Gastroenterology. Management of Crohn's disease in adults. Am J Gastroenterol 2001;96:635-43.
13. Hedin C, Whelan K, Lindsay JO. Evidence for the use of probiotics and prebiotics in inflammatory bowel disease: a review of clinical trials. Proc Nutr Soc 2007;66:307-15.
14. Kirschner BS. Differences in the management of inflammatory bowel disease in children and adolescents compared to adults. Neth J Med 1998;53:S13-8.
15. Landy J, Al-Hassi HO, McLaughlin SD, *et al*. Review article: faecal transplantation therapy for gastrointestinal disease. Aliment Pharmacol Ther 2011;34:409-15.
16. Langholz E, Munkholm P, Krasilnikoff PA, Binder V. Inflammatory bowel diseases with onset in childhood: clinical features, morbidity, and mortality in a regional cohort. Scand J Gastroenterol 1997;32:139-47.
17. Meijer BJ, Dieleman LA. Probiotics in the treatment of human inflammatory bowel diseases: update 2011. J Clin Gastroenterol 2011;45:S139-44.
18. Shapira SN, Christofk HR. Metabolic Regulation of Tissue Stem Cells. Trends Cell Biol. 2020 Jul;30(7):566-576. doi: 10.1016/j.tcb.2020.04.004. Epub 2020 Apr 28. PMID: 32359707).
19. Basson A. Vitamin D. Crohn's disease in the adult patient: a review. J Parenter Enteral Nutr. 2014;38:438–58.
20. Roth MP, Petersen GM, McElree C, Vadheim CM, Panish JF, Rotter JI. Familial empiric risk estimates of inflammatory bowel disease in Ashkenazi Jews. Gastroenterology. 1989;96(4):1016-20.
21. Lee YK, Menezes JS, Umesaki Y, Mazmanian SK. Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proc Natl Acad Sci USA. 2011;108(suppl 1):4615-4622.
22. Teng F, Klinger CN, Felix KM, *et al*. Gut microbiota drive autoimmune arthritis by promoting differentiation and migration of Peyer's patch T follicular helper cells. Immunity. 2016;44(4):875-888.
23. Donohoe DR, Garge N, Zhang X, *et al*. The microbiome and butyrate regulate energy metabolism and autophagy in the mammalian colon. Cell Metab. 2011;13(5):517-526.
24. Smith PM, Howitt MR, Panikov N, *et al*. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. Science. 2013;341(6145):569-573.
25. Mowat C, Cole A, Windsor A, Ahmad T, Arnott I, Driscoll R, *et al*. Guidelines for the management of inflammatory bowel disease in adults. Gut 2011;60:571-607.
26. Schloss PD, Westcott SL, Ryabin T, Hall JR, Hartmann M, Hollister EB, *et al*. Introducing mothur: open-source, platform-independent, community-supported software for describing and comparing microbial communities. Appl Environ Microbiol 2009;75:7537-41.
27. Basson A. Vitamin D. Crohn's disease in the adult patient: a review. J Parenter Enteral Nutr. 2014;38:438–58.
28. Xu XR, Liu CQ, Feng BS. Dysregulation of mucosal immune response in pathogenesis of inflammatory bowel disease. World J Gastroenterol. 2014;20:3255–64.
29. Adamiak T, Walkiewicz-Jedrzejczak D, Fish D, Brown C, Tung J, Khan K, et al. Incidence, clinical characteristics, and natural history of pediatric IBD in Wisconsin: a population-based epidemiological study. Inflamm Bowel Dis. 2013;19(6):1218-23.
30. Den Besten G, Bleeker A, Gerding A, *et al*. Short-chain fatty acids protect against high-fat diet-induced obesity via a PPARγ-dependent switch from lipogenesis to fat oxidation. Diabetes. 2015;64(7):2398-2408.
31. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009) Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. https://doi.org/10.1371/journal.pmed.1000097.
32. Balshem H *et al*. Grade guidelines: 3 ratng the quality of evidence. Journal of Clinical Epidemiology, Maryland Heights, v. 64, n. 4, p. 401-406, 2011
33. Higgins J, Green S. Cochrane Handbook for Systematic Reviews of Interventions. Version 5.1.0 (updated March 2011). The Cochrane Collaboration; 2011.
34. Cox SR, Lindsay JO, Fromentin S, Stagg AJ, McCarthy NE, Galleron N, Ibraim SB, Roume H, Levenez F, Pons N, Maziers N, Lomer MC, Ehrlich SD, Irving PM, Whelan K. Effects of Low FODMAP Diet on Symptoms, Fecal Microbiome, and Markers of Inflammation in Patients With Quiescent Inflammatory Bowel Disease in a Randomized Trial. Gastroenterology. 2020 Jan;158(1):176-188.e7. doi: 10.1053/j.gastro.2019.09.024. Epub 2019 Oct 2. PMID: 31586453.
35. Cox SR, Prince AC, Myers CE, Irving PM, Lindsay JO, Lomer MC, Whelan K. Fermentable Carbohydrates (FODMAPs) Exacerbate Functional Gastrointestinal Symptoms in Patients With Inflammatory Bowel Disease: A Randomised, Double-blind, Placebo-controlled, Cross-over, Re-challenge Trial. J Crohns Colitis. 2017 Dec 4;11(12):1420-1429. doi: 10.1093/ecco-jcc/jjx073. PMID: 28525543.
36. Pedersen N, Ankersen DV, Felding M, Wachmann H, Végh Z, Molzen L, Burisch J, Andersen JR, Munkholm P. Low-FODMAP diet reduces irritable bowel symptoms in patients with inflammatory bowel disease. World J Gastroenterol. 2017 May 14;23(18):3356-3366. doi: 10.3748/wjg.v23.i18.3356. PMID: 28566897; PMCID: PMC5434443.
37. Bodini G, Zanella C, Crespi M, Lo Pumo S, Demarzo MG, Savarino E, Savarino V, Giannini EG. A randomized, 6-wk trial of a low FODMAP diet in patients with inflammatory bowel disease. Nutrition. 2019 Nov-Dec;67-68:110542. doi: 10.1016/j.nut.2019.06.023. Epub 2019 Jul 1. PMID: 31470260.
38. Papada E, Amerikanou C, Torović L, Kalogeropoulos N, Tzavara C, Forbes A, Kaliora AC. Plasma free amino acid profile in quiescent Inflammatory Bowel Disease patients orally administered with Mastiha (Pistacia lentiscus); a randomised clinical trial. Phytomedicine. 2019 Mar 15;56:40-47. doi: 10.1016/j.phymed.2018.08.008. Epub 2018 Aug 13. PMID: 30668352.
39. Jian L, Anqi H, Gang L, Litian W, Yanyan X, Mengdi W, Tong L. Food Exclusion Based on IgG Antibodies Alleviates Symptoms in Ulcerative Colitis: A Prospective Study. Inflamm Bowel Dis. 2018 Aug 16;24(9):1918-1925. doi: 10.1093/ibd/izy110. PMID: 29788288.
40. Albenberg L, Brensinger CM, Wu Q, Gilroy E, Kappelman MD, Sandler RS, Lewis JD. A Diet Low in Red and Processed Meat Does Not Reduce Rate of Crohn's Disease Flares. Gastroenterology. 2019 Jul;157(1):128-136.e5. doi: 10.1053/j.gastro.2019.03.015. Epub 2019 Mar 11. PMID: 30872105; PMCID: PMC6726378.

41. Svolos V, Hansen R, Nichols B, Quince C, Ijaz UZ, Papadopoulou RT, Edwards CA, Watson D, Alghamdi A, Brejnrod A, Ansalone C, Duncan H, Gervais L, Tayler R, Salmond J, Bolognini D, Klopfleisch R, Gaya DR, Milling S, Russell RK, Gerasimidis K. Treatment of Active Crohn's Disease With an Ordinary Food-based Diet That Replicates Exclusive Enteral Nutrition. Gastroenterology. 2019 Apr;156(5):1354-1367.e6. doi: 10.1053/j.gastro.2018.12.002. Epub 2018 Dec 11. PMID: 30550821.
42. Levine A, Wine E, Assa A, Sigall Boneh R, Shaoul R, Kori M, Cohen S, Peleg S, Shamaly H, On A, Millman P, Abramas L, Ziv-Baran T, Grant S, Abitbol G, Dunn KA, Bielawski JP, Van Limbergen J. Crohn's Disease Exclusion Diet Plus Partial Enteral Nutrition Induces Sustained Remission in a Randomized Controlled Trial. Gastroenterology. 2019 Aug;157(2):440-450.e8. doi: 10.1053/j.gastro.2019.04.021. Epub 2019 Jun 4. PMID: 31170412.
43. Racine A, Carbonnel F, Chan SS, Hart AR, Bueno-de-Mesquita HB, Oldenburg B, van Schaik FD, Tjønneland A, Olsen A, Dahm CC, Key T, Luben R, Khaw KT, Riboli E, Grip O, Lindgren S, Hallmans G, Karling P, Clavel-Chapelon F, Bergman MM, Boeing H, Kaaks R, Katzke VA, Palli D, Masala G, Jantchou P, Boutron-Ruault MC. Dietary Patterns and Risk of Inflammatory Bowel Disease in Europe: Results from the EPIC Study. Inflamm Bowel Dis. 2016 Feb;22(2):345-54. doi: 10.1097/MIB.0000000000000638. PMID: 26717318.
44. Braly K, Williamson N, Shaffer ML, Lee D, Wahbeh G, Klein J, Giefer M, Suskind DL. Nutritional Adequacy of the Specific Carbohydrate Diet in Pediatric Inflammatory Bowel Disease. J Pediatr Gastroenterol Nutr. 2017 Nov;65(5):533-538. doi: 10.1097/MPG.0000000000001613. PMID: 28825603; PMCID: PMC5653423.
45. Machado JF, Oya V, Coy CS, Morcillo AM, Severino SD, Wu C, Sgarbieri VC, Vilela MM. Whey and soy protein supplements changes body composition in patients with Crohn's disease undergoing azathioprine and anti-TNF-alpha therapy. Nutr Hosp. 2015 Apr 1;31(4):1603-10. doi: 10.3305/nh.2015.31.4.8362. PMID: 25795947.
46. Brotherton CS, Taylor AG, Bourguignon C, Anderson JG. A high-fiber diet may improve bowel function and health-related quality of life in patients with Crohn disease. Gastroenterol Nurs. 2014 May-Jun;37(3):206-16. doi: 10.1097/SGA.0000000000000047. PMID: 24871666; PMCID: PMC4260718.
47. Sökülmez P, Demirbağ AE, Arslan P, Dişibeyaz S. Effects of enteral nutritional support on malnourished patients with inflammatory bowel disease by subjective global assessment. Turk J Gastroenterol. 2014 Oct;25(5):493-507. doi: 10.5152/tjg.2014.4955. PMID: 25417609.
48. Kyaw MH, Moshkovska T, Mayberry J. A prospective, randomized, controlled, exploratory study of comprehensive dietary advice in ulcerative colitis: impact on disease activity and quality of life. Eur J Gastroenterol Hepatol. 2014 Aug;26(8):910-7. doi: 10.1097/MEG.0000000000000127. PMID: 24942954.
49. Hanai H, Iida T, Takeuchi K, Arai H, Arai O, Abe J, Tanaka T, Maruyama Y, Ikeya K, Sugimoto K, Nakamura T, Nakamura K, Watanabe F. Nutritional therapy versus 6-mercaptopurine as maintenance therapy in patients with Crohn's disease. Dig Liver Dis. 2012 Aug;44(8):649-54. doi: 10.1016/j.dld.2012.03.007. Epub 2012 Apr 27. PMID: 22542605.
50. Kang Y, Kim S, Kim SY, Koh H. Effect of short-term partial enteral nutrition on the treatment of younger patients with severe Crohn's disease. Gut Liver. 2015 Jan;9(1):87-93. doi: 10.5009/gnl13345. PMID: 25170058; PMCID: PMC4282862.
51. Green N, Miller T, Suskind D, Lee D. A Review of Dietary Therapy for IBD and a Vision for the Future. Nutrients. 2019 Apr 26;11(5):947. doi: 10.3390/nu11050947. PMID: 31035465; PMCID: PMC6566428.
52. Voitk, A.J.; Brown, R.A.; McArdle, A.H.; Hinchey, E.J.; Gurd, F.N. Clinical uses of an elemental diet: Preliminary studies. *Can. Med. Assoc. J.* 1972, *107*, 123–129.
53. Voitk, A.J.; Echave, V.; Feller, J.H.; Brown, R.A.; Gurd, F.N. Experience with elemental diet in the treatment of inflammatory bowel disease. Is this primary therapy? *Arch. Surg.* 1973, *107*, 329–333.
54. Ricour, C.; Duhamel, J.F.; Nihoul-Fekete, C. Use of parenteral and elementary enteral nutrition in the treatment of Crohn's disease and ulcerative colitis in children. *Arch. Fr. Pediatr.* 1977, *34*, 505–513.
55. Navarro, J.; Vargas, J.; Cezard, J.P.; Charritat, J.L.; Polonovski, C. Prolonged constant rate elemental enteral nutrition in Crohn's disease. *J. Pediatr. Gastroenterol. Nutr.* 1982, *1*, 541–546.
56. Canani, R.B.; Costanzo, M.D.; Leone, L.; Pedata, M.; Meli, R.; Calignano, A. Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World J. Gastroenterol.* 2011, *17*, 1519–1528.
57. Van Immerseel, F.; Ducatelle, R.; De Vos, M.; Boon, N.; Van De Wiele, T.; Verbeke, K.; Rutgeerts, P.; Sas, B.; Louis, P.; Flint, H.J. Butyric acid-producing anaerobic bacteria as a novel probiotic treatment approach for inflammatory bowel disease. *J. Med. Microbiol.* 2010, *59*, 141–143.
58. Smith, P.M.; Howitt, M.R.; Panikov, N.; Michaud, M.; Gallini, C.A.; Bohlooly-y, M.; Glickman, J.N.; Garrett, W.S. The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis. *Science* 2013, *341*, 569–573.
59. Thorburn, A.N.; Macia, L.; Mackay, C.R. Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity* 2014, *40*, 833–842.
60. Chassaing, B.; Koren, O.; Goodrich, J.K.; Poole, A.C.; Srinivasan, S.; Ley, R.E.; Gewirtz, A.T. Dietary emulsifiers impact the mouse gut microbiota promoting colitis and metabolic syndrome. *Nature* 2015, *519*, 92–96.
61. Limketkai, B.N.; Iheozor-Ejiofor, Z.; Gjuladin-Hellon, T.; Parian, A.; Matarese, L.E.; Bracewell, K.; MacDonald, J.K.; Gordon, M.; Mullin, G.E. Dietary interventions for induction and maintenance of remissionin inflammatory bowel disease. *Cochrane Database Syst. Rev.* 2019, *2*, CD012839.
62. Knight-Sepulveda, K.; Kais, S.; Santaolalla, R.; Abreu, M.T. Diet and inflammatory bowel disease. *Gastroenterol. Hepatol.* 2015, *11*, 511–520.
63. Halmos, E.P.; Gibson, P.R. Dietary management of IBD–insights and advice. *Nat. Rev. Gastroenterol. Hepatol.* 2015, *12*, 133–146.
64. Day, A.S.; Lopez, R.N. Exclusive enteral nutrition in children with Crohn's disease. *World J. Gastroenterol.* 2015, *2*, 6809–6816.
65. Sigall-Boneh, R.; Pfeffer-Gik, T.; Segal, I.; Zangen, T.; Boaz, M.; Levine, A. Partial enteral nutrition with a Crohn's disease exclusion diet is effective for induction of remission in children and young adults with Crohn's disease. *Inflamm. Bowel Dis.* 2014, *20*, 1353–1360.
66. Suskind, D.L.; Cohen, S.A.; Brittnacher, M.J.; Wahbeh, G.; Lee, D.; Shaffer, M.L.; Braly, K.; Hayden, H.S.; Klein, J.; Gold, B.; *et al*. Clinical and fecal microbial changes with diet therapy in active inflammatory bowel disease. *J. Clin. Gastroenterol.* 2018, *52*, 155.
67. Borrelli, O.; Cordischi, L.; Cirulli, M.; Paganelli, M.; Labalestra, V.; Uccini, S.; Russo, P.M.; Cucchiara, S. Polymeric di*et al*one versus corticosteroids in the treatment of active pediatric Crohn's disease: A randomized controlled open-label trial. *Clin. Gastroenterol. Hepatol.* 2006, *4*, 744–753.
68. Day, A.S.; Whitten, K.E.; Sidler, M.; Lemberg, D.A. Systematic review: Nutritional therapy in paediatric Crohn's disease. *Aliment. Pharmacol. Ther.* 2008, *27*, 293–307.
69. Gorard, D.A.; Hunt, J.B.; Payne-James, J.J.; Palmer, K.R.; Rees, R.G.; Clark, M.L.; Farthing, M.J.; Misiewicz, J.J.; Silk, D.B. Initial response and subsequent course of Crohn's disease treated with elemental diet or prednisolone.*Gut* 1993, *34*, 1198–1202.
70. Rajendran, N.; Kumar, D. Role of diet in the management of inflammatory bowel disease. *World J. Gastroenterol.*2010, *16*, 1442–1448.
71. Quince, C.; Ijaz, U.Z.; Loman, N.; Eren, A.M.; Saulnier, D.; Russell, J.; Haig, S.; Calus, S.; Quick, J.; Barclay, A.;*et al*.

Extensive modulation of the fecal metagenome in children with crohn's disease during exclusive enteral nutrition. *Am. J. Gastroenterol.* 2015, *110*, 1718–1729.
72. Ni, J.; Wu, G.D.; Albenberg, L.; Tomov, V.T. Gut microbiota and IBD: Causation or correlation? *Nat. Rev. Gastroenterol. Hepatol.* 2017, *14*, 573–584.
73. Lane, E.R.; Lee, D.; Suskind, D.L. Dietary therapies in pediatric inflammatory bowel disease: An evolving inflammatory bowel disease paradigm. *Gastroenterol. Clin.* 2017, *46*, 731–744.
74. Suskind DL, Wahbeh G, Cohen SA, Damman, C.J.; Klein, J.; Braly, K.; Shaffer, M.; Lee, D. Patients perceive clinical benefit with the specific carbohydrate diet for inflammatory bowel disease. *Dig. Dis. Sci.* 2016, *61*, 3255–3260.
75. Suskind DL; Wahbeh G, Gregory N, Vendettuoli H, Christie D. Nutritional therapy in pediatric Crohn disease: The specific carbohydrate diet. *J. Pediatr. Gastroenterol. Nutr.* 2014, *58*, 87–91.
76. Kakodkar S, Farooqui AJ, Mikolaitis SL, Mutlu EA. The specific carbohydrate diet for inflammatory bowel disease: A case series. *J. Acad. Nutr. Diet.* 2015, *115*, 1226–1232.
77. Cohen, S.A.; Gold, B.D.; Oliva, S.; Lewis, J.; Stallworth, A.; Koch, B.; Laura, E.; Mason, D. Clinical and mucosal improvement with specific carbohydrate diet in pediatric Crohn disease. *J. Pediatr. Gastroenterol. Nutr.* 2014, *59*, 516–521.
78. Lee D, Swan CK, Suskind D, Wahbeh G, Vanamala J, Baldassano RN, Leonard MB, Lampe JW. Children with Crohn's Disease Frequently Consume Select Food Additives. Dig Dis Sci. 2018 Oct;63(10):2722-2728. doi: 10.1007/s10620-018-5145-x. Epub 2018 Jun 4. PMID: 29862484; PMCID: PMC6290903.
79. Olendzki, B.C.; Silverstein, T.D.; Persuitte, G.M.; Ma, Y.; Baldwin, K.R.; Cave, D. An anti-inflammatory diet as treatment for inflammatory bowel disease: A case series report. *Nutr. J.* 2014, *13*, 5.
80. Chiba, M.; Abe, T.; Tsuda, H.; Sugawara, T.; Tsuda, S.; Tozawa, H.; Fujiwara, K.; Imai, H. Lifestyle-related disease in Crohn's disease: Relapse prevention by a semi-vegetarian diet. *World J. Gastroenterol.* 2010, *16*, 2484–2495.
81. MacLellan, A.; Moore-Connors, J.; Grant, S.; Cahill, L.; Langille, M.G.I.; Van Limbergen, J. The impact of Exclusive Enteral Nutrition (EEN) on the gut microbiome in crohn's disease: A review. *Nutrients* 2017, *9*, 447.
82. Gerasimidis, K.; Bertz, M.; Hanske, L.; Junick, J.; Biskou, O.; Aguilera, M.; Garrick, V.; Russell, R.K.; Blaut, M.; McGrogan, P.; Edwards, C.A. Decline in presumptively protective gut bacterial species and metabolites are paradoxically associated with disease improvement in pediatric Crohn's disease during enteral nutrition. *Inflamm. Bowel Dis.* 2014, *20*, 861–871.
83. Ananthakrishnan, A.N. Epidemiology and risk factors for IBD. Nat. Rev. Gastroenterol. Hepatol. 2015, 12, 205–217.
84. Jowett, S.L.; Seal, C.J.; Pearce, M.S.; Phillips, E.; Gregory, W.; Barton, J.R.; Welfare, M.R. Influence of dietary factors on the clinical course of ulcerative colitis: A prospective cohort study. *Gut* 2004, *53*, 1479–1484.
85. Lee, D.; Baldassano, R.N.; Otley, A.R.; Albenberg, L.; Griffiths, A.M.; Compher, C.; Chen, E.Z.; Li, H.; Gilroy, E.; Nessel, L.; *et al*. Comparative effectiveness of nutritional and biological therapy in North American children with active crohn's disease. *Inflamm. Bowel Dis.* 2015, *21*, 1786–1793.
86. Rapozo DC, Bernardazzi C, de Souza HS. Diet and microbiota in inflammatory bowel disease: The gut in disharmony. World J Gastroenterol. 2017 Mar 28;23(12):2124-2140. doi: 10.3748/wjg.v23.i12.2124. PMID: 28405140; PMCID: PMC5374124.
87. Altajar S, Moss A. Inflammatory Bowel Disease Environmental Risk Factors: Diet and Gut Microbiota. Curr Gastroenterol Rep. 2020 Oct 12;22(12):57. doi: 10.1007/s11894-020-00794-y. PMID: 33044636.

****