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Mediterranean diet diminishes the effects of Crohn's disease and improves its parameters: A systematic review

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Abstract

Background: The pathogenesis and clinical course of Crohn's disease (CD) is influenced by diet. Mediterranean Diet (MD) helps Crohn's patients through many mechanisms. **Aims:** This study aimed to evaluate the effect of the MD on CD patients and to evaluate such effect on body parameters. **Methods:** PubMed, Science Direct, Web of Science, MEDLINE and Cochrane central library were searched for MD and CD from 2010 to 2020. Included studies met the following criteria: (1) male and female adults (18–75 years) with a confirmed diagnosis of CD; (2) MD as an intervention; (3) original interventional Trial, Cross-Sectional Analysis, or Prospective Cohort Studies. **Results:** Five studies were included, involving 83,564 participants. A small number of patients with CD fulfilled the P-MDS criteria, the overall scores were low, 4.7 and 4.5 for females and males respectively. Patients with an inactive disease whose adherence to MD was greater, the MD score was negatively correlated with disease activity ($p < 0.001$) and positively with IBDQ ($p = 0.008$). Twenty-seven percent had a prevalence of impaired adherence to a MD (mMED score = 0–2), giving such a population a risk attributed to 12% for the later CD. Seventy-point reduction in CDAI + decreased fecal CRP / calprotectin, calprotectin <250 mcg/gm or >50% decrease from baseline and hsCRP < 5 mg/L or >50% from baseline. **Conclusions:** MD showed anti-inflammatory properties. Adherence to MD was associated with improvement in CD patients and negatively correlated with the disease activity, in addition to a lower risk of developing CD later in life.

Keywords

Crohn's disease, mediterranean diet, gut microbiome

Introduction

Crohn's disease (CD) is one of the diseases listed under Inflammatory Bowel Diseases (IBD), characterized by chronically relapsing gastrointestinal (GI) tract inflammation (Magro et al., 2017, Gomollón et al., 2017). Subsequently, the role of the diet may be reduced since diet is one of the main factors shaping the human gut microbiome. Unbalanced diets can contribute to the development of dysbiosis in the host, which can have a variety of negative effects. This preserves and stimulates, directly and indirectly, enteritis (intestinal inflammation), thus promoting adipose tissue growth, which is an important source of pro-inflammatory cytokines (Chicco et al., 2021). The Mediterranean diet (MD) is characterized as a distinctive diet that was established in the middle of olive tree cultivation areas in the Mediterranean basin (Trichopoulou et al., 2014) and is characterized by high consumption of fruits, vegetables, legumes, nuts and grains, monounsaturated fat like olive oil, a medium amount of dairy products, fish and wine, and low consumption of meat and meat products, saturated fats, and sweets. This diet has been associated with a number of beneficial health impacts, including a

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decrease in inflammation and a protective effect against diseases such as rectal and colon cancer (Chicco et al., 2021; Song et al., 2015).

There are studies that have shown that higher adherence to the MD is associated with a significant reduction in the risk of developing later-onset Crohn's Disease (Khalili et al., 2020). Additionally, evidence supporting a substantial relationship between a healthy lifestyle, including adherence to MD, and decreased mortality in CD patients was provided (Lo et al., 2021). The aim of this study was to examine the relationship between the MD and Crohn's disease and its parameters. Also, the effect of MD on gut microbiome and health outcomes will be discussed.

Table 1. Inclusion and exclusion criteria.

	Inclusion	Exclusion
Population	Adult, Older Adult, Males and Females, 18 Years to 75 Years, Diagnosis of Crohn's Disease.	Animals, Pregnancy or lactation, Hospitalized patients, Children, Ileostomy or colostomy, Exclusive enteral nutrition/ partial enteral nutrition.
Intervention	Mediterranean Diet	No intervention using MD, Antibiotics treatment, Antioxidant Therapy, Dietary Supplement, Low n-6 PUFA Diet, Specific Carbohydrate Diet, Functional Foods, Other diet patterns.
Control	Placebo, baseline measurements.	No comparison, no control group.
Outcomes	Symptomatic remission; Clinical and inflammatory parameters; C-reactive protein; Fecal calprotectin; Remission rate; Response rate; Crohn's Disease Activity Index (CDAI); Quality of life; Disease characteristics (severity and relapse).	No clear findings or Poor conclusive results.
Study Design	Interventional (Clinical Trial), Cross-Sectional Analysis, Prospective Cohort Studies.	Weak or poor-quality assessment, Non-related.

Methods

Design of primary studies

A systematic review of clinical trial, cross-sectional analysis, and cohort studies was conducted to evaluate the effect of the Mediterranean diet on Crohn's patients and their dietary adherence. The review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standards (Moher et al., 2009) throughout its execution and reporting. Prospero has assigned the review a registration number CRD42021259966 in 11/07/2021, https://www.crd.york.ac.uk/PROSPERO.

Data sources

PubMed, Science Direct, Web of Science, MEDLINE, and Cochrane library were searched independently by MJ and MA from 2010 to 2020, any disagreement was settled by AA and consensus. The following medical subject heading terms were combined with the Boolean operators "AND" or "OR": "Crohn's Disease", "Mediterranean Diet", "Treatment", "Intervention", "Association". Although no time or language constraints were imposed, the study was limited to human studies. Titles and abstracts were independently screened to identify eligible studies. After that, the full-text articles were screened for inclusion. Finally, the total number of studies included in this research was determined by applying the population, intervention, control, outcomes, and study design in Table 1.

Searching strategy

The search flow chart is detailed in Figure 1. A total of 194 articles were identified through searching (PubMed, 12; Science Direct, 166; Web of Science, 8; MEDLINE, 3 and Cochrane library, 5). After removing duplicates (n = 16), reviewing the titles and abstracts, removing the irrelevant studies (n = 151), and removing the reviews (n = 12), 15 studies were evaluated for full-text analysis. Then,10 additional studies were excluded through the PICOS application. There were 7 articles that did not belong to the required study design and 3 articles weren't specific to Crohn's disease. Finally, 5 studies (Khalili et al., 2020; Taylor et al., 2018; Lo et al., 2021; Papada et al., 2020; University of Pennsylvania, 2020) were included in the systematic review. One of the studies was Cross-Sectional Analysis (Taylor et al., 2018), another was prospective cohort studies (Khalili et al., 2020), and 3 more were interventional (Clinical Trial) studies (University of Pennsylvania, 2020; Roll, 2016; Papada et al., 2020).

Inclusion and exclusion criteria

The final analysis includes all studies that fulfilled the following criteria: (1) adult and/or older adult (18–75 years),

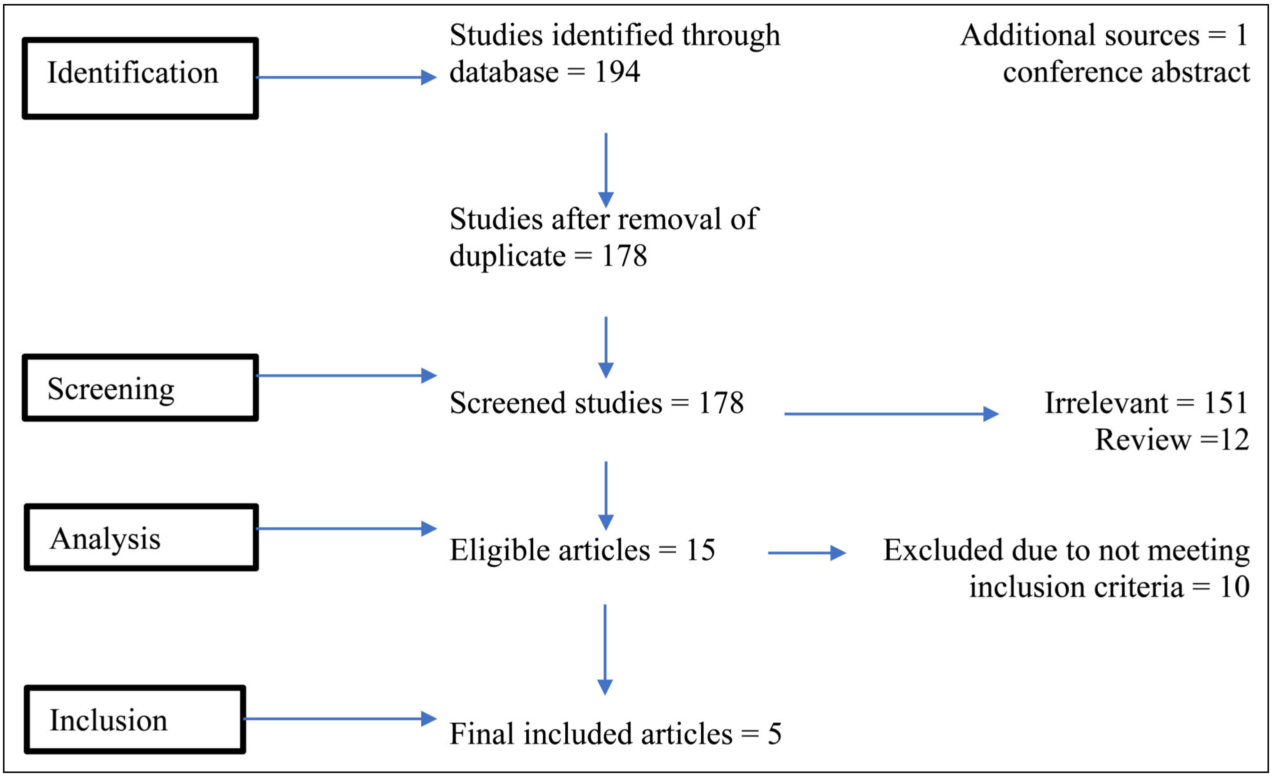

Figure 1. PRISMA flowchart showing trial progress during each stage of the selection process. CT (Clinical Trial), CSA (Cross-Sectional Analysis), PCS (Prospective Cohort Studies), CD (Crohn's Disease).

male and female patients with a confirmed diagnosis of CD; (2) studies have accredited MD as an intervention or treatment; and (3) studies followed the interventional (Clinical Trial), Cross-Sectional Analysis, or Prospective Cohort design. Non-interventional studies such as; systematic reviews, reviews, editorials, meta-analyses, letters and guidelines that did not display original data were excluded from this review. Moreover, all studies that have involved patients with IBD were excluded if the CD population data could not be distinguished. Table 1 has detailed the inclusion and exclusion criteria of this research.

Data extraction

Each study was qualitatively evaluated; the following data were extracted from the included studies: study authors and year of publication, number of participants, study design, intervention/duration, and outcomes as presented in Table 2.

Quality appraisal

The five studies were evaluated for their quality and danger of bias using quality assessment methods (Study Quality Assessment Tools, NHLBI, NIH, 2021). Fourteen criteria were included in the checklist After evaluation, the studies were classified into: good (10–14), fair (6–9), poor (less than 5) according to their scores. The quality assessment for each study appears separately in Table 2, taking into account that the appropriate tool was used for each study based on the type of study design.

Results

Database search and study characteristics

The search strategy identified a total of 194 citations, of which 15 were evaluated. After applying the inclusion and exclusion criteria as presented in Table 1. Five studies were eligible for systematic review (Figure 1), and were the primary source for testing the effect of the Mediterranean diet on Crohn's patients.

After assessing the quality and risk of bias in the selected studies through Study Quality Assessment Tools, there were 4 studies of good quality (Khalili et al., 2020; University of Pennsylvania, 2020; Roll, 2016; Papada et al., 2020), and one fair (Taylor et al., 2018). The following results summarized in Table 2 were selected from the outcomes of the selected studies.

Dietary characteristic and mediterranean diet adherence

Three studies out of 5 have assessed the level of adherence to the MD in Crohn's patients, these studies have agreed that adherence to MD was relatively weak.

Table 2. Characteristics and data extraction from included studies.

Study author(s), Year	Study design	Participants	Intervention/ Duration	Outcomes	Quality assessment
(Taylor et al., 2018).	Cross-sectional study	There were 87 participants, but only 67 patients continued. These 67 patients with CD had a mean age of 45 years and had a mean BMI of being overweight. Control: Representative Sample (N = 1547).	Micronutrient intakes of CD patients with a representative sample of individuals. The macro- and micronutrient intakes of male and female CD patients. P-MDS of male and female CD patients.	Contrasted with the representative sample, patients with CD: 1. Had comparable energy, carbohydrate, protein, and total fat intake. 2. MUFA, omega-6 and 3, PUFA and were lower in CD patients and dietary fibre intake was higher ($p < 0.05$). 3. Phosphorus, vitamins D, C, niacin, thiamin, magnesium, potassium, and zinc were all significantly lower in all CD patients. 4. Few patients with CD met the P-MDS standard and total scores were low (M = 4.5, SD = 1.1 in males and M = 4.7, SD = 1.8 in females).	Fair 8/14
(Papada et al., 2020).	Interventional (Clinical Trial)	86 patients with CD. Active (N = 41), Inactive (N = 45). Patients were recruited between May 2016 and June 2017.	MD scoring method was recorded for the past 6 months.	1. The MD score was positively correlated with the IBDQ, while it was negatively correlated with CRP and HBI. 2. Active CD patients had significantly higher levels of IL-6 and lower levels of IL-10. 3. Committing to MD is correlated with improved quality of life in CD patients and it is negatively related to disease activity.	Good 11/14
(Khalili et al., 2020).	Two large prospective cohort studies	83147 were eligible for analysis, age range: 45–79 years. Men = 45052, Women = 38095. 164 incident cases of CD and 395 incident cases of UC.	mMED score, the mean follow-up time of participants was 17 years.	1. Major committing to a Mediterranean diet is connected with a lower risk of later-onset CD. 2. In two large prospective cohorts in Sweden, poor committing to a Mediterranean diet gave the population a 12% attributable risk of developing CD at a later date.	Good 13/14
(Roll, 2016).	Interventional (Clinical Trial)	100 participants, 18 to 75 Years. Seventy eligible patients.	1. Behavioral: Mediterranean diet (8 weeks course). 2. Behavioral: Low residue diet (8 weeks course).	Primary Outcome Measures: 1. CDAI: change from baseline. Secondary Outcome Measures:	Good 12/14

(continued)

Table 2. (continued)

Study author(s), Year	Study design	Participants	Intervention/ Duration	Outcomes	Quality assessment
				1. CRP: change from baseline. 2. Fecal calprotectin: change from baseline. 3. Remission rate- CDAI<150 + normal CRP/ fecal calprotectin. 4. Response rate- 70 points reduction in CDAI + decreased fecal CRP / calprotectin.	
(University of Pennsylvania, 2020).	Interventional (Clinical Trial)	194 participants, 18 Years and older.	Specific Carbohydrate and Mediterranean style Diets for 6 weeks.	Primary Outcome Measures: 1. Symptomatic remission: assessed by sCDAI - abdominal pain, diarrhea, and general well-being. 2. Reduction in bowel inflammation: calprotectin <250 mcg/gm and >50% decrease from baseline. Secondary Outcome Measures: 1. Clinical remission: assessed by the HBI. 2. Reduction in systemic inflammation: reduced hsCRP < 5 mg/L >50% from baseline.	Good 11/14

CD (Crohn's Disease), BMI (Body Mass Index), P-MDS (Mediterranean Diet Scores), MUFA (Mono Unsaturated Fatty Acid), PUFA (Poly Unsaturated Fatty Acid), SD (Standard Deviation), IBDQ (Inflammatory Bowel Disease Questionnaire), CRP (C-Reactive Protein), HBI (Harvey-Bradshaw Index), IL (Interleukin), mMED (modified Mediterranean diet), UC (Ulcerative Colitis), CDAI (Crohn's Disease Activity Index), sCDAI (short Crohn's Disease Activity Index), hsCRP (high sensitivity C-Reactive Protein).

According to Taylor et al. (2018) a small number of Crohn's patients met the P-MDS criteria for eating legumes, olive oil, or consuming sofrito sauce. Twenty-four percent of the females and 36% of the males fulfilled the P-MDS criteria for nuts, while one-fifth of the female patients and a quarter of the male patients met the criteria for P-MDS servings of fruit. As for the consumption of fish and/or shellfish, the average was 0 per week, and 32% of the females and 21% of the males ate three or more servings per week. Nearly half of patients restricted sweets and baked goods to less than three times a week, while more than 70% of the patients met serving recommendations for limiting red or processed meats, sugar-sweetened beverages, and butter. Compared to the typical sample, female CD patients had lower intakes of omega-3, omega-6, and PUFA, whereas male CD patients had lower intakes of MUFA. As for dietary fibre intake compared to the representative sample, it was significantly higher in CD patients. Vitamin Intake, compared to the representative sample, reduced intake of pyridoxine and riboflavin was observed in female patients only. Females and males with CD had significantly less niacin, thiamine, and vitamins D and C. In males only, with CD, a decrease in the intake of folate and vitamin K and higher amounts of pyridoxine, thiamine, biotin, and niacin were noted. Vitamins E, A, D, choline, pantothenic acid, folate, and biotin compared to DRIs were insufficient in female and male CD patients. Mineral Intake, the DRI of chromium, potassium, calcium, zinc, or magnesium was not met by female and male CD patients. Compared to the representative sample, female and male patients had lower intakes of zinc, magnesium, potassium, and phosphorous, while in female patients the sodium consumption was higher but consumed less sodium, iron, and phosphorous compared to the affected males.

With regard to Papada et al. (2020) 86 patients diagnosed with CD fulfilled the study's inclusion criteria. Regarding adherence to MD, patients with inactive CD, the MD Score was higher compared to patients with active disease ($p = 0.005$, 26.8 ± 5.0 vs. 30.2 ± 5.8). In males who have an inactive CD compared to females; the intake of energy, protein, carbohydrates, saturated fatty acids, cholesterol, fats, iron, selenium, and calcium was significantly higher, while caffeine was significantly lower. Intake levels of vitamin C ($p = 0.003$) and protein ($p = 0.015$) were individually higher in the remission group. The Harvey Bradshaw Index (HBI) in inactive disease was significantly lower ($P < 0.001$) while the Inflammatory Bowel Disease Questionnaire (IBDQ) score in inactive disease was higher ($p < 0.001$).

In the cohort study Khalili et al. (2020) with 83,147 participants, have found only 164 CD cases eligible for the study analysis. Reduced risk of developing Crohn's disease was associated with a higher mMED score ($P_{trend} = 0.02$). Relatively poor adherence to MD had a prevalence of 27% at baseline (ie, mMED score = 0–2), presenting a 12% for later-onset CD risk attributable to the population (95%, CI 3% to 26%), assuming there was a causal relationship between diet and Crohn's disease. Reduced risk of developing CD was also associated with higher (above average) consumption of vegetables and fruits (Multivariable (MV) -adjusted HR = 0.83, 95% CI 0.60 to 1.15), non-refined grains (MV-adjusted HR = 0.78, 95% CI 0.55). To 1.10), fermented dairy (MV-adjusted HR = 0.82, 95% CI 0.59 to 1.13), and olive oil use (MV adjusted HR = 0.70, 95% CI 0.50 to 0.98). The MV-adjusted HR of CD among participants with above the median consumption of legumes and nuts was 0.70 (95% CI 0.50 to 0.98).

Parameters

Three studies out of 5 showed results of the effectiveness of the MD on Crohn's patients through several parameters (CDAI, Fecal calprotectin, HBI, IBDQ, inflammation, CRP). The studies agreed that the inflammatory parameters decreased due to the effectiveness of the MD, and there was a change in the symptomatic and clinical remission for better.

According to Taylor et al. (2018), 86 patients diagnosed with CD have fulfilled the study's inclusion criteria. Active Crohn's patients had significantly higher levels of IL-6 ($p \leq 0.001$) and fibrinogen ($p = 0.039$), and lower levels of IL-10 ($p = 0.025$). There was a significant positive association between MD score and IBDQ ($p < 0.001$, $r = - 0.400$), while the correlation between MD score with CRP levels, and HBI was significantly negative with ($p = 0.027$, $r = - 0.268$) and ($p < 0.001$, $r = - 0.400$) respectively. However, no significant association was observed between IL-10 ($p = 0.137$) and MD score or between IL-6 ($p = 0.125$) and MD score.

For the study by Roll (2016), 70 eligible patients out of 100 were included. There was a change from baseline in Crohn's Disease Activity Index (CDAI), C-reactive protein (CRP), and Fecal calprotectin. Where remission rate was: normal fecal calprotectin / CRP; CDAI <150, and response rate: decreased fecal calprotectin/ CRP; CDAI decrease in 70 points.

In the University of Pennsylvania study (2020) 194 adults have participated. Using Harvey Bradshaw Index (HBI) Assessed Clinical remission, and the Short Crohn's Disease Activity Index (sCDAI), symptomatic remissions (abdominal pain, diarrhea, and general well-being) were evaluated. Such symptoms have shown improvement in the subjects adhered to the MD. Reduction> 50% from baseline in bowel and systemic inflammation, Calprotectin <250 mcg / gm and hsCRP <5 mg / L were reported.

Discussion

A previously published study, to assess the association between food intake and disease course in 103 CD patients by using a cross-sectional design, half with active disease (Tasson et al., 2017). In this study, potatoes and legumes were inversely associated with an active disease risk (known as fecal calprotectin> 150), with nearly 80% of legume consumers in the top quartile having a lower risk of developing active disease. Patients' eating large amounts of meat coincides with an increased risk of active disease. It is compelling to note that in the current study; only three subjects consumed three or more servings of legumes, while 30% of male patients showed excessive meat consumption.

Dietary MUFA intake in patients with CD was low, and according to a recent study (Principi, 2018), the amount of energy intake and dietary fats in a mixed sample of IBD was higher compared to healthy subjects. However, no differences were observed in carbohydrate and protein intake. In the representative sample, both females and males surpassed the DRI for salt, although male intake was considerably greater than female consumption, maybe an alternative to eating more processed meals. There are signs that an increase in inflammatory cytokine production and increased colitis is achieved by a diet rich in sodium chloride in animal models (Monteleone et al., 2017). However, dietary sodium intake is not adequately reported in inflammatory bowel disease (IBD).

In the sample of CD patients, the nutritional composition was different from the P-MDS criteria. Olive oil was rarely used, and for fruits, including fruit juice, legumes, or vegetables, only a small number of patients met the criteria for P-MDS, with an average consumption of 50% less than the three or more fruits recommended in daily servings. The P-MDS standards for fruits and vegetables are similar to North American nutritional recommendations. For nuts and fish, 80% of patients consumed inadequate food, and 30% of males, according to P-MDS, exceeded red and processed meat recommendations.

A subsequent study found that when patients consumed a Mediterranean diet supplemented with nuts or extra virgin olive oil, interleukin-6 (IL-6), high-sensitivity C-reactive protein (hsCRP), and tumour necrosis factor (TNF) levels decreased significantly when compared to those who consumed a low-fat diet (Casas et al., 2016). The study findings raise curiosity about the relationships between nutritional adequacy, dietary patterns, and the pathogenesis of IBD. The mechanical protective roles of MD types in inflammatory bowel disease are reasonable. It is mediated by

Table 3. Observational and intervention studies exploring the influence of Mediterranean diet or its typical ingredients on gut microbiome and human health.

Reference	N° of subject	Study design*	Type of diet	Study population	Control group	Type of dietary data collected	Duration	Effect on the gut microbiome*	Effect on the health
(Bolte et al., 2021)	554	Observational study	Habitual diet (subjects divided based on the consumption of vegetable products)	Patient with Crohn's disease (CD), ulcerative colitis (UC) and irritable bowel syndrome (IBS)	Yes, healthy subject	FFQ	Habitual long-term diet	↑ *Roseburia (R. hominis)*, *Faecalibacterium (F. prausnitzii)* and *Eubacterium* spp. ↓ opportunistic bacteria ↓ *E. coli, Bacteroides fragilis* and *Parabacteroides*	↑ anti-inflammatory effects and production of SCFAs; ↑ pathways involved in the synthesis of acetate and the urea cycle for detoxification of ammonium
(De Filippis et al., 2016)	153	Observational study	Habitual diet (omnivore, vegetarian or vegan diets)	Healthy adults	No, subjects divided based on MD adherence	7-day weighed food diary	Habitual long-term diet	↑ Firmicutes (*Lachnospira*) and Bacteroidetes (*Prevotella*) ↑ fibre-degrading taxa	↑ SCFA ↓ TMAO
(Picchianti Diamanti et al., 2020)	60	Observational study	MD	Subject with Rheumatoid arthritis (RA)	No, subjects divided based on MD adherence	14-item questionnaire for the assessment of adherence to the MD	Habitual long-term diet	↑ Cyanobacteria; ↓ Euryarchaeota, Nitrospinae, Planctomycetes, Tenericutes and Verrucomicrobia; ↑ *Paenibacillaceae*; ↑*Candidatus Saccharimonas*, *Coprobacillus*, *Intestinibacillus*, *Nitratiruptor* and *Paenibacillus*; ↓ *Lactobacillus*, *Catabacter*, *Clostridioides*, *Blautia*. ↑ *Adlercreutzia equolifaciens, Bacteroides coprophilus, Coprobacillus cateniformis, Lactococcus lactis* ↓ *Bacteroides uniformis, Butyricimonas virosa, Dorea formicigenerans, Intestinimonas butyriciproducens, Methanobrevibacter smithii, Paraprevotella xylaniphila*	↓ Disease activity and C- reactive protein

(continued)

Table 3. (continued)

Reference	N° of subject	Study design*	Type of diet	Study population	Control group	Type of dietary data collected	Duration	Effect on the gut microbiome*	Effect on the health
(Garcia-Mantrana et al., 2018)	27	Observational study	MD	Healthy subjects (normal weight, over-weight and obese)	No, subject divided based on MD adherence	FFQ	Habitual long-term diet	↓Firmicutes/Bacteroidetes ratio; ↓ *Clostridium*; ↑*Christensenellaceae*; ↑ *Bifidobacterium* spp. ↑ *Catenibacterium*	↑acetate, propionate and total SCFA
(Ghosh et al., 2020)	323	Randomized, multicentre, controlled, parallel trial	MD	Pre-frail elderly subjects (65-80 y.o.)	Yes, elderly subjects following the habitual diet	7-days food record	12 months	↑ *F. prausnitzii, Roseburia, Eubacterium, Bacteroides thetaiotaomi- cron, Prevotella copri* and *Anaerostipes hadrus;* ↓ *Ruminococcus torques, Collinsella aerofaciens, Coprococcus comes, Dorea formicigenerans, Clostridium ramosum, Veillonella dispar, Flavonifractor plautii* and *Actinomyces lingnae.*	↓ inflammatory markers, ↑ improvement of cognitive function ↑markers of lower frailty
(Haro et al., 2016)	20	Ongoing prospective, randomized, opened, controlled trial	MD and a low-fat, high-complex carbohydrate diet (LFHCC)	Obese subject with coronary heart disease (CHD) (20-75 y.o.)	No, comparison between the two dietary intervention	Not recorded	12 months	↓ *Prevotella* ↑ *Roseburia* and *Oscillospira* ↑ *Parabacteroides distasonis*	↑ insulin sensitivity index; protective influence for the prevention of T2D
(Ismael et al., 2021)	9	Single-arm pilot study	Individualized MD	Subject with type 2 diabetes (66 ± 9 y.o.)	No, comparison with the baseline	24-h dietary recalls (two non-consecutive, 15 days apart, to evaluate dietary adherence)	3 months	↑ *Prevotella/Bacteroides* ratio; ↑ Bacterial richness and diversity	↓ diastolic blood pressure in subjects with high adherence to the MD; ↓ HbA1c and HOMA-IR ↓ fasting glucose levels
(Karl et al., 2017)	41	Randomized, single-blind, parallel controlled trial	Habitual diet enriched in WG or refined cereals	Healthy adults	Yes, subjects consuming a diet poor in fibre	Randomized, single-blind, parallel-arm controlled trial	1,5 months	↑ *Lachnospira* and *Roseburia*, ↓ *Enterobacteriaceae* in WG	↓ Glycemia in WG
(Li et al., 2021)	303	Cross-sectional design	Healthy plant-based diet	Healthy men free of major chronic diseases, (71 ± 4 y.o.)	No, subjects divided based on adherence to the healthy plant-based diet	FFQ	12 months	↑ *Bacteroides cellulosilyticus* and *Eubacterium eligens* ↓ *Ruminococcus torques, Ruminococcus gnavus, Clostridium leptum, Lachnospiraceae* bacterium and	↑ HDL cholesterol ↓ triacylglycerol, HbA1c, BMI and metabolic risk score

(continued)

Table 3. (continued)

Reference	N° of subject	Study design*	Type of diet	Study population	Control group	Type of dietary data collected	Duration	Effect on the gut microbiome*	Effect on the health
								Erysipelotrichaceae bacterium	
(Luisi et al., 2019)	18	Intervention study	MD enriched in High Quality Extra Virgin Olive Oil (MD-HQ-EVOO)	Overweight/obese subjects	Yes, normal weight controls, following MD	Not recorded	3 months	↑ Lactic Acid Bacteria/ng of DNA	↓ Myeloperoxidase and 8-hydroxy-2-deoxyguanosine, markers of inflammation and oxidative stress; ↑ IL-10 (anti-inflammatory cytokine) ↑ IL-10 and adiponectin
(Marlow et al., 2013)	8	Pilot study	Mediterranean inspired anti-inflammatory diet	Subject with active yet stable Crohn's disease symptoms (31-60 y.o.)	No, comparison with the baseline	Self-reported questionnaire	1,5 months	↑ Bacteroidetes, *Clostridium* cluster IV and *Clostridium* cluster XIVa ↓ Proteobacteria and *Bacillaceae*	↓ established biomarkers of inflammation (CRP and Cytokinesis blocked micronuclei numbers)
(Martínez et al., 2013)	28	Randomized cross-over trial	Habitual diet enriched with a daily dose of 60 g of whole-grain barley (WGB), brown rice (BR) or a mixture of the two (BR + WGB)	Healthy subject (age 25.9 ± 5.5 y.o.); 13 overweight subjects	No, comparison with the baseline and between the three dietary treatments	Weekly diaries	4.1 months	↑ microbial diversity, ↑ Firmicutes ↓ Bacteroidetes (*Bacteroides*) ↑ *Blautia* (all dietary treatments) ↑ *Roseburia*, *Bifidobacterium*, *Dialister* *E. rectale*, *R. faecis* and *R. intestinalis* (WGB)	↓ plasma interleukin-6 and peak postprandial glucose (BR + WGB); ↓ fasting glucose levels; ↓ total cholesterol
(Meslier et al., 2020)	43	Randomized, controlled, parallel trial	MD	Overweight/ obese, healthy adults	Yes, overweight/ obese subjects following the habitual diet	7-days food record	2 months	↑ *Faecalibacterium prausnitzii, Roseburia* and *Lachnospiraceae* ↓*Ruthenibacterium lactatiformans, Flavonifractor plautii, Parabacteroides merdae, Ruminococcus torques, Ruminococcus gnavus* and *Streptococcus thermophilus*	↓ total plasma cholesterol, insulin resistance and systemic inflammation ↑ urinary urolithins, fecal bile acid degradation and insulin sensitivity
(Mitsou et al., 2017)	116	Cross-sectional study	MD	Healthy adults (18–65 y.o.)	No, subjects	Semi-quantitative FFQ	Habitual long-term diet	↓ *Escherichia coli*; ↑	↑ Defecation frequency; acetate

(continued)

Table 3. (continued)

Reference	N° of subject	Study design*	Type of diet	Study population	Control group	Type of dietary data collected	Duration	Effect on the gut microbiome*	Effect on the health
					divided on MD adherence			*Bifidobacteria/E. coli* ratio; ↑ *Candida albicans*	and total SCFA ↓ Valerate
(Muralidharan et al., 2021)	171	Randomized, controlled trial	Energy restricted MD (associated with physical activity)	Overweight/obese men and women (55–75 y.o.) with metabolic syndrome	Yes, subject following a non-energy restricted MD	FFQ	12 months	↓ *Butyricicoccus*, *Haemophilus*, *Ruminiclostridium* 5 and *Eubacterium hallii*; ↑ *Coprobacter*; ↑ *Lachnospira* and *Lachnospiraceae* NK4A136 group	↓ Weight, BMI, waist circumference and concentrations of triglycerides, glucose and glycated hemoglobin; ↑ HDL cholesterol
(Nagpal et al., 2019)	11	Randomized, double-blind, crossover, single-center pilot trial	Modified Mediterranean-ketogenic diet and AHAD (American Heart Association Diet)	Elderly subject (64.6 ± 6.4 y.o.) with mild cognitive impairment (MCI) and early MCI	Yes, cognitively normal	Food records	4.5 months (6 weeks 1st diet – 6 weeks washout – 6 weeks 2nd diet)	↓ *Bifidobacterium* and *Lachnobacterium*; ↑ *Enterobacteriaceae, Akkermansia, Slackia, Christensenellaceae* and *Erysipelotriaceae*	↓ gene families related to the Alzheimer's disease; ↓ lactate (improved memory and cognition); ↑ SCFA (propionate and butyrate)
(Pagliai et al., 2020)	23 (11 MD e 12 VD)	Crossover study	Low-calorie MD	Overweight omnivores with low-to-moderate cardiovascular risk (58.6 ± 9.8 y.o.)	Yes, vegetarian diet (VD)	Not recorded	3 months	MD: ↑ *Lachnoclostridium* and *Enterorhabdus*; ↓ *Parabacteroides*; VD: ↑ *Streptococcus* and *Anaerostipes*; ↓ *Clostridium sensu stricto* and *Odoribacter*	MD: ↑Cardiovascular protection; ↓ pro-inflammatory cytokines; ↑ SCFA ↑ propionic acid
(Pastor-Ibáñez et al., 2021)	37	Single-centre randomised controlled open-label clinical study	MD supplemented with EVOO and walnuts (SMD)	HIV infected Individuals (median age 47 y.o.)	Yes, subjects following the habitual diet	Validated 14-item MD adherence questionnaire	3 months	↑ diversity and richness; ↑ *Bifidobacterium*; Burkholderiales, *Butyrivibrio*, *Catenibacterium*, and *Succinivibrio* ↓ *Bacteroides*	↓ immune activation and IFN-γ-producing T-cells; improved their lipid profile; ↓ total cholesterol and B-lipoprotein levels
(Pisanu et al., 2020)	23	Intervention study	Hypocaloric MD	Overweight/obese adults	Yes, normal-weight subjects (only at baseline)	3-days food record	3 months	↑ Proteobacteria, Bacteroidetes taxa (*Prevotella stercorea*, *Bacteroides* spp.), ↓Firmicutes taxa (*Lachnospiraceae*, *Ruminococcaceae*) and *Sutterella*	↓ body weight and fat mass
(Roager et al., 2019)	50	Randomised,	WG diet (≥75 g/day) and a	Weight stable	No, comparison between the	Study diary	5,5 months (8 w diet – 6 w	↑ *Faecalibacterium prausnitzii* and *Prevotella*	↓ body weight, fat mass, sagittal

(continued)

Table 3. (continued)

Reference	N° of subject	Study design*	Type of diet	Study population	Control group	Type of dietary data collected	Duration	Effect on the gut microbiome*	Effect on the health
		controlled cross-over trial	refined grain diet (<10 g/day) in random order	subject (20-65 y.o.)	two dietary intervention	throughout both interventions	washout – 8 w diet)	*copri*; ↓ *Bacteroides thetaiotaomicron*	abdominal diameter and waist circumference; ↓ systemic low-grade inflammatory marker CRP, proinflammatory cytokines, IL-6 and IL1β
(Tagliamonte et al., 2021)	43	Randomised, controlled, intervention trial	Isocaloric MD	Overweight and obese subjects with lifestyle risk factors for metabolic disease (43 ± 1.4 y.o.)	Yes, overweight/ obese, habitual Western diet and sedentary lifestyle.	7-day Food Diary	2 months	↑ *Roseburia faecis*, *R. hominis*; *F. prausnitzii* and several members of *Lachnospiraceae*; ↑ *Akkermansia muciniphila*	↓ plasma AEA (anti-inflammatory effects); ↓ plasma anandamide concentrations; ↑ OEA/PEA ratio and the OEA/AEA ratio (reduction in plasma cholesterol)
(Tap et al., 2015)	19	Randomized, crossover study	Habitual diet with higher fibre intake (with 10 or 40 g dietary fibre per day)	Young healthy normal weight adults (19 to 25 y.o.)	No, comparison between the two dietary intervention	A plant-based food questionnaire (for 3 days before the intervention diet)	1,5 months	↑ *Prevotella, Coprococcus* and *Dorea;* ↓ *Bacteroides*	↑ caproate and valerate; ↑ multiple glycoside transporters; ↑ fermentation (Genes involved in methanogenesis were overexpressed)
(Vanegas et al., 2017)	41	Randomized, controlled, parallel-design human trial	Diet enriched in whole grain (WG)	Healthy adults who maintain their body weights (40–65 y.o.)	Yes, Subject who consume refined wheat (RW) in their diet	Food checklist on a weekly basis	1,5 months	↑ *Lachnospira* and *Roseburia* ↓ *Enterobacteriaceae* (pro-inflammatory)	↑ plasma total alkyresorcinols (biomarker of WG intake) ↑ acetate and total SCFAs ↑ LPS-induced production of TNF-a (marker for the inflammatory response more-robust →response to antigens)
(Vitaglione et al., 2015)	36	A placebo-controlled, parallel-group randomized trial	Diet enriched in whole grain (WG)	Healthy overweight/ obese subjects	Yes, overweight/ obese subjects with refined	7-d food diary recall	2 months	↑ Bacteroidetes, Firmicutes ↑ *Bacteroides*	↓ inflammatory TNF-a; ↑ interleukin (IL)-10 ↑ fecal ferulic

(continued)

Table 3. (continued)

Reference	N° of subject	Study design*	Type of diet	Study population	Control group	Type of dietary data collected	Duration	Effect on the gut microbiome*	Effect on the health
		with a double-arm parallel design		with low intake of fruit and vegetables and sedentary lifestyle	wheat (RW) consumption			and *Lactobacillus*. ↓ Clostridium;	acid (FA) and circulating serum dihydroferulic acid (DHFA)
(Walter et al., 2013)	28	Non-controlled, randomized crossover study	Habitual diet enriched with whole grain barley (WGB), brown rice (BR) or a mixture of the two (WGB + BR) in the form of flakes (60 g daily dose)	17 females and 11 males, (25.9 ± 5.5 y.o.), 13 subjects were classified as overweight	No, comparison with the baseline	Not recorded	4,1 months	WGB and WGB + BR ↑ Firmicutes ↓ Bacteroidetes ↓ *Bacteroides* ↑ *Blautia, Bifidobacterium, Dialister, Eubacterium rectale, Roseburia faecis* and *Roseburia intestinalis* ↓*Coriobacteriaceae*	↓ plasma interleukin-6 (IL -6) in WGB + BR (reduction was highest in overweight subjects -> reduction of systemic Inflammation); ↓ total cholesterol, fasting glucose levels and postprandial peak glucose levels (in overweight and woman WGB + BR)
(Wang et al., 2021)	307	Observational study	MD	Adult males (45–80 y.o.)	No, subjects divided based on MD adherence	SFFQs (3 months before and after the biospecimen collection)	Long-term adherence to a healthy Mediterranean-style diet	↑ *F. prausnitzii*, *Eubacterium eligens* and *Bacteroides cellulosilyticus*; ↓ *Clostridium leptum* and *C. aerofaciens*	↓cardiometabolic disease risk; ↓ secondary bile acid biosynthesis; ↑ d-fructuronate degradation and mannan degradation; ↓ lactose and galactose degradation; ↑ SCFA
(Wastyk et al., 2021)	36 (18 = High fibre diet; 18 = high fermented-foods diet)	Randomized, prospective study	High-fibre diet (HFD)	Healthy adults (51 ± 12 y.o.), predominantly women (73%) and white (81%)	No, comparison with the baseline	Online screening questionnaire and a clinic visit	4.1 months	↑ *Lachnospira*	↓ isobutyric, isovaleric and valeric acids; ↑ carbohydrate-active enzymes; ↑ Fecal butyrate ↓ B cell frequency ↑stool microbial protein density

SCFA, Short-Chain Fatty Acids; TMAO, N-oxide of trimethylamine; MD, Mediterranean Diet; WG, Whole-Grains; FFQ, Food Frequency Questionnaire; AEA, arachidonoylethanolamide; OEA/AEA, oleoylethanolamide/arachidonoylethanolamide ratio; OEA/PEA, oleoylethanolamide/palmitoylethanolamide ratio; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HbA1c, glycated haemoglobin.
*as reported in the original study.

microbiome changes, antioxidant effects, and anti-inflammatory effects.

Early referral to active nutritional intervention programmes and/or supplementation should be considered in patients who do not consume these foods optimally. Also, P-MDS plays a critical role in determining low consumption of micronutrient-dense foods such as legumes, vegetables, fruits, olive oil, and nuts.

MD score was higher in patients with inactive CD, and it was clear that patients were more likely to follow MD while in a remission state. Comparing the wide range of the MD score with the smaller scores makes it more valuable. On the other hand, small scores may not provide accurate forecasts when the outcome is continuous rather than binary or may fail to reflect the intrinsic and extreme aspects of a pattern or behaviour (Casas et al., 2016).

Among the results, MD score was positively correlated with IBDQ and negatively with CRP and HBI. After making several adjustments (disease duration, body mass index, age, smoking, sex, anti-inflammatory drug use, and disease site) MD score was linearly and negatively associated with HBI and a positive linear correlation with IBDQ. In another study, they used a different tool to assess adherence to CD patients in remission with the Mediterranean diet, showing that those who met the criteria for PREDIMED (P-MDS) were very few in relation to MD, and overall results were low.

IL-6 levels in patients with active CD were significantly higher than inactive CD, and IL-10 levels were lower. Compared with previously published studies, active CD patients revealed several abnormalities in immune regulation, including immune IL-10 and pro-inflammatory IL-6 (Panagiotakos et al., 2006).

In two large prospective cohort studies, it was shown that the risk of developing CD is inversely related to high adherence to the Mediterranean diet. Several previous studies have shown that there is a relationship between the risk of developing IBD and the nutrients present in high amounts in a Mediterranean diet (Fonseca-Camarillo and Yamamoto-Furusho, 2015; Andersen et al., 2018).

Impact of mediterranean diet on gut microbiome and possible health outcome

The human gut is inhabited by billions of microorganisms that collectively constitute the gut microbiome. This complex community tightly interacts with the human host and several studies highlighted the impact of the human microbiome on the onset and progression of several diseases, including inflammatory bowel diseases (De Filippis et al., 2016). Indeed, the gut microbiome produces a plethora of metabolites, that may influence human health either in a positive or negative way. What we eat is also feeding our gut microbial symbionts, that metabolize compounds that are undigestible for the human host and transform them in a wide range of bioactive compounds (Ercolini and Fogliano, 2018). From the fermentation of complex polysaccharides some microbial species can produce short-chain fatty acids (SCFA), mainly acetate, butyrate and propionate, that have a recognized anti-inflammatory, anticarcinogenic and immune-regulatory activity (Vanegas et al., 2017). Also plant polyphenols can be converted to several molecules. Ellagitannins, rich in pomegranates and nuts, can be converted to urolithins, associated with an antioxidant and anti-aging activity (Li et al., 2021), as well as to a reduced cardiometabolic risk (Wang et al., 2021). In addition, glucosinolates rich in cruciferous vegetables are converted to isothiocyanates, suggested to have an anticarcinogenic activity (Bolte et al., 2021). The production of these beneficial metabolites is influenced both by the gut microbiome composition and by the availability of the right dietary precursors. Indeed, some studies demonstrated that agrarian populations living in remote regions of Africa or South-America (the so-called non-Westernized populations) and habitually consuming a diet rich in complex polysaccharides and poor in animal-based fats and proteins, usually show a different gut microbiome compared with Western subjects. There is a general agreement that Western diet and lifestyle led to a depletion of gut microbial diversity and a reduction of beneficial fibre-degrading bacteria, such as *Prevotella*, *Treponema*, *Succinivibrio*, and *Lachnospira* (Obregon-Tito et al., 2015; Schnorr et al., 2014; Segata, 2015; Vangay et al., 2018; Wu et al., 2016). Consistently, the long-term consumption of diets rich in vegetable products is associated with a healthier metabolome and specific traits in the gut microbiome as shown in Table 3 (Tarallo et al., 2021; De Filippis et al., 2016; Bolte et al., 2021; Roncal et al., 2019). Higher fecal levels of beneficial SCFA is reported in long-term vegetarians/vegans compared with omnivores, besides lower concentration of trimethylamine-N-oxide (TMAO), produced from metabolization of carnitine and choline by the gut microbiome and subsequent oxidation in the liver (De Filippis et al., 2016). Some reports linked TMAO with the development of atherosclerosis and cardiovascular diseases (Roncal et al., 2019). A diet rich in animal foods and simple sugars also promotes higher abundance of *Ruminococcus gnavus*, *Bacteroides fragilis*, *Blautia* spp. and *Enterobacteriaceae* and an inflammatory metabolic profile, both in healthy subjects and in patients with intestinal diseases (Inflammatory Bowel Syndrome, Chron's disease, ulcerative colitis; (Bolte et al., 2021). However, some studies demonstrated that it is not necessary being strictly vegetarian/vegan to boost the development of a beneficial microbiome. The habitual consumption of a Mediterranean diet, that is an omnivore dietary pattern, that contemplate high consumption of foods of vegetable origin, such as fruits and legumes, has been linked with the development of beneficial gut microbes and associated metabolome (De Filippis et al., 2016; Wang et al., 2021). Indeed, omnivore subjects with higher adherence to the Mediterranean diet showed higher concentration of SCFA, lower levels of urinary TMAO (De Filippis et al., 2016) and a decreased cardiometabolic risk (Wang et al., 2021).

Researchers tried to understand how to modulate the gut microbiome through a dietary intervention (Table 3). Several studies focused on the supplementation of specific dietary components known to have a beneficial role, mainly fermentable fibre. Fibre supplementation for short periods (2 to 8 weeks) led to an increase in well-known fibre-degrading microbial species (e.g. *Prevotella*, *Eubacterium*, *Bifidobacterium, Roseburia, Faecalibacterium*), that correlated with a health-promoting metabolome (increase in SCFA and polyphenols; reduction in inflammatory markers). Besides supplementation of Mediterranean diet-related nutrients, also interventions with a more complex dietary pattern were carried out (Table 3). A 2-months intervention with an isocaloric Mediterranean diet in obese and overweight subjects led to an increase in *Faecalibacterium prausnitzii* and other beneficial fibre-degrading taxa, and a reduction of the pro-inflammatory *Ruminococcus gnavus*, as well as a reduction of cholesterol and insulin resistance (Meslier et al., 2020). In addition, the Mediterranean diet was effective in providing the right substrates to the gut microbiome for the production of beneficial metabolites: an increase in urolithins and a decrease in fecal bile acids (BA's) (Meslier et al., 2020). BA concentration is usually linked with the consumption of a high-fat diet and a dysregulated BA elimination was correlated to a dysbiosis in CD (Ogilvie and Jones, 2012). In addition, higher prevalence of genes involved in BA production was found in microbial genomes from CD subjects (Heinken et al., 2019). A 1-year intervention with the Mediterranean diet in elderly subjects led to consistent changes in gut microbiome and metabolome (Ghosh et al., 2020). Fibre-degrading taxa (*F. prausnitzii*, *Roseburia*, *Eubacterium*) were positively correlated with the Mediterranean diet adherence and with markers of improved cognitive functions, while negatively linked with inflammatory markers, BA and p-cresol concentration (Ghosh et al., 2020).

Taken together, literature evidences suggest that Mediterranean diet intervention may remodel the intestinal microbiome, leading to a metabolic state associated with health.

Conclusion

The Mediterranean diet has been shown to have anti-inflammatory properties. Adherence to its components is associated with improved symptoms in CD patients, and negatively correlated with disease activity. A greater commitment to MD was associated with a lower risk of developing CD at a later time. There is an urgent need for more future studies to focus on the benefits of MD in patients with CD.

Author's contribution

MJ and MA formulated the research question and conducted initial search, AA checked the results and contributed in writing the SC and DF contributed in the writing and approved the final version of the manuscript.

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