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

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ABSTRACT

Background & Aims: Recent research has shown that Western-style diets have been associated with an increased risk of inflammatory bowel diseases (IBD). Our aim was to examine the link between an anti-inflammatory diet and the maintenance of IBD remission, as well as to assess the potential therapeutic advantages of this dietary approach in preserving IBD remission.
Methods: The inclusion and exclusion criteria were applied to a total of 189 individuals with IBD, with 21 individuals not meeting the criteria. Therefore, 168 eligible patients were enrolled in the study and allocated to either an anti-inflammatory diet or a regular diet, based on their personal preference.
Results: A cohort of 168 IBD adult patients was recruited for the study: 88 patients with ulcerative colitis and 80 with Crohn's disease. The intervention group received an anti-inflammatory diet consisting of the removal of red and processed meat, fried foods, high-lactose foods, fast food, white bread, sugar, and vegetable oils rich in omega-6 for a period of 1 year. The clinical response was maintained in 80 patients (95.2%) in the intervention group and in 72 patients (85.7%) in the control group (p-value=0.036). Although not statistically significant, fecal calprotectin was higher in the control group than in the intervention group at follow-up.
Conclusions: Patients who adhered to an anti-inflammatory diet exhibited a higher rate of maintenance of clinical remission. Furthermore, improvement in inflammation tests was observed in the intervention group, reinforcing the proposition that IBD is a lifestyle-related disease.

Key words: diet - Crohn's disease – ulcerative colitis – remission– inflammatory markers – fecal calprotectin.

Abbreviations: CD: Crohn's disease; CDED: CD exclusion diet; CRP: C-reactive protein; EEN: exclusive enteral nutrition; ESR: erythrocyte sedimentation rate; FODMAP: fermentable oligosaccharides, disaccharides, monosaccharides and polyols; IBD: inflammatory bowel disease; RCT: randomized controlled trial; UC: ulcerative colitis.

INTRODUCTION

Inflammatory bowel disease (IBD) comprises two distinct chronic inflammatory conditions affecting the gastrointestinal tract, namely ulcerative colitis (UC) and Crohn's disease (CD). These conditions are characterized by recurrent episodes of remission and flare-ups, manifesting through symptoms such as abdominal pain, diarrhea, extraintestinal manifestations, and malnutrition [1]. Despite an incomplete understanding of its underlying mechanisms, emerging evidence indicates that the pathogenesis of IBD involves a complex interplay of various factors, including genetics, environmental influences, alterations in the gut microbiota, and dysregulation of the immune system [2-4].

Inflammatory bowel disease has been observed to influence dietary behaviors and intake, as evidenced by a recent analysis revealing that approximately three-quarters of patients engage in dietary restrictions targeting food and beverages believed to trigger gastrointestinal symptoms. A recent systematic review encompassing 29 studies found that a considerable proportion of IBD patients, ranging from 41% to 93%, adopt restrictive dietary behaviors [5]. Consequently, it is not surprising that impaired nutrient intakes and suboptimal nutritional status are prevalent among individuals with IBD [6, 7]. Another systematic review revealed that energy, fiber, folate, and calcium intakes fall below recommended levels in IBD patients, and fiber intake is lower compared to healthy controls [8].

A significant percentage of patients, ranging from 80% to 89%, express a desire for dietary guidance from their healthcare providers [9]. Patients often report encountering inconsistent information regarding diet in the context of IBD, and their experiences with accessing dietary advice vary. To compensate for the lack of information and support, some patients adopt (mal)adaptive behaviors concerning food and eating. These behaviors may include efforts to identify suitable foods, meticulously scrutinizing food labels, preparing separate meals, engaging in fasting or avoiding social eating situations, and prioritizing proximity to restroom facilities when dining outside of their home environment [10].

Dietary interventions have been explored in patients with IBD yielding varying outcomes. In a comprehensive placebo-controlled study, the efficacy of fish oil supplementation was not observed in patients with UC.

The best known and scientifically supported dietary intervention for IBD is exclusive enteral nutrition (EEN), recognized as a primary dietary approach for inducing remission in CD. The Crohn's Disease Exclusion Diet (CDED) has surfaced as a promising alternative, addressing the considerable challenges and obstacles associated with EEN. These dietary strategies, along with others exhibiting efficacy in IBD, adhere to the exclusion principle, grounded in compelling evidence that certain foods may be detrimental in the context of IBD [11]. Another dietary approach showed promising results after elimination of potentially immunogenic or intolerant food groups (staged elimination of grains, legumes, nightshades, dairy, eggs, coffee, alcohol, nuts and seeds, refined/processed sugars, oils, and food additives) with improved symptoms and endoscopic inflammation in patients with IBD [12]. Association studies have also revealed a potential protective effect of consuming vegetables, fruits, fish, and dietary fiber against the development of CD; however, no similar association has been consistently observed for UC [13, 14].

Our hypothesis postulates that a diet rich in processed foods, food additives, red meat, and animal fat can disrupt the gut microbiota and induce immunological dysfunction, thereby increasing the susceptibility to IBD through dysbiosis. Conversely, a fiber-rich diet supplemented with omega-3 fatty acids is believed to be crucial in diet-based therapeutic approaches, as it may contribute to the restoration of IBD pathophysiology. We assert that our theory is novel, thought-provoking, and extensively supported, providing a promising avenue for further exploration of this subject matter.

The primary objective of this study was to examine whether there is an association between adherence to an anti-inflammatory diet and the maintenance of remission in individuals with IBD. We also sought to evaluate the effectiveness and safety of this dietary intervention compared to a non-dietary control group, while exploring its potential therapeutic benefits in sustaining remission in IBD patients.

METHODS

Study Design and Patients

A prospective, non-randomized case-control clinical trial was conducted and enrolled IBD patients in clinical remission, who were under observation in the Gastroenterology Outpatient Unit of Fundeni Clinical Institute from September 2021 to April 2023. Remission status was determined based on the CDAI score (below 150 points) for individuals with CD or the partial Mayo score (below 3 points) for those diagnosed with UC.

The study's inclusion criteria encompassed individuals aged over 18 years, with a confirmed diagnosis of IBD established through endoscopic, radiologic, and histologic assessments at least 6 months prior to study entry. Moreover, participants were required to have maintained a stable IBD treatment regimen, indicating no modifications in therapy within the preceding 12 weeks before enrollment, and to be in clinical remission at the time of inclusion.

Exclusion criteria comprised the presence of active disease, patients with short bowel syndrome, other gastrointestinal disorders including malignancies and infectious conditions, prior engagement in an established dietary program, pregnancy and unwillingness to participate in the study.

A total of 168 patients satisfied the established inclusion criteria and were subsequently allocated to either the anti-inflammatory diet (Supplementary file, Table I) or their standard diet based on their choice to participate in the intervention arm or in the control arm.

An anti-inflammatory diet is characterized by its potential to mitigate inflammation levels and, consequently, mitigate the risk of chronic conditions such as IBD. Key components of an anti-inflammatory diet encompass the inclusion of tomatoes, olive oil, green leafy vegetables, nuts, fatty fish, and fruits. Conversely, it necessitates the avoidance of certain food items, including red meat, processed meat, commercially produced baked goods, white flour-based bread and pasta, deep-fried items, foods rich in added sugars, sugar-sweetened beverages, and trans fats commonly found in margarine, microwave popcorn, refrigerated biscuits and dough, as well as nondairy coffee creamers.

During the initial visit, patients underwent a comprehensive assessment, including complete blood count, C-reactive protein (CRP) levels, erythrocyte sedimentation rate (ESR), and fecal calprotectin.

Additionally, participants completed a questionnaire (Supplementary file, Table II) regarding their dietary preferences over the past year, adapted from a retrospective cohort study involving Eastern and Western European populations. This questionnaire, validated based on the last 3 months' dietary habits, revealed significant differences in the consumption of various food categories between the entire IBD cohort and the healthy control group. The IBD cohort showed significantly elevated consumption of sweets, sweetened beverages, processed and high-fat meats, fried foods, salt, store-bought ice cream, and mayonnaise compared to the healthy control group. Conversely, intake of seeds, nuts, and yogurt was lower among individuals with IBD. There was no difference regarding coffee or water consumption between the groups [19]. Consequently, a tailored dietary plan for IBD patients (Supplementary file, Table I) was developed based on these observed distinctions. The decision to include homemade ice cream and sorbet was influenced by the increased consumption in IBD patients previously demonstrated, in order to increase the adherence to the diet of the intervention arm.

We assembled these food lists after carefully examining popular IBD special diets such as Mediterranean [20] and low fermentable oligosaccharides, disaccharides, monosaccharides and polyols (FODMAP) [21]. Opting for a food-list approach due to its simplicity, we ensured approval from our nutritionist to mitigate nutritional deficiencies commonly associated with IBD special diets. After initial assessment, all patients were assigned based on their choice to two different arms: one arm that adopted an anti-inflammatory diet for twelve months (84 patients) and the other arm that maintained their habitual diet (84 patients). Each patient underwent a 30- to 45-minute consultation explaining their assigned diet, with ongoing monitoring by a clinician for changes in disease status and diet compliance over the twelve-month intervention. The dietary arm avoided prohibited foods but had flexibility in their choices, while the quantity of food was not specified, and caloric intake was initially determined by our dietitian. The control arm kept their dietary behavior based on their responses to the food questionnaire (Supplementary file, Table II). Standard treatment remained unchanged for all patients.

Initially, we aimed to evaluate compliance by eliminating prohibited foods (Supplementary file, Table I) and encouraging increased consumption of fruits, vegetables, lean meat, cereals, and olive oil. Our nutritional goal was to maintain a consistent caloric intake, with a focus on redirecting calories from the prohibited food list to the recommended food list.

Initially, we considered a daily food diary for patients, but it proved ineffective due to limited compliance. Subsequently, we adopted a telemedical approach, assessing dietary compliance every 4 weeks for the intervention arm. Each participant in the intervention group received a phone call every 4 weeks to confirm adherence to the prohibited foods list and consumption of foods from the approved list. A 10% score was assigned to each category, with a maximum of 100% and a mean percentage of dietary intake was obtained every 4 weeks. At the end of the study, diet compliance was predominantly evaluated in the outpatient clinic, supplemented by telemedicine when necessary. Anthropometric measures, including weight and height, were recorded, and body mass index (BMI) was calculated at the study beginning and at the end. Patients were questioned about dietary changes at 6 and 12 months, with no reported differences. Following this period, patients underwent clinical assessments and additional tests, including a full blood count, CRP, ESR, and fecal calprotectin.

Ethical Considerations

The research was carried out in adherence to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of Fundeni Clinical Institute (protocol code: 86, approval date: 5 October 2021). Written informed consent was acquired from all participants included in the study.

Sample Size

The necessary sample size for each group was determined to be 75 patients, factoring in a type I error of 5% ($\alpha = 0.05$) and a type II error of 20% ($\beta = 0.20$, power = 80%), as well as the primary outcome variable representing the anticipated disparity in mean IBD clinical scores between the intervention and control groups. This calculation was conducted under the assumption of an Odds Ratio (OR) of 0.3, and a controls-to-cases ratio of 1:1.

Statistical Analysis

The data analysis was conducted employing the statistical software SPSS (version 20.0, IBM Corporation, Armonk, NY, USA). The assessment of data normality was executed through the Kolmogorov-Smirnov test. Quantitative variables exhibiting a parametric distribution were presented as mean and standard deviation, while those with a non-parametric distribution were summarized as median with the range between minimum and maximum values. For comparative analysis, the independent sample t-test was utilized for normally distributed data, while the Mann-Whitney U test was employed for non-normally distributed data. Categorical variables were expressed as percentages and subjected to comparison using Fisher's exact test. A two-sided hypothesis testing approach was applied, and a p-value less than 0.05 was deemed indicative of statistical significance.

RESULTS

Participants

The inclusion criteria were applied to a cohort of 189 patients, leading to the exclusion of fifteen individuals who exhibited active disease and one who declined study participation. Of the remaining 173 patients diagnosed with IBD who consented to engage in the study after comprehensive elucidation of the dietary intervention, one participant perceived the dietary regimen as overly restrictive in relation to their lifestyle. Additionally, three participants were lost to follow-up, and one was disqualified from inclusion due to deterioration in their bowel disease necessitating modification of treatment. Consequently, a total of 168 patients satisfied the established inclusion criteria and were subsequently allocated to either the anti-inflammatory diet or the standard diet based on their individual preference (Fig. 1).

Baseline demographic characteristics and disease phenotype are provided in Table I. The two groups were generally well balanced, except for biologic treatment, which displayed higher prevalence in the control group compared to the anti-inflammatory diet group (p=0.033). Additionally, the diet group exhibited significantly elevated usage of other IBD treatments, primarily 5-ASA (p=0.022).

Table II provides the baseline characteristics of subjects based on the disease type. The groups are significantly different regarding gender (in the CD group 35% are males compared to 59.1% in the UC group, p-value=0.002), the appendectomy status (20% in the CD group compared to 4.5% in the UC group) and disease-related surgery (45% in the CD group compared to none in the UC group).

Dietary Intake and Compliance

At the beginning of the study, each patient was required to complete a dietary habits questionnaire (Supplementary file, Table II). There were no statistically significant differences regarding their food intake between the two arms prior to study recruiting. Furthermore, when considering the disease subtypes (CD or UC), no statistically significant distinctions were observed.

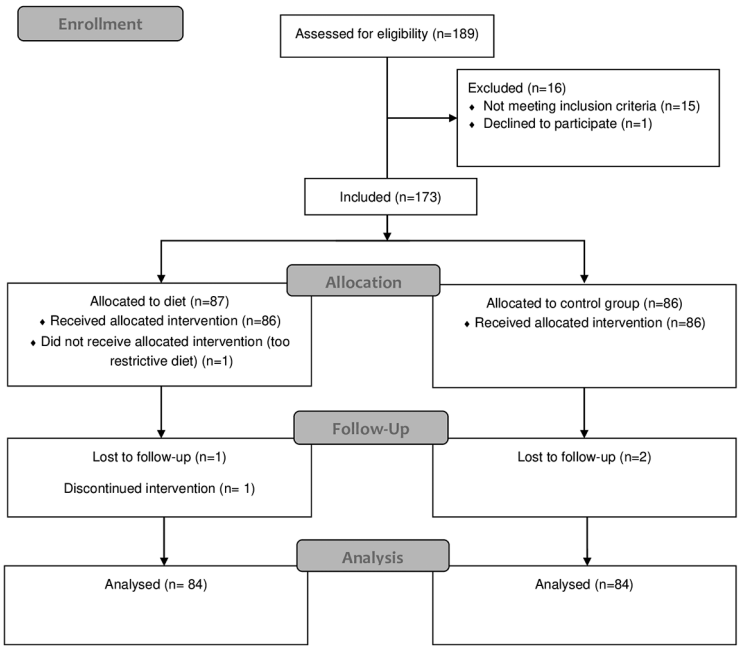

Fig. 1. CONSORT diagram.

The nutritional status exhibited minor intra-group variations at the study's conclusion, with no statistically significant findings (p=0.260).

Dietary compliance was quantified by evaluating the percentage of avoided and consumed foods (10% for each food category, Supplementary Table I), and it was calculated based on the mean percentage of dietary intake every 4 weeks. All participants were incorporated into the conclusive analysis, as their overall adherence surpassed 75%.

The overall rate of dietary compliance reached 88% (i.e., adherence ranging from 76% to 100%) over the 52-week duration of the study, as illustrated in Fig. 2. Regarding disease subtypes, 82% of patients with Crohn's disease reported adhering to the dietary regimen within the 76-100% range on a 4-week basis, while in the ulcerative colitis cohort, this figure rose to 94% of patients who similarly reported adherence within the specified percentage range.

Disease Activity and Inflammatory Markers

All patients were in a state of clinical remission at the inception of the study. For patients diagnosed with CD, an initial assessment revealed a mean CDAI score of 65.85 points in the dietary intervention group, ranging from 5 to 148, and a mean score of 50.05 points in the control group, with values spanning from 18 to 118. The calculated p-value for these measurements was 0.272. After the 52-week duration of the study, patients in the dietary intervention group exhibited a mean CDAI score of 77.15 points, within the range of 4 to 167, in contrast to patients in the control group, who demonstrated a mean score of 94.50 points (ranging from 31 to 227). The p-value associated with this comparison was 0.441.

In the case of patients diagnosed with UC, the median MAYO score at the study's initiation was 0 points in the intervention group, with a range from 0 to 2, the same values being displayed in the control group. A 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 (ranging from 0 to 6). The p-value associated with this comparison was 0.636. In the dietary group, an initial fecal calprotectin concentration exceeding 250 micrograms per gram was observed 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, the prevalence of fecal calprotectin concentrations exceeding 250 micrograms per gram decreased to 9.5% in the dietary group, whereas in the control group, it remained higher at 16.7% (p-value = 0.171).

Within the UC subpopulation, an initial fecal calprotectin concentration exceeding 250 micrograms per gram was documented in 27.3% of patients in the dietary group, while in the control group, this threshold was reached by 18.2% of individuals (p=0.446). At the end of the study, the proportion of patients with fecal calprotectin concentrations surpassing 250 micrograms per gram remained constant at 9.1% in both study arms (p=1).

Among patients with CD, an initial fecal calprotectin concentration exceeding 250 micrograms per gram was noted in 17.9% of individuals in both study arms (p=1). However, at the end of the study, the percentage of patients in the dietary group exhibiting elevated fecal calprotectin levels was 10, compared to 25 in the control group (p=0.139). In the overall IBD population and within the UC subpopulation, there were no statistically significant disparities in parameters such as hemoglobin, CRP, or fibrinogen, neither at the beginning of the study nor at the 52-week time point.

However, in the CD subpopulation, a notable difference in CRP levels was observed between the dietary and control groups (p=0.026). At the commencement of the study, the dietary group displayed a mean CRP level of 6.49 mg/dL, whereas the control group exhibited a mean CRP level of 4.42 mg/dL.

Table I. Baseline characteristics of the study groups

Parameter	All patients N=168	Anti-inflammatory diet N=84	Control N=84	p*
Gender (male), n (%)	80 (47.6)	40 (47.6)	40 (47.6)	1.000
Age (years), median (range)	41.5 (18-77)	43.5 (23-77)	39.5 (18-72)	0.371
BMI, n (%)				0.341
Underweight	4 (2.4)	0 (0)	4 (4.8)	
Normal	101 (60.1)	57 (67.8)	44 (52.4)	
Overweight	57 (33.9)	23 (27.4)	34 (40.5)	
Obesity	6 (3.6)	4 (4.8)	2 (2.4)	
Education level, n (%)				0.119
less than basic education	2 (1.2)	0 (0)	0: 2 (2.4)	
basic education	13 (7.7)	7 (8.3)	1: 6 (7.1)	
intermediate education	52 (31)	22 (26.2)	2: 30 (35.7)	
advanced education	101 (60.1)	55 (65.5)	3: 46 (54.8)	
Income, n (%)				0.956
no income	16 (9.5)	6 (7.1)	10 (11.9)	
minimum wage	10 (6)	4 (4.8)	6 (7.1)	
average wage	78 (46.4)	44 (52.4)	34 (40.5)	
more than average wage	64 (38.1)	30 (35.7)	34 (40.5)	
Non-smokers, n (%)	135 (80.4)	70 (83.3)	65 (77.4)	0.556
No alcohol consumption, n (%)	104 (61.9)	54 (64.3)	50 (59.5)	0.634
Appendectomy, n (%)	20 (11.9)	10 (11.9)	10 (11.9)	0.544
Surgical intervention, n (%)	35 (20.8)	14 (16.7)	21 (25)	0.296
Disease type, n (%)				1.000
Ulcerative colitis (UC)	88 (52.4)	44 (52.4)	44 (52.4)	
Crohn's disease (CD)	80 (47.6)	40 (47.6)	40 (47.6)	
CD age at onset, n (%)				0.741
A1: <17 years	1 (1.2)	0 (0)	1 (2.5)	
A2: 17-39 years	55 (68.8)	28 (70)	27 (67.5)	
A3: >39 years	24 (30)	12 (30)	12 (30)	
CD disease localization, n (%)				0.390
L1: terminal ileum	24 (30)	14 (35)	10 (25)	
L2: colon	35 (43.8)	17 (42.5)	18 (45)	
L3: ileocolon	18 (22.5)	8 (20)	10 (25)	
L4: upper GI	3 (3.7)	1 (2.5)	2 (5)	
CD behaviour, n (%)				0.460
B1: non-constricting/non-penetrating	32 (40)	20 (50)	12 (30)	
B2: stricturing	29 (36.3)	9 (22.5)	20 (50)	
B3: penetrating	19 (23.7)	11 (27.5)	8 (20)	
+p: perianal disease modifier	22 (27.5)	13 (32.5)	9 (22.5)	0.210
UC extent, n (%)				0.543
E1: proctitis	12 (13.6)	8 (18.2)	4 (9.1)	
E2: left-side colitis	52 (59.1)	24 (54.5)	28 (63.6)	
E3: pancolitis	24 (27.3)	12 (27.3)	12 (27.3)	
Immunosuppressive treatment, n (%)				0.083
Azathioprine	30 (17.9)	11 (13.1)	19 (22.6)	
Methotrexate	4 (2.4)	1 (1.2)	3 (3.6)	
Biologic treatment, n (%)	136 (81.1)	62 (73.9)	74 (88.2)	
Infliximab	48(28.6)	22 (26.2)	26 (31)	
Adalimumab	44 (26.2)	24 (28.6)	20 (23.8)	0.033
Vedolizumab	32 (19.1)	10 (11.9)	22 (26.2)	
Ustekinumab	8 (4.8)	4 (4.8)	4 (4.8)	
Tofacitinib	4 (2.4)	2 (2.4)	2 (2.4)	
Combo therapy, n (%)	30 (17.9)	10 (11.9)	20 (23.9)	0.069
Other IBD treatment, n (%)	28 (16.7)	19 (22.6)	9 (10.7)	0.022

*p-value is calculated for the difference between the group that received the anti-inflammatory diet and the control group.

Table II. Baseline characteristics of the study participants based on the disease type

Parameter	Crohn's disease N=80	Ulcerative colitis N=88	p
Gender (male), n (%)	28 (35)	52 (59.1)	0.002
Age (years), median	40.5 (23-72)	42 (18-77)	0.146
Education level, n (%)			0.769
less than basic education	0 (0)	2 (2.3)	
basic education	8 (10)	4 (4.5)	
intermediate education	24 (30)	28 (31.8)	
advanced education	48 (60)	54 (61.4)	
Income, n (%)			0.056
no income	6 (7.5)	10 (11.4)	
minimum wage	0 (0)	10 (11.4)	
average wage	40 (50)	38 (43.2)	
more than average wage	34 (42.5)	30 (34)	
Non-smokers, n (%)	60 (75)	76 (86.4)	0.077
No alcohol consumption, n (%)	52 (65)	52 (59.1)	0.525
Appendectomy, n (%)	16 (20)	4 (4.5)	0.003
Surgical intervention, n (%)	36 (45)	0 (0)	<0.001

*p-value is calculated for the difference between Crohn's disease group and ulcerative colitis group.

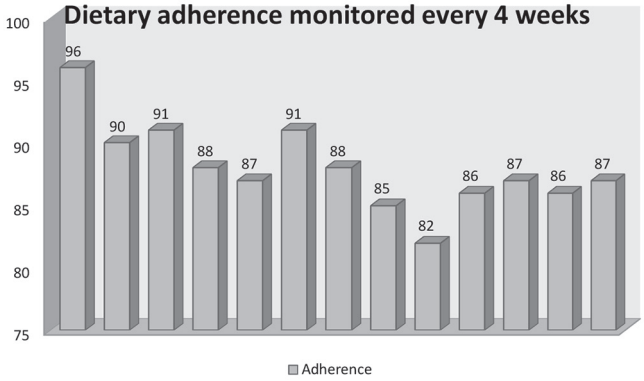

Fig. 2. Dietary compliance rate in the diet arm monitored every 4 weeks.

Conversely, at the conclusion of the 52-week study period, no statistically significant distinctions were noted in CRP levels between the two groups (p=0.519). Hemoglobin and fibrinogen levels remained comparable between the groups at the study's commencement and closure.

Among subjects with elevated fecal calprotectin levels (>250 micrograms/gram), those who underwent more frequent monitoring showed that 19% of individuals in the dietary group required a modification in their therapeutic regimen during the course of the study. In comparison, 21.4% of subjects in the control group experienced a similar need for therapy change (p-value=0.702). These individuals were not classified as clinical relapsers; instead, they underwent rigorous monitoring focused on elevated fecal calprotectin levels.

Within the CD subgroup, there was a 15% rate of therapy modification in the dietary group as opposed to a 25% rate in the control group (p=0.402). In the UC subgroup, the dietary group displayed a therapy change requirement of 22.7% in contrast to 18.2% in the control group (p=0.792).

It is important to note that the decision to change the treatment course was based on various clinical assessments such as therapeutic drug monitoring, endoscopy, intestinal ultrasound, or computed tomography - enterography.

At the 52-week interval, clinical remission was sustained in 95.2% of individuals in the dietary group in contrast to 85.7% of individuals in the control group (p=0.036) (Fig. 3). In the CD subgroup, 95% of patients in the dietary group had a CDAI score below 150 points, whereas only 80% of patients in the control group achieved this level of score (p=0.044). However, in the UC subgroup, no statistically significant distinctions were observed with regard to clinical remission between the two groups (p=0.4).

Regarding BMI, there were no statistically significant differences between groups at 52-week interval (p-value=0.260). Other biochemical parameters included in the final analysis were hemoglobin and fibrinogen, but there were also no significant differences neither at the beginning of the study (hemoglobin p=0.643 and fibrinogen p=0.769), nor at the end of the study (hemoglobin p=0.829 and fibrinogen p=0.9).

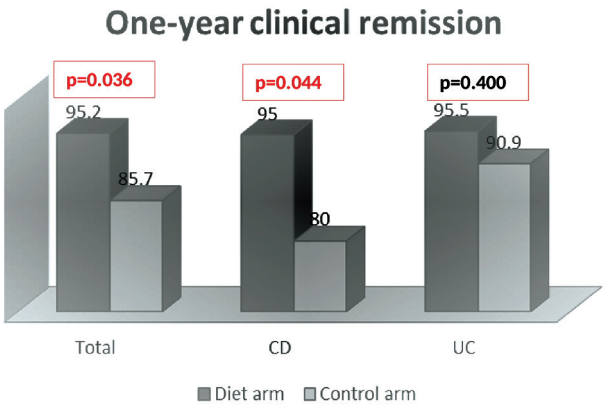

Fig. 3. Clinical remission at the end of the study in IBD population and Crohn's disease and ulcerative colitis groups.

DISCUSSION

Diet significantly influences the initiation and progression of IBD. Despite the escalating interest in this area within recent years, there is currently no universally effective dietary strategy for all IBD patients, as their ability to mitigate intestinal inflammation remains inadequately established. This rising interest is mirrored by patients who often inquire about dietary recommendations. There is a shortage of extended interventional clinical trials that prospectively examine the sustained advantages of dietary interventions in IBD patients. In individuals with Crohn's disease (CD), the CDED presents a dietary strategy that has demonstrated encouraging outcomes in promoting remission among both children and adults with mild to moderate luminal disease [11]. However, most studies encompassed parenteral nutrition or exclusive enteral nutrition as part of their dietary regimen, contrasting with our approach which solely relies on an appropriate anti-inflammatory diet.

In this investigation, our primary objective was to evaluate the impact of an anti-inflammatory diet on the clinical course of inflammatory bowel disease. A prior observational study, contrasting two distinct European cohorts of IBD patients (Romanian and Belgian), unveiled noteworthy variations in dietary patterns between IBD patients and control subjects. The study identified higher consumption rates of certain items such as sweets, sweetened beverages, processed and fatty meat, fried food, salt, store-bought ice cream, and mayonnaise among IBD patients, while the control group exhibited higher consumption rates of seeds, nuts, and yogurt [19]. Leveraging insights from this observational study, we designed our investigation to enroll IBD patients and scrutinize the efficacy and adherence to the anti-inflammatory diet in this population.

This prospective case-control trial aimed to assess the efficacy of an anti-inflammatory diet in sustaining clinical remission in patients with IBD, including those with CD and UC. Initial findings from the research indicated that individuals adhering to an anti-inflammatory diet experienced a higher frequency of maintaining clinical remission, and there was an observable trend of improvement in inflammation tests within the intervention group [22]. Building upon these promising outcomes, we opted for more homogeneous groupings and extended the follow-up period to 52 weeks. The outcomes revealed a higher proportion of individuals maintaining clinical remission in the overall IBD population and specifically in the CD subgroup compared to those not adhering to a dietary approach. Additionally, among individuals with elevated fecal calprotectin at screening, the dietary group showed a slightly reduced need for treatment switch compared to the control group. Notably, in the CD subgroup, the disparity was significantly pronounced, with a 15% treatment switch rate in the dietary group versus 25% in the control group.

The findings align with existing literature; specifically, a randomized controlled trial (RCT) and five observational studies, encompassing 283 participants, indicated that a partial enteral nutrition (PEN) regimen exhibited superiority over a control diet in preventing clinical relapse over a follow-up period spanning from 6 weeks to 2 years [23-28]. Takagi et al. [24] used an intervention group that had a therapy regimen in which half of the daily calorie requirement is provided by an elemental diet and the remaining half by a free diet, and a free diet group, which demonstrated the effectiveness of an elemental diet in CD. In a study by Jones et al. [29], a comparison between a symptoms-guided diet and a high-fiber diet revealed that the former was linked to a decreased risk of clinical relapse. Halmos et al. [30] also demonstrated that in CD patients experiencing clinical remission, modifying the intake of dietary FODMAPs is linked to significant changes in fecal microbiota. These changes align more closely with a prebiotic effect observed in an irritable bowel/healthy cohort when FODMAPs are increased [30].

On the other hand, a RCT involving 202 participants revealed no discernible distinction in preventing a 48-week clinical relapse between low and high consumption of red or processed meats [31]. Even in a subgroup analysis where two RCTs with high-carbohydrate controls were fiber-rich, there remained no significant difference between intervention groups in preventing a 1- to 2-year clinical relapse [32, 33].

Fecal calprotectin stands out as a precise and sensitive marker for detecting intestinal inflammation. In the context of IBD, a normal level exhibits a robust negative predictive value. Conversely, levels exceeding the assay reference threshold (typically set at 50 micrograms/gram of stool) demonstrate a relatively low positive predictive value. Modifying this threshold enhances the positive predictive value, with only a marginal reduction in the negative predictive value [43-36]. Extensive evidence suggests that fecal calprotectin surpasses traditional inflammatory markers in predicting endoscopic activity in IBD. Additionally, certain studies propose the utility of fecal calprotectin in guiding treatment strategies for individuals with IBD [37]. In routine clinical monitoring of patients in clinical remission, a single measurement of fecal calprotectin to predict relapse is insufficient. Numerous longitudinal studies, assessing fecal calprotectin at baseline and establishing a connection between short-term predictions and positive predictive value over one year or more, highlight the need for serial measurements. However, the interpretation of such sequential calprotectin measures remains a subject of debate, given the limited availability of relevant data [38-40]. We selected fecal calprotectin as one of the inflammatory biomarkers to monitor due to its strong negative predictive value for IBD relapse and its non-invasive nature.

Examining the outcomes of inflammatory biomarkers, both in the overall IBD population and specifically within the UC subpopulation, no statistically significant differences were observed in parameters such as fecal calprotectin, hemoglobin, CRP, or fibrinogen, both at the study's commencement and the 52-week interval. Nonetheless, within the CD subpopulation, a noteworthy dissimilarity in CRP levels emerged between the dietary and control groups ($p=0.026$) at the study's initiation, a distinction that diminished by the study's conclusion. In terms of inflammation biomarkers, a RCT employing the CDAI and CRP to define clinical relapse discovered no distinction in the 12-month relapse between a low-refined carbohydrate diet and a fiber-rich diet [32]. Another RCT, which involved eight participants and compared a 21-day consumption of a low fermentable oligo-, di-, monosaccharides, and polyols diet, a typical Australian diet, and a habitual diet, found no variance in the rise of calprotectin above a predefined threshold of 150

mg/g [30]. Additionally, in an RCT comparing low and high red meat consumption with 36 participants, no significant differences were observed in calprotectin levels or the proportion of participants with calprotectin >150 mg/g or >250 mg/g at week 20 [31]. These findings align with our results.

Regarding UC patients, our cohort did not yield any positive outcomes. In the literature, two RCTs investigated dietary approaches in UC patients in remission to maintain the remission state. These studies did not demonstrate a benefit from a carrageenan-free or anti-inflammatory diet for sustaining clinical remission over a period of 26 to 52 weeks, although the individual studies were relatively small [17, 41]. In a RCT involving 53 participants, it was reported that calprotectin concentrations at 26 weeks did not exhibit significant changes in individuals adhering to an anti-inflammatory diet. In contrast, those following a control diet experienced a significant increase in calprotectin levels. Moreover, a lower proportion of participants on an anti-inflammatory diet had calprotectin levels exceeding 150 mg/g at the 26-week mark, although it should be noted that not all participants had normal calprotectin concentrations at baseline [17]. The RCT comparing a carrageenan-free diet with a carrageenan-containing diet observed no disparity in calprotectin concentrations at the 52-week mark among the 10 participants [41].

The discernible differences in outcomes are not attributable to random chance, given the homogeneity of the groups concerning disease phenotype, inflammatory markers, and the necessity for therapy adjustments. Among individuals exhibiting elevated fecal calprotectin levels (>250 micrograms/gram), those subjected to more frequent monitoring revealed that 19% of participants in the dietary group necessitated modification in their therapeutic regimen throughout the study, compared to 21.4% in the control group experiencing a similar need for therapy change (p=0.702).

In the CD subgroup, the dietary group exhibited a 15% rate of therapy modification, contrasting with a 25% rate in the control group (p=0.402). For the UC subgroup, the dietary group displayed a therapy change requirement of 22.7%, as opposed to 18.2% in the control group (p=0.792).

Our study has several strengths. The uniqueness of this investigation lies in the development of a dietary regimen derived from our prior observational study, which involved the comparison of cohorts from distinct regions (East versus Western Europe). This diet excluded food categories that exhibited statistical significance in the context of IBD patients when compared to control subjects [19].

While various diets have been suggested for individuals with IBD, conflicting findings exist for several foods, and the comprehensive impact of certain foods on IBD remains undetermined. In our proposed anti-inflammatory diet, IBD patients were provided with a list of foods established to be either safe or beneficial for IBD, as well as those that should be avoided due to their adverse effects. A notable strength of this study is its prospective nature, conducted as a clinical trial involving 168 IBD patients. It is essential to acknowledge the limited number of studies in the literature specifically addressing the adult IBD population, as the majority have been centered on pediatric IBD subjects and then generalized to clinical practice.

Another advantageous aspect of our study was the extended duration of the anti-inflammatory diet and subsequent follow-up, spanning a period of 12 months. This timeframe was considered reasonable for gauging the potential for long-term remission or disease flares. Despite the relatively modest number of patients opting for the diet, they successfully adhered to the 12-month regimen without encountering difficulties, suggesting that the anti-inflammatory diet is well-tolerated over more extended periods, facilitating the maintenance of remission.

Our study is subject to certain limitations, notably the absence of a designated control diet. Single-arm studies‘ findings are susceptible to being confounded by the inherent progression of disease activity, introducing potential biases. Additionally, the potential for subjects to self-select into either the dietary or control arm poses a risk of selection bias. The adherence rate may be impacted 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 bias stemming from self-selection is the placebo effect of the diet, which can influence the clinical score of disease activity. In order to avoid this bias, we correlated the clinical score with inflammatory markers.

CONCLUSIONS

An anti-inflammatory diet demonstrates efficacy in sustaining clinical remission within the IBD population, with notable effectiveness evident primarily in the CD subpopulation. Additionally, there is a discernible trend of improvement in inflammation tests, including fecal calprotectin, within the intervention group. This further supports the hypothesis that IBD is influenced by lifestyle factors, particularly those associated with a westernized diet. The anti-inflammatory diet proves to be well-tolerated and is linked to elevated rates of sustained long-term clinical remission. However, these positive and promising outcomes necessitate validation through larger-scale, randomized and controlled clinical trials.

Conflicts of interest: None to declare.

Authors‘ contribution: C.M.P, T.S. and M.N. conceived and desingned the study. M.C., C.T., C.G.M., L.T. and C.A.C. collected the data. D.I. performed the statistical analysis and drafted the manuscript. T.M., and M.M. revised and edited the manuscript. E.L. and M.D. were the project administration. All authors critically revised the manuscript, approved the final version to be published, and agree to be accountable for all aspects of the work.

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