**„CAROL DAVILA" UNIVERSITY OF MEDICINE
AND PHARMACY, BUCHAREST
DOCTORAL SCHOOL
MEDICINE**

THE ROLE OF AN EXCLUSION DIET (REDUCING THE INTAKE OF DISACCHARIDES, SATURATED FATS, EMULSIFIERS, RED MEAT AND ULTRA-PROCESSED FOODS) IN MAINTAINING REMISSION OF CHRONIC INFLAMMATORY BOWEL DISEASES

PHD THESIS SUMMARY

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1.1. Hypothesis and Research Methodology

Taking into account that diet is a modifiable environmental precipitating factor in the occurrence of disease flare-ups, the aim of this study is to determine whether there is a correlation between an exclusion diet and the maintenance of clinical remission in patients with inflammatory bowel diseases (IBD) who have achieved clinical remission. It was a prospective, non-randomised clinical trial on 139 inflammatory bowel disease patients from Fundeni Clinical Institute, Bucharest that were on clinical remission from September 2021 to June 2022. The subjects were divided into 2 study arms according to their own willingness to follow an exclusion diet or not:

- Arm 1: follow an exclusion diet for 6 months (45 subjects)
- Arm 2: maintain their previous lifestyle without changes to their usual diet (94 subjects).

At the first visit, all subjects underwent blood tests including complete blood count (CBC), C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), fibrinogen and fecal calprotectin. Additionally, clinical disease activity was assessed using the Mayo score and CDAI score, depending on the type of inflammatory bowel disease present. At the end of the study, each subject underwent another clinical disease activity assessment along with laboratory tests, including CBC, CRP, ESR, and fecal calprotectin.

1.2. Results

All patients included in the study were in clinical remission. At the begining of the study the median value of CDAI score for patients who had Crohn's disease (CD) was 72,5 points in the intervention group and 49 points in the control group, without having a statistical significance (p-value = 0,183). At the end of the study the median value of CDAI score was 51 points in the intervention group and 55 points in the control group, without having a statistical significance (p-value = 0,224) (Figure 1).
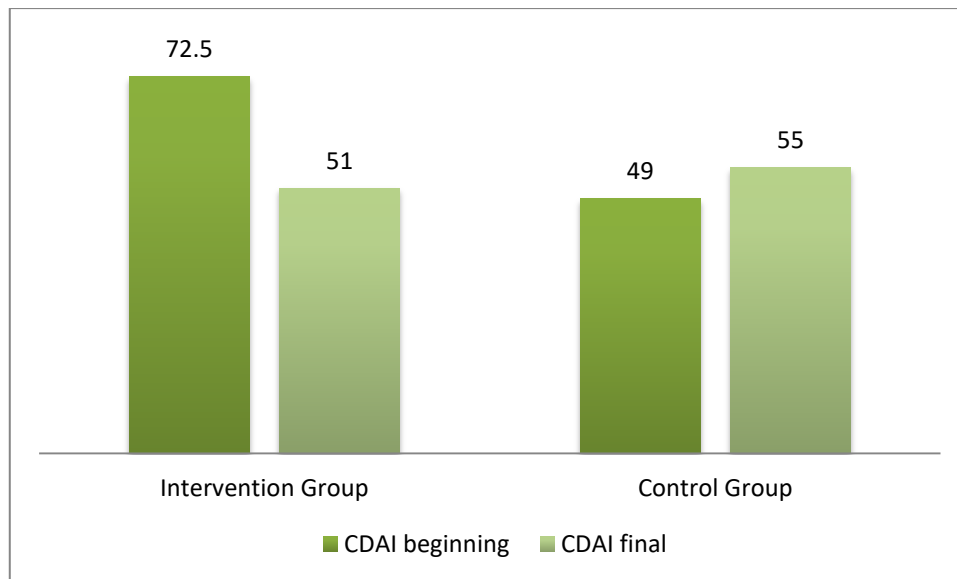
Figure 1. CDAI score within the two groups

For ulcerative colitis (UC) patients, at the begining of the study the Mayo median score was 0 points in both arms, with a minimum value of 0 points and a maximum value of 2 points, similar for both arms (p-value = 0,641). At the end of the study the Mayo median score was 0 points in both arms, with a minimum value of 0 points and a maximum value of 2 points in the intervention group and a maximum value of 7 points in the control group, without statistical significance (p-value = 0,801).

Clinical remission was maintained in all of the patients from the intervention group (100%), no matter the inflammatory bowel disease type, while in the control group 90 patients maintained clinical remission (95,7%), but we did not achieve statistical significance (p-value = 0,157). If we take into consideration only the patients with Crohn's disease, in the intervention group everyone maintained clinical remission, while in the control group 52 patients maintained clinical remission (94,3%), with a p-value of 0,258. Among patients with ulcerative colitis, in the intervention group all of the patients maintained clinical remission, while in the control group, 38 patients maintained clinical remission (97.4%), with a p-value of 0.443 (Figure 2).
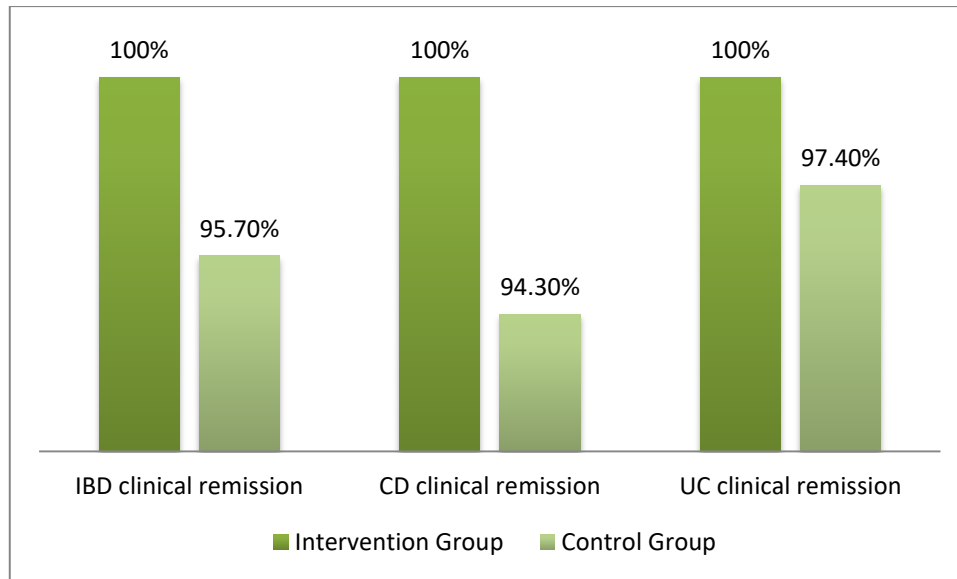
Figure 2. Maintenance of clinical remission at 6 months after the intervention

The biochemical markers monitored in this study were fecal calprotectin, hemoglobin, C-reactive protein, fibrinogen, and erythrocyte sedimentation rate (ESR). Elevated fecal calprotectin (>300 micrograms/gram) at the beginning of the study was reported in 20% of patients in the intervention group and 21.3% of patients in the control group, with no statistically significant difference (p-value = 0.416). Patients with higher fecal calprotectin levels (>300 micrograms/gram) underwent closer monitoring. Among these 29 patients, 17.3% underwent a change in the treatment line, 44.8% had optimized therapy, and 37.9% did not change their treatment. These decisions were based on therapeutic drug monitoring, endoscopy, or enterography. At the end of the study, elevated fecal calprotectin (>300 micrograms/gram) was reported in 15.6% of patients in the intervention group and 10.6% of patients in the control group (p-value = 0.067).

The ESR showed a significant difference between the two groups at the beginning of the study (p-value = 0.019), with a median value of 29 erythrocytes per hour (minimum 5, maximum 62) in the intervention group and a median value of 16 erythrocytes per hour (minimum 4, maximum 48) in the control group. By the end of the study, ESR values were statistically comparable between the two groups, with a p-value of 0.440. Regarding hemoglobin, fibrinogen, and C-reactive protein levels, no statistically significant differences were observed either at the beginning or at the end of the study.

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1.3. Discussion

The results of the study were published as an original article in the journal Medicina® (MDPI) [1]. The aim of this study was to quantify the effects of an exclusion diet on the progression of inflammatory bowel diseases. An observational study comparing the dietary habits of two populations (Eastern European and Western European) served as the basis for the dietary model used in this study [2].

The diet used in this study excluded red and processed meat. Another study in the literature found an association between the consumption of red and processed meat and the subsequent development of inflammatory bowel diseases [3]. Other studies have reported an increased relapse rate in UC [4], but not in Crohn's disease in patients who consume red or processed meat [5]. Such discrepancies in the literature may be caused by the different types of studies applied, the various diets implemented, as well as regional dietary habits (Western European or Asian habits).

The role of dairy products in inflammatory bowel diseases has often been debated in the scientific literature. Dairy products are typically avoided by individuals with UC because lactose has been associated with this condition [6]. More than half of our population reported daily consumption of lactose-rich products, regardless of the group they were part of. Our proposal was to exclude these products and replace them with yogurt, low-fat cheese, and lactose-free milk.

A fiber-rich diet likely reduces the probability of developing inflammatory bowel disease, and therefore, fiber consumption protects against the onset of these types of conditions [7]. Ananthakrishnan et al. [8] claim that a fiber-rich diet can reduce the risk of Crohn's disease by 40%. However, there is no protective effect against UC. Using a fiber-rich diet, the intervention group achieved 100% clinical remission, regardless of the type of inflammatory bowel disease. At the same time, other food categories associated with a high risk of relapse in inflammatory bowel diseases were also excluded.

An interesting aspect in our cohorts is that only 33.3% of patients in the intervention group benefited from immunosuppressive therapy, compared to 68.1% of patients in the control group (p-value < 0.001). Regarding biological therapy, in the Crohn's disease subgroup, there was a significant difference (77.3% in the exclusion diet group versus 96.4% in the control group) (p-value = 0.009). This difference between the

groups could be associated with a lower risk of relapse in the control group, possibly due to more effective disease control.

One of the biological markers sensitive to intestinal inflammation is fecal calprotectin. In the STORI trial, patients who discontinued anti-TNF treatment with mucosal healing and fecal calprotectin levels above 300 micrograms/gram had a relapse rate of 30%, compared to patients who experienced both mucosal healing and low calprotectin levels, who had relapse rates between 10% and 20% [9, 10].

Using the same fecal calprotectin threshold as in the STORI trial, in our population fecal calprotectin did not correlate with the clinical score either at the beginning or at the end of the study, regardless of the group. This could be explained by the better-adjusted therapy in the control arm, given that immunosuppressive therapy was present in 68.1% of these patients compared to only 33.3% of patients in the intervention group.

1.4. Conclusions

In conclusion, we found a better trend in maintaining clinical remission in patients who followed the exclusion diet, but unfortunately, we did not reach statistical significance, likely due to the lack of homogeneity between the groups regarding therapy. There was also a trend of improvement in inflammation markers in the interventional group, but not when it came to fecal calprotectin. This strengthens our argument that IBD is a lifestyle-related disease, driven by a Westernized diet. The exclusion diet is well-tolerated (with only one withdrawal at the beginning of the study) and is associated with higher long-term clinical remission rates. These results are positive and promising, and they need to be confirmed in controlled, randomized, multicenter clinical studies.

2. Second Study: Diet Optimization in Inflammatory Bowel Disease: Impact on Disease Relapse and Inflammatory Markers. A 1-year Prospective Trial

2.1. Hypothesis and Research Methodology

Based on the hypothesis that a diet rich in processed foods, food additives, red meat, and animal fats can disrupt the gut microbiota and induce immunological dysfunctions, thereby increasing susceptibility to IBD, while a diet rich in dietary fiber and omega-3 fatty acids may help restore the pathophysiology of IBD, this study proposes a diet based on the above observations for patients diagnosed with IBD who are in clinical remission.

The main objective of this study was to determine whether there is an association between adherence to an anti-inflammatory diet and the maintenance of clinical remission in individuals with IBD. Additionally, we aimed to evaluate the efficacy and safety of this dietary intervention compared to a non-dietetic control group. The study was a clinical, prospective, non-randomized case-control study conducted on 168 patients registered at the Fundeni Clinical Institute in Bucharest, diagnosed with UC or CD, in clinical remission between September 2021 and April 2023.

The subjects were divided into 2 study arms according to their own willingness to follow an exclusion diet or not:

- Arm 1: follow an exclusion diet for 12 months (84 patients)
- Arm 2: maintain their previous lifestyle without changes to their usual diet (84 patients).

First, we monitored compliance regarding the elimination of forbidden foods. Subsequently, we also focused on increasing the incorporation of as many categories from the allowed food group as possible. From a nutritional standpoint, we aimed to maintain a stable caloric intake, avoiding weight loss or weight gain.

Anthropometric measures, including weight and height, were recorded for all patients, and the body mass index (BMI) was calculated at the beginning and end of the study. Patients were questioned about dietary changes at 6 and 12 months, with no differences reported. After this period, patients underwent clinical evaluations and

additional tests, including a complete blood count, C-reactive protein, ESR, and fecal calprotectin.

2.2. Results

The overall compliance rate with the dietary plan reached 88% (with adherence ranging from 76% to 100%) over the 52 weeks of the study. 82% of patients with Crohn's disease reported adherence to the diet within the 76-100% range, calculated every 4 weeks, while in the UC cohort, this rate increased to 94%. (Figure 3).
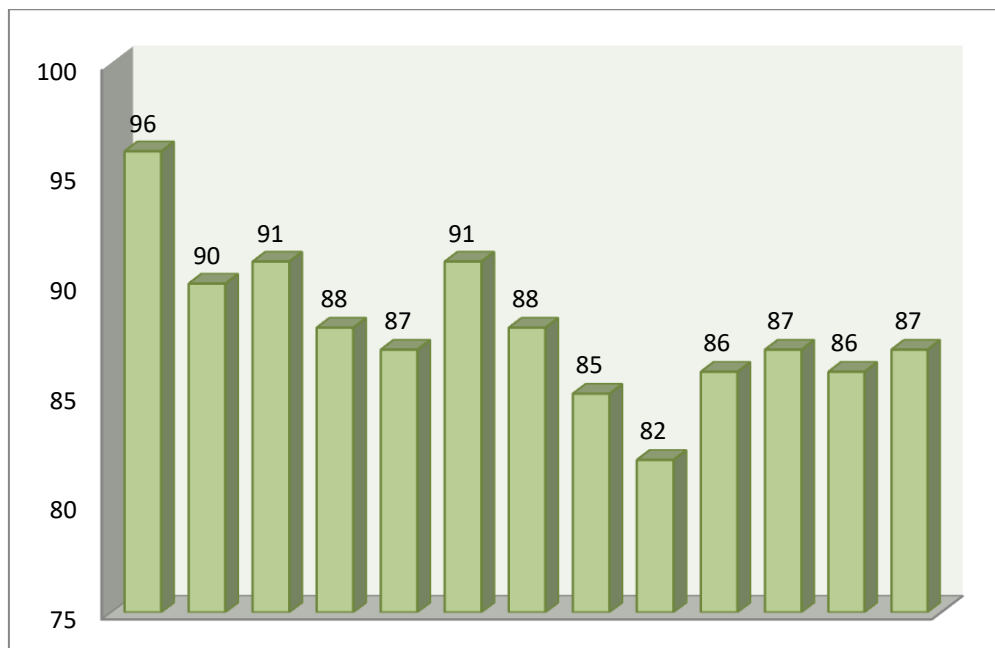

Figure 3. Compliance with the dietary plan every 4 weeks

For patients diagnosed with Crohn's disease, the initial assessment revealed a median CDAI clinical score of 65.85 points in the intervention group, ranging from 5 to 148 points, and a median score of 50.05 points in the control group, with values ranging from 18 to 118 points (p-value = 0.272). At the end of the study, patients in the intervention group had a median CDAI clinical score of 77.15 points, ranging from 4 to 167 points, compared to patients in the control group, who had a median score of 94.50 points (ranging from 31 to 227 points), but no statistically significant difference was observed between the groups (p-value = 0.441).

In patients diagnosed with UC (ulcerative colitis), the median MAYO score at the beginning of the study was 0 points in the intervention group, with a range from 0 to 2

points, and the same values were reported in the control group. The calculated p-value for these initial measurements was 0.740. At the end of the study, both groups reported a median MAYO score of 0 points, with values ranging from 0 to 6 points (p-value = 0.636).

In the intervention group, the initial fecal calprotectin concentration exceeding 250 micrograms per gram was reported in 21.4% of cases, while in the control group, this threshold was reached in 19% of cases (p-value = 0.443). After 52 weeks, fecal calprotectin levels exceeding 250 micrograms per gram decreased to 9.5% in the intervention group, while in the control group it remained elevated in 16.7% of subjects (p-value = 0.171).

In the subgroup diagnosed with Crohn's disease, a notable difference in C-reactive protein levels was observed between the two groups (p-value = 0.026) at the start of the study. At baseline, the intervention group had a median C-reactive protein value of 6.49 mg/dL, while the control group had a median C-reactive protein value of 4.42 mg/dL. However, at the end of the 52-week study period, no statistically significant differences in C-reactive protein levels were observed between the two groups (p-value = 0.519).

In the Crohn's disease subgroup, 15% of subjects in the intervention arm required a change in therapy during the study, compared to 25% in the control group (p = 0.402). In the UC subgroup, 22.7% of subjects in the intervention group required a change in therapy during the study, compared to 18.2% in the control group (p = 0.792).

At the end of the study, clinical remission was maintained in 95.2% of cases in the intervention group, compared to 85.7% in the control group (p-value = 0.036). In the Crohn's disease subgroup, 95% of the intervention group had a CDAI score below 150 points, while only 80% of patients in the control group reached this score level, with a statistically significant difference (p-value = 0.044). However, in the UC subgroup, no statistically significant differences in clinical remission were observed between the two groups (p-value = 0.400) (Figure 4).
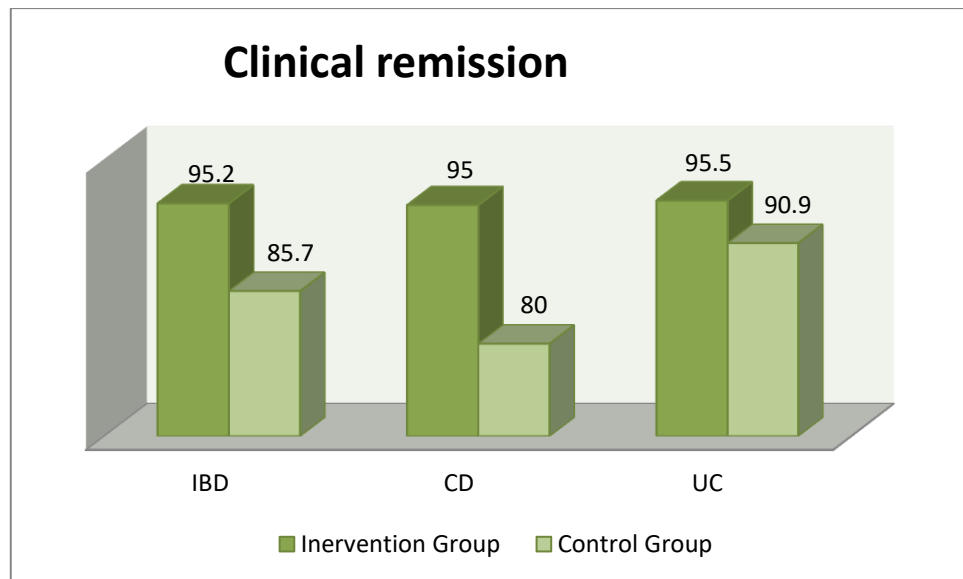
Figure 4. Clinical remission within the studied groups

2.3. Discussion

The main results of this study were published as an article in The Journal of Gastrointestinal and Liver Diseases® (JGLD) [11]. In patients with Crohn's disease, Crohn's Disease Exclusion Diet presents a dietary strategy that has shown encouraging results in promoting remission both in children and adults with mild to moderate luminal disease [12]. However, most studies have included parenteral nutrition or exclusive enteral nutrition as part of their dietary regimen, in contrast to our approach, which relies solely on an appropriate anti-inflammatory diet.

The initial results of the research indicated that individuals who adhered to an anti-inflammatory diet had a higher frequency of maintaining clinical remission and a tendency for improvement in inflammatory tests throughout the dietary intervention [1].

Building on these promising results, we opted for more homogeneous study groups and extended the follow-up period to 52 weeks. The results revealed a higher proportion of individuals maintaining clinical remission in the general IBD population and especially in the Crohn's disease subgroup compared to those who did not adhere to a dietary approach. Furthermore, among individuals with elevated fecal calprotectin levels at screening, the intervention group required a therapy change at a lower rate than the control group. Notably, in the Crohn's disease subgroup, the difference was significantly more

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pronounced, with a treatment change rate of 15% in the interventional group compared to 25% in the control group.

These results are consistent with the literature. A randomized clinical trial and five observational studies that included 283 subjects highlighted that a regimen including partial enteral nutrition showed superiority compared to the absence of a dietary plan in preventing relapse in patients with IBD over a period ranging from 6 weeks to 2 years [13-18].

Fecal calprotectin is a sensitive and accurate marker for detecting intestinal inflammation, surpassing traditional inflammatory markers in predicting endoscopic activity in patients with IBD. Additionally, some studies propose the utility of fecal calprotectin in guiding treatment strategies for individuals with IBD [19]. Our study used fecal calprotectin as an inflammatory marker, considering its negative predictive value for disease relapse and its non-invasive nature. When examining the results of inflammatory markers, both in the IBD population and the subgroup with UC, no significant statistical differences were found regarding fecal calprotectin, hemoglobin, C-reactive protein, or fibrinogen either at the beginning or at the end of the study. However, in the Crohn's disease subgroup, there were significant differences between the groups at the beginning of the study regarding C-reactive protein, with higher values reported in the intervention group at baseline compared to the control group (p-value = 0.026), differences that disappeared by the end of the study.

The differences obtained in this study cannot be considered random, given the homogeneity of the groups regarding disease phenotype, inflammatory markers, and the need for therapeutic adjustments. Among individuals with elevated fecal calprotectin levels (>250 micrograms per gram), 19% of participants in the intervention group required a modification of their treatment regimen throughout the study, compared to 21.4% in the control group, which had a similar need for therapy change (p-value = 0.702).

2.4. Conclusions

An anti-inflammatory diet demonstrates efficacy in maintaining clinical remission within the population with inflammatory bowel diseases, with notable effectiveness primarily observed in patients with Crohn's disease. Additionally, there is a visible trend of improvement in inflammatory markers, including fecal calprotectin, within the intervention

group. This supports the hypothesis that IBD is influenced by lifestyle and environmental factors, particularly those associated with a Western-style diet. The anti-inflammatory diet proves to be well tolerated and is associated with increased rates of sustained long-term clinical remission.

3. Third Study: A Comprehensive Review of Dietary Approaches in Maintaining Remission of Inflammatory Bowel Diseases in Adults

3.1. Hypothesis and Research Methodology

Finding the etiology of IBD remains an active area of research. Although epidemiological evidence suggests that certain dietary components may play a role in triggering this condition, the food categories that influence disease progression and exacerbation remain unclear. Various elements in the diet have been proposed as potential aggravating factors, with pro-inflammatory properties, including processed foods and the additives associated with them [20, 21].

This narrative review aims to explore the evidence regarding the effectiveness of various frequently studied dietary interventions and certain dietary patterns in maintaining clinical, endoscopic and histological remission in adult patients with inflammatory bowel diseases. The purpose of this review is to present the strengths and inherent limitations of the current data in the literature, providing healthcare professionals with a systematic framework to guide patients regarding dietary interventions. This framework serves as a foundation for future research aiming to investigate the role of diet in maintaining clinical remission in inflammatory bowel diseases.

We conducted a literature review in multiple databases, including PubMed, using the "advanced" and "MeSH" tools, with the following keywords: (inflammatory bowel disease AND diet AND remission) [title]; (crohn's disease AND diet AND remission) [title]; (ulcerative colitis AND diet AND remission) [title]. The selected publication period considered relevant was 2014-2024, with priority given to the most recent studies.

3.2. Results

The main results of this study were published as an article in the journal Medicina® (MDPI) [22].

The Western diet is involved in altering the gut microbiota in healthy individuals, characterized by a high intake of refined sugars, omega-6 polyunsaturated fats, and fast food, along with an insufficient intake of fruits, vegetables, and fiber. A significant portion of modern food sources undergoes extensive processing, modification, and long-distance

transportation, differing from traditional dietary practices where local foods are consumed shortly after harvest [23, 24].

The Mediterranean diet is considered beneficial for the diversity of the gut microbiome and metabolome through specific mechanisms, offering potential long-term benefits such as reducing the risk of cardiovascular diseases, metabolic syndrome, and neoplasms.Chicco et al. [25] conducted an independent study to validate the effectiveness of a Mediterranean diet specifically adapted for patients with inflammatory bowel diseases. In this study, 142 individuals diagnosed with IBD received nutritional guidance. After a six-month intervention period, both patients with UC and those with Crohn's disease who followed the Mediterranean diet showed reduced disease activity, lower levels of inflammatory biomarkers and an improvement in their quality of life.

The importance of assessing the nutritional status of patients with inflammatory bowel diseases lies in the frequent association of nutritional deficiencies with an unfavorable disease course. Malnutrition and a wide range of nutritional deficiencies are common complications, yet often overlooked in these patients, being especially prevalent among those with Crohn's disease and those who have undergone repeated surgeries. Malnutrition is associated with negative consequences in inflammatory bowel diseases, such as increased emergency room visits, prolonged hospitalizations, unplanned surgeries, higher mortality rates, reduced response to therapy and compromised quality of life [26-28].

Malnutrition in patients diagnosed with inflammatory bowel diseases is caused by a range of factors, including reduced oral intake, increased energy and protein requirements, as well as heightened gastrointestinal losses due to inflammatory processes, malabsorption, disease activity, short bowel syndrome and the use of certain medications. A significant proportion of patients exhibit a pronounced tendency to avoid foods (28–89%) and adopt restrictive eating behaviors (41–93%), deeply impacting their quality of life related to nutrition [29, 30].

Several dietary interventions have been evaluated for maintaining remission in adult patients with inflammatory bowel diseases. The Crohn's Disease Exclusion Diet is structured as a progressive three-phase dietary regimen. The initial phase lasts for 6 weeks and includes partial enteral nutrition, which provides 50% of the nutritional requirements, alongside 14 specific foods containing protein, resistant starch, or pectin. The basic

hypothesis of this diet supports that dietary elements typical of the Western diet (characterized by low fiber content and high levels of fats, sugar, and additives) have harmful effects on the gut microbiota, thereby contributing to the development of Crohn's disease [13].

A plant-based diet involves limiting animal-derived fats and proteins, representing a semi-vegetarian approach. Chiba et al. [31] demonstrated a reduced risk of relapse over a two-year period in 16 patients with Crohn's disease who were in clinical remission.

A low-fat diet limits fat intake to 10% of total calories and reduces red meat consumption to half a portion per day, while including a total of 25 grams of dietary fiber daily. Fritsch et al. [32], in a study involving 17 patients with UC in clinical remission, identified a positive correlation between adherence to a low-fat diet and reductions in inflammatory markers and intestinal dysbiosis. A significant advantage of this dietary regimen is its safety profile, as it does not lead to nutritional deficiencies and does not affect patients' quality of life.

The low-meat diet restricts the consumption of red and processed meats to one serving per month or less. The results of the FACES study conducted by Albenberg et al. [5] did not show any significant association between the level of red and processed meat consumption and the time to symptomatic relapse in patients with Crohn's disease in remission.

The IgG-based food exclusion diet is a six-month intervention that involves restricting foods based on the presence of specific IgG antibodies to 14 food antigens, including eggs, wheat, milk, corn, rice, soy, and chicken, among others. An observational study conducted by Jian et al. [33] on 97 patients with UC, either in remission or with mild to moderate active disease, found that the group following the exclusion diet had a lower frequency of stools compared to the group with an unchanged diet.

An anti-inflammatory diet, characterized by foods rich in dietary fiber, prebiotics, antioxidants, probiotics, and omega-3 polyunsaturated fatty acids, while limiting the consumption of red meat, sugar, and alcohol, was evaluated in a randomized clinical trial involving 28 patients with UC in remission [34]. The study revealed comparable relapse rates and similar fecal calprotectin levels at 6 months between participants who followed

the anti-inflammatory diet (5 out of 14) and those who received nutrition counseling based on the Canada Food Guide (4 out of 14).

An exclusion diet, which involves reducing the intake of disaccharides, saturated fats, emulsifiers, red meat, and ultra-processed meat, was examined for its effectiveness in maintaining remission in patients with IBD over a six-month period. Nitescu et al [1] found that patients who followed the exclusion diet for the specified duration had a higher remission rate.

Enteral nutrition is recognized as a well-established, minimally invasive therapeutic strategy with a low-risk profile, demonstrating efficacy in the treatment of inflammatory bowel diseases. Exclusive enteral nutrition involves the consumption of liquid formulas only, eliminating solid foods. Additionally, enteral nutrition can be administered as partial enteral nutrition, involving the replacement of 35–50% of the regular food intake with enteral nutrition [35]. When enteral nutrition is used in conjunction with biologic therapy, there is evidence suggesting improved outcomes [36]. However, there is insufficient evidence to demonstrate the efficacy of exclusive enteral nutrition as a therapeutic approach for both pediatric and adult patients with UC [37].

3.3. Conclusions

Diet plays a crucial role in the management of inflammatory bowel diseases, including prevention, active disease treatment and addressing complications such as malnutrition. Currently, there is no specific dietary approach recommended for maintaining remission in IBD. However, despite limited empirical evidence, many patients continue to experiment with various dietary approaches. The dietary approach should be tailored to the unique nutritional status and goals of each patient with IBD, which may evolve over time. Implementing more complex nutritional strategies for managing IBD is most effectively achieved through collaborative interdisciplinary efforts between gastroenterologists and dietitians.

II. Conclusions and Personal Contributions

The aim of this thesis was to establish a causal relationship between the adoption of an exclusion diet consisting of reducing the intake of disaccharides, saturated fats, emulsifiers, red meat and ultraprocessed foods and the maintenance of remission in adult patients with inflammatory bowel diseases. Additionally, the studies conducted sought to evaluate the effectiveness and safety of this dietary intervention, as well as the potential therapeutic benefits in these subjects.

The studies were conducted on subjects in clinical remission at the time of study enrollment, without corticosteroid treatment, complications of inflammatory bowel disease or other significant comorbidities requiring therapeutic interventions.

The studies conducted in this thesis have demonstrated that a diet reduced in disaccharides, saturated fats, emulsifiers, red and ultraprocessed meat results in the maintenance of clinical remission in the population with inflammatory bowel diseases, with notable effectiveness primarily observed in patients with Crohn's disease. Additionally, there is a visible trend of improvement in inflammatory markers, including fecal calprotectin, in patients following this type of diet.

The studies conducted present several strengths. The uniqueness of this investigation lies in the development of a dietary regimen derived from our previous observational study, which involved comparing two cohorts from distinct regions (Eastern Europe versus Western Europe).

In the diet proposed in this thesis, patients with IBD were provided with a list of food categories that have been demonstrated to be safe and beneficial for these conditions, as well as another list of food categories shown to perpetuate the inflammatory process. Another strength of this study is the prospective design and the large number of patients involved. It is crucial to recognize the limited number of studies in the literature addressing the adult population with IBD, as most of these studies have been conducted on pediatric subjects and then generalized to the adult population.

Another strength of the studies is the long duration of the intervention and the monitoring of the subjects. This timeframe was considered reasonable for evaluating the

potential for long-term clinical remission or disease reactivation. Despite the relatively modest number of patients opting for the diet, all of them showed good compliance without encountering difficulties, suggesting that the exclusion diet is well tolerated over longer periods and facilitates the maintenance of clinical remission.

The studies conducted were also subject to certain limitations, especially the absence of a designated control diet. The findings of single-arm interventional studies are susceptible to being confounded by the inherent progression of disease activity. Moreover, the ability of subjects to choose whether to be in the interventional group or the control arm presents a risk of selection bias. Adherence rates may be influenced by the individual's decision to adhere to the diet and this factor could contribute to the high adherence observed in the intervention group of our study. Another limitation stemming from subject self-selection is the placebo effect of the diet, which can influence the clinical disease activity score. However, to mitigate this limitation, we correlated the clinical score with inflammatory markers.

The first study, titled " Role of an Exclusion Diet (Reduced Disaccharides, Saturated Fats, Emulsifiers, Red and Ultraprocessed Meats) in Maintaining the Remission of Chronic Inflammatory Bowel Diseases in Adults" which is found in this thesis on pages 31-71, demonstrated that by using an exclusion diet, the intervention group achieved 100% clinical remission, regardless of the type of inflammatory bowel disease.

Additionally, there is a trend of improvement in inflammation markers in the intervention group, but this is not the case for fecal calprotectin. In our population, fecal calprotectin did not correlate with the clinical score at either the beginning or the end of the study, regardless of the group. This could be explained by the better-adjusted therapy in the control arm, considering that immunosuppressive therapy was present in 68.1% of these patients, compared to only 33.3% of patients in the interventional group.

The second study, titled "Diet Optimization in Inflammatory Bowel Disease: Impact on Disease Relapse and Inflammatory Markers. A 1-year Prospective Trial" which can be found on pages 72-106 of this thesis, demonstrated that a higher proportion of individuals maintain clinical remission in the general IBD population, particularly in the Crohn's disease subgroup, compared to those who do not follow a dietary approach. Furthermore, among individuals with elevated fecal calprotectin levels at screening, the

intervention group required therapy changes at a lower rate than the control group. Notably, in the Crohn's disease subgroup, the difference was significantly more pronounced, with a treatment change rate of 15% in the interventional group compared to 25% in the control group.

In the Crohn's disease subgroup, there were significant differences between the groups at the study's baseline regarding C-reactive protein (CRP), with higher levels of CRP reported in the intervention group at the start of the study compared to the control group (p-value = 0.026). These differences disappeared by the end of the study.

At the end of the study, clinical remission was maintained in 95.2% of cases in the intervention group, compared to 85.7% in the control group (p-value = 0.036). In the Crohn's disease subgroup, 95% of the intervention group had a CDAI score below 150 points, while only 80% of patients in the control group reached this score level, with a statistically significant difference (p-value = 0.044). However, in the subgroup of subjects with UC, no statistically significant differences were observed regarding clinical remission between the two groups (p-value = 0.400). The exclusion diet proved to be well tolerated, with an adherence rate of 88% over 52 weeks, lower in patients with Crohn's disease (82%) compared to those with UC (94%).

The third study, titled " A Comprehensive Review of Dietary Approaches in Maintaining Remission of Inflammatory Bowel Diseases in Adults" found in the present thesis on pages 107-120, conducted a literature review and highlighted that while some diets lacking solid evidence of improving outcomes in irritable bowel syndrome may offer benefits to certain patients, there are inherent risks associated with restrictive diets, including negative impacts on nutrition and quality of life. Additionally, several diets may unintentionally promote unhealthy or disordered eating behaviors, particularly due to the lack of well-defined time frames for their use.

The dietary approach should be tailored to the unique nutritional status and goals of each patient with IBD, which may evolve over time. The implementation of more complex nutritional strategies for managing IBD is most effectively achieved through collaborative interdisciplinary efforts between gastroenterologists and dietitians.

Essentially, the exclusion diet studied in this thesis leads to the long-term maintenance of clinical remission in patients with IBD. It also improves both inflammatory markers and fecal calprotectin in these patients. This diet can be applied to both Western European and Eastern European populations, demonstrating good adherence (88%) and can be maintained for long periods of time without adverse effects (up to 52 weeks).

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IV. The list of published scientific papers

1. Nitescu M, **Istratescu D,** Preda CM, Manuc TE, Louis E, Manuc M, Stroie T, Catrinoiu M, Tieranu CG, Badea LE, Tugui L, Andrei A, Diculescu MM. Role of an Exclusion Diet (Reduced Disaccharides, Saturated Fats, Emulsifiers, Red and Ultraprocessed Meats) in Maintaining the Remission of Chronic Inflammatory Bowel Diseases in Adults. Medicina (Kaunas). 2023 Feb 9;59(2):329. doi: 10.3390/medicina59020329. PMID: 36837530; PMCID: PMC9959761.

(Article fron chapter: 1st Study: Role of an Exclusion Diet (Reduced Disaccharides, Saturated Fats, Emulsifiers, Red and Ultraprocessed Meats) in Maintaining the Remission of Chronic Inflammatory Bowel Diseases in Adults; pages 31-71).

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Article link: https://www.mdpi.com/1648-9144/59/2/329.

2. Preda CM, **Istratescu D**, Nitescu M, Manuc T, Manuc M, Stroie T, Tieranu C, Meianu CG, Andrei A, Ciora CA, Louis E, Diculescu M. Diet Optimization in Inflammatory Bowel Disease: Impact on Disease Relapse and Inflammatory Markers. A 1-year Prospective Trial. J Gastrointestin Liver Dis. 2024 Jun 29;33(2):184-193. doi: 10.15403/jgld-5482. PMID: 38944867.

(Article fron chapter: 2nd Study: Diet Optimization in Inflammatory Bowel Disease: Impact on Disease Relapse and Inflammatory Markers. A 1-year Prospective Trial; pages 72-106).

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3. **Istratescu D**, Preda CM, Manuc T, Meianu C, Stroie T, Diculescu M. A Comprehensive Review of Dietary Approaches in Maintaining Remission of Inflammatory Bowel Diseases in Adults. Medicina (Kaunas). 2024 Jun 28;60(7):1068. doi: 10.3390/medicina60071068. PMID: 39064497; PMCID: PMC11278540.

(Article fron chapter: 3rd Study: A Comprehensive Review of Dietary Approaches in Maintaining Remission of Inflammatory Bowel Diseases in Adults; pages 107-120).

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