

Is the Mediterranean Diet in Inflammatory Bowel Diseases Ready for Prime Time?

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Abstract

Background: The rising incidence of inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), specifically in the developing world, suggests an important environmental effect. Amongst environmental influences, dietary factors, particularly the adoption of a westernized diet, have been specifically noticed. In contrast, the Mediterranean diet (MED), characterized by high intake of fruits, vegetables, whole grains, legumes, nuts, olive oil, and moderate consumption of animal and ultra processed foods, has shown potential positive effects in IBD.

Methods: Here we conducted a narrative review focusing on the evidence regarding the role of MED in IBD prevention and management.

Results: Epidemiological studies suggest inverse association of MED with CD development. Furthermore, adherence to MED has been associated with clinical improvement in active CD and maintenance of lower levels of inflammatory markers in UC, along with improved quality of life and lower mortality rates in IBD patients. Mechanistically, MED promotes a diverse and beneficial gut microbiota, possesses anti-inflammatory properties through polyphenols and dietary fats, and may modulate oxidative stress. In clinical practice, MED may be adapted to diverse disease phenotypes and cultural preferences, and is a sustainable, easy to maintain dietary approach.

Conclusion: Current evidence may support the integration of MED into clinical practice in IBD care. In future research, the efficacy of MED in specific IBD phenotypes should be assessed.

Key words: Mediterranean diet; inflammatory bowel disease; Crohn's disease; ulcerative colitis; prevention.

Introduction

Inflammatory bowel diseases (IBD), including Crohn's disease (CD) and ulcerative colitis (UC), are characterized by chronic inflammation of the gastrointestinal tract with a significant rise in incidence rates worldwide.¹ The precise etiology of IBD remains elusive; however, it is postulated that dysregulated immune responses, influenced by complex interactions involving intestinal barrier function, microbial composition, and environmental factors in genetically susceptible individuals, contribute to the development of IBD.² Notably, diet plays a prominent role as an environmental factor capable of affecting intestinal inflammation and the composition of the gut microbiota.

Dietary factors have been implicated in the development of IBD, particularly with the adoption of a more Westernized diet.³ Studies have shown that migrants from IBD low-incidence countries who adopt a Westernized diet acquire a higher risk of developing IBD, which is further increased in the second generation.^{4,5} This dietary shift includes increased consumption of fat, animal protein, and sugar, while fruit and vegetable intake decreases.

Beyond diet composition, the Western diet is characterized by a high consumption of ultra-processed food (UPF). In recent years, there has been growing evidence that links between UPF intake and IBD, specifically CD⁶ development. It is plausible that as opposed to the Western diet, a healthy diet like the Mediterranean diet (MED) will exert positive effects on IBD.⁷ MED is a plant-rich diet characterized by a daily high intake of fruits and vegetables (rich in fibre, antioxidants, and vitamins), olive oil, whole grains, legumes, and nuts, moderate consumption of animal products including oily fish (rich in mono- and polyunsaturated fatty acids), dairy products and poultry, and limited consumption of red meat and processed foods. Moderate consumption of red wine is also recommended during meals, as well as other lifestyle aspects like physical activity.^{8,9}

MED has been previously correlated with beneficial outcomes in several chronic diseases¹⁰ and specifically immune-mediated diseases, like psoriasis^{11,12} and rheumatoid arthritis.^{13–15} Consumption of recommended MED components, including fruits,^{16–18} vegetables,^{19,20} whole grains,²¹ olive oil,²² red wine,²³ and yogurt,²⁴ have been linked with positive outcomes in IBD.

Here, we reviewed the evidence behind the potential role of MED in the prevention and management of IBD.

IBD prevention

Dietary recommendations for IBD prevention are limited. The European Society for Clinical Nutrition and metabolism (ESPEN) recommends a diet that is rich in fruits, vegetables, and sources of omega 3 as opposed to omega 6 fatty acids. In the latest version, ESPEN added a recommendation to reduce UPF intake in the prevention section.²⁵

In a recent meta-analysis comprised of 5 cohort studies involving over 1 million participants with 13,594,422 person-years of follow-up, the association between risk of IBD and consumption of UPF was assessed. Notably, higher consumption of UPF was associated with an increased risk of developing CD, while higher consumption of unprocessed/minimally processed foods was associated with a lower risk of CD. No significant associations were found between UPF consumption and the risk of developing UC.⁶

In a Dutch prospective population-based cohort study, following 125,445 healthy individuals, of which 97 developed CD and 224 developed UC, dietary patterns and their association with IBD risk were analyzed. A Western dietary pattern, characterized by a high intake of snacks, prepared meals, non-alcoholic beverages, condiments, and sauces along with low vegetables and fruit consumption, was associated with increased risk of developing CD. A carnivorous dietary pattern characterized by high consumption of red meat, poultry, and processed meat, was associated with an increased UC risk. Neither a healthy Dutch dietary pattern nor MED pattern, analyzed by the alternative MED score, did not correlate with IBD risk. The authors speculated that participants in this study consumed a more Westernized MED compared to the traditional MED, which might have mediated the (lack of) association.²⁶ This was also shown in the European Prospective Investigation into Cancer cohort showing no significant associations between dietary patterns including MED and IBD onset across 256 incident cases of UC and 117 of CD and 4 matched controls per case.²⁷ On the contrary, Khalili et al. evaluated 164 cases of CD and 395 cases of UC among 83,147 healthy participants in 2 Swedish cohorts. Adherence to MED, assessed by mMED score, was inversely associated with the onset of CD, (HR = 0.42, 95 percent CI 0.22–0.80, $p_{\text{trend}} = 0.03$) but not UC.²⁸ In addition, low adherence to MED was shown to be positively associated with the diagnosis of UC (OR: 2.3; 1.2–4.5), but not with CD in a cross-sectional analysis comparing 264 patients with IBD and 203 controls.²⁹ The variability in findings across epidemiological studies could be attributed to the customization of scoring systems of MED assessment to suit-specific populations.

Another aspect of modifiable lifestyle factors and the risk of developing IBD was assessed using large prospective cohorts from North America and Europe. A healthy lifestyle score (HLS) comprised of dietary and lifestyle factors was associated with a reduced risk of developing both CD and UC. Dietary factors included in the HLS were high consumption of fruits, vegetables, nuts, and dietary fibres, ≥ 2 servings of fish per week, no or up to moderate alcohol consumption, and low consumption of red meat. Other lifestyle factors included maintaining a normal BMI, being a non-smoker, and physically active. Notably, the HLS dietary and lifestyle factors share common characteristics with the MED lifestyle.³⁰

Furthermore, a recent analysis of data derived from the US Biobank showed that adherence to a healthy lifestyle can mediate the genetic risk, assessed by polygenic risk score. Individuals with high genetic risk and adopting a healthy lifestyle had 50 percent reduction in the risk of developing CD or UC.³¹

In summary, the evidence supports the notion that MED lifestyle components may modify the risk of IBD development. The importance of low UPF consumption is common to many of the dietary patterns contributing to the prevention of IBD, thus we believe that recommendations for IBD prevention should focus on a healthy, low-processed dietary pattern, such as MED.

Influence on disease activity

In a large American randomized clinical trial, DINE-CD, MED was compared to the specific carbohydrate diet (SCD), which is popular among patients with IBD and was previously suggested as a dietary strategy to control inflammation.³² MED- and SCD-induced similar rates of remission in patients with active CD within 6 weeks (43.5 percent vs. 46.5 percent).³³ Reduction of >50 percent in fecal calprotectin was achieved in 30 percent of patients with elevated calprotectin at baseline. Notably, these remission rates are relatively lower compared to other investigated dietary strategies for active CD, such as the Crohn's disease exclusion diet (CDED)³⁴ or exclusive enteral nutrition in adult patients with CD.³⁵ Future research is needed to assess whether MED in combination with partial enteral nutrition or elimination of specific food triggers like gluten improves remission rates in active CD patients following MED as an induction strategy.

In an Egyptian RCT that included fifty-four patients with active CD forty-six patients with active UC, pediatric patients with mild-to-moderate active disease on a stable medical therapy were randomized to receive MED intervention (KIDMED score ≥ 8) or to continue with their regular diet. Clinical scores and inflammatory markers improved in both groups; however, patients in the MED group demonstrated a greater reduction in clinical scores, fecal calprotectin, and inflammatory cytokines.³⁶

Recently, MED was investigated in patients with quiescent UC in a Canadian RCT comparing MED to the habitual Canadian diet. As opposed to the control group in which the majority of patients had elevated fecal calprotectin at week 12, MED was associated with maintaining low fecal calprotectin levels. MED also resulted in more short-chain fatty acid (SCFA) production compared to the control group.³⁷ Notably, MED composition shares similarities with currently investigated diets for UC induction that aim to increase fermentable fibres, fruits, and vegetables and to reduce animal protein intake.^{38,39}

Adherence to MED was shown by our group to be inversely associated with fecal calprotectin levels in a cohort of 153 patients with UC after pouch surgery and we noted a non-significant trend showing that higher adherence to MED was inversely associated with the development of pouchitis over 8 years of follow-up.⁴⁰

Adherence to MED was inversely associated with fecal calprotectin levels in 125 Italian pediatric patients in clinical remission. Patients with normal calprotectin levels (<70 mcg/g) had a higher KIDMED score (5.82 ± 2.35 vs. 4.85 ± 2.16 ; $P = 0.027$).⁴¹

Additional health benefits in patients with IBD

Chicco et al. recruited 165 patients with IBD to a prospective, uncontrolled interventional study aiming to assess the effect of MED on disease activity, obesity, obesity-related complications, and QoL in patients with IBD. Among the 142 patients who adhered to MED after 6 months of follow-up, decreased BMI, weight circumference, and hepatic steatosis were observed. After 6 months, fewer patients with stable therapy had active disease compared with baseline. In addition, QoL improved in both patients with CD and UC.⁴² Papada et al. evaluated the adherence to MED in eighty-six patients with CD in Greece. Adherence to MED was greater in the forty-five patients in remission compared with forty-one patients with active disease. The MedDiet score correlated positively with the inflammatory bowel disease questionnaire, reflecting its association with a better QoL.⁴³

Vrdoljak et al. evaluated the adherence to MED in fifty patients with CD and forty-four with UC in Croatia. The average Med Service Score (MDSS) was 6 (5–7), with only nine patients fulfilling the criteria for MED adherence. Adherence was low particularly to the recommended consumption of olive oil, fruit, and vegetables, with only up to 25 percent, 14.9 percent, and 10.6 percent of patients meeting the MED recommendations. MDSS positively correlated with HDL levels. Importantly, 84 percent of the patients expressed their willingness to extend their nutritional knowledge and to visit nutritional education programs.⁴⁴

Moreover, among healthy lifestyle factors like normal weight, light alcohol consumption, non-smoking, and physically active lifestyle, adherence to MED is associated with lower rates of mortality. Lo et al. analyzed data from the Nurses Health Studies (NHS + NHS2) and the Health Professional follow-up study (HPFS). Overall, the researchers detected 83 deaths among 363 patients with CD and 80 among 465 patients with UC. Patients with IBD who had 3–5 healthy lifestyle factors demonstrated a significant reduction in all-cause mortality. Specifically, adherence to MED (mMED > 4) was inversely associated with the mortality rate in patients with IBD (HR, 0.69; 95 percent CI, 0.49–0.98). Of note, in a sub-analysis stratifying across disease type, adherence to MED was inversely associated with mortality in patients with CD but not UC, this might be derived from the lower sample size in the sub-analysis, but could also suggest that in patients with CD, MED is a stronger mediator of mortality risk, compared to patients with UC, which could be more affected by other lifestyle factors like smoking and alcohol intake.⁴⁵

Potential mechanisms

Diet is well recognized as one of the most important factors affecting the gut microbiome. Both long-term dietary patterns and short-term dietary changes⁴⁶ affect the gut microbiota. According to data derived from the American Gut Project, dietary plant diversity has a significant impact on gut microbiome composition with a higher abundance of SCFA-producing bacteria.⁴⁷ MED is a high-fibre diet and dietary consumption of several of the MED-recommended food components including fruits, vegetables, red wine, yogurt, nuts, fish, and potatoes has been previously associated with increased microbial diversity in healthy individuals.⁴⁸

Adherence to MED was associated with positive microbiome-related metabolomic profiles in 153 healthy

individuals in Italy. It is associated with increased fecal SCFAs and decreased urinary trimethylamine oxide levels, a potential risk factor for cardiovascular disease.⁴⁹ Studies also showed that the MED influenced taxonomic features, including increased *Faecalibacterium prausnitzii* and *Roseburia*, and decreased *Ruminococcus gnavus*, *Collinsella aerofaciens*, and *Ruminococcus torques*.^{50,51} Wang et al. discovered that the protective effect of the MED against cardiometabolic disease risk was stronger in individuals with depleted *Prevotella copri* levels.⁵²

Zhang et al. recruited forty patients with quiescent CD (HBI < 5) in Canada for an intervention trial. Patients with low fibre and high red meat baseline intakes ($n = 15$) were assigned to the non-diversified diet (NDD) and received dietary guidance according to MED principles, while others ($n = 25$) were assigned to the diversified diet (DD) and received conventional management. Baseline microbial composition differed among groups in beta diversity and in the abundance of *Faecalibacterium* which was lower and *Escherichia/Shigella* which was higher in the NDD group. The NDD intervention according to the MED principles for 12 weeks resulted in an increase in *Faecalibacterium* in the NDD group that resembled the DD group at the end of the intervention.⁵³

Microbial alterations were also shown in patients with quiescent UC. Increased abundances of *Alistipes finegoldii*, *Flavonifractor plautii*, and *Ruminococcus bromii* as well as an increase in the total fecal SCFA concentrations were observed following 12 weeks of MED intervention.³⁷

Consumption of specific components of MED such as fruits and vegetables positively correlated with microbial diversity in patients with UC after pouch surgery, as opposed to the consumption of sweets, snacks, and soft drinks which were inversely correlated with microbial diversity. Lower microbial diversity preceded the development of pouchitis,⁵⁴ which potentially is mediated by diet. Higher fruit consumption was associated with lower rates of pouchitis and correlated with SCFA producers including *Faecalibacterium*, even after controlling for disease activity and antibiotic use.¹⁸ Moreover, Butyrate production was shown to have a role in pouchitis, and dietary fibres, specifically from fruits, vegetables including starchy vegetables were associated with levels of butyrate-producing enzymes.⁵⁵

In the Genetic, Environmental, Microbial project that follows 2,289 healthy first-degree relatives of patients with CD (age 6–35 years), a MED-like dietary cluster was inversely associated with fecal calprotectin. The MED-like cluster correlated with a microbial cluster characterized with SCFA producers such as *Faecalibacterium*.⁵⁶ This association was in line with our group pilot intervention trial of twenty healthy participants following an interactive MED-based lifestyle intervention.⁵⁷

Additional evidence for the potential beneficial role of MED in IBD was obtained from a small pilot trial in eight patients with CD. Six weeks of a MED-inspired diet resulted in decreased CRP and alterations in expression levels of various genes, including regulation genes of NF- κ B activity and signal transducer and activator of transcription 3, but no significant alterations in microbial composition detected.⁵⁸

The anti-inflammatory effects of MED might also derive from the high intake of polyphenols. Higher adherence to MED is associated with a higher intake of vitamins, minerals, dietary anti-oxidants, and polyphenols in patients with IBD.⁴⁰ Dietary polyphenols can neutralize reactive oxygen species

and reduce oxidative stress, and modulate signalling pathways involved in inflammation, such as NF- κ B and MAPK, thereby suppressing the production of pro-inflammatory molecules.⁵⁹ MED is also characterized by a unique dietary fat composition, with extra virgin olive oil that is rich in mono-unsaturated fatty acids, as the main source of oil. Poly-unsaturated fatty acids, including omega 6/3 fatty acids intake are hypothesized to fuel the inflammatory process.⁶⁰ A recent review covered the possible mechanisms behind the potential beneficial role in IBD including suppressing inflammatory pathways and cytokines, associations with improved disease activity and histopathological scores, and increased microbial diversity.⁶¹

Conclusions

We have reviewed the evidence behind the potential role of MED in the prevention and management of IBD (Fig. 1). As opposed to the Westernized diet, high in UPF, which is associated with an increased risk of IBD, the adoption of MED has been linked to positive outcomes in IBD. Epidemiological data suggest a potential role for MED in reducing the risk of IBD development, furthermore, MED is associated with moderate clinical and inflammatory improvement in patients with active CD, and with maintaining low fecal calprotectin levels in patients with quiescent UC. Additionally, adherence to MED has been associated with improved quality of life and lower

mortality rates in patients with IBD. Mechanistically, MED influences the gut microbiome, increasing microbial diversity and promoting the growth of beneficial bacteria. It also exerts anti-inflammatory effects through the intake of polyphenols and the composition of dietary fats.

While it is not clear whether MED exerts its effect due to the included or excluded foods, it is likely that the combination of these factors contributes to its beneficial effects. Specifically, both reduction of red meat, saturated fat, and UPF, as well as the increase of fibre-rich plant sources, antioxidants, and olive oil can positively modify inflammation and microbial composition and function. Additionally, the lifestyle components accompanying MED, like active lifestyle, stress reduction, and eating local and seasonal have an additional, potentially synergistic effect, beyond diet composition.

MED has been studied in various countries, making it a dietary pattern with widespread applicability worldwide. Its emphasis on whole, unprocessed foods and a balanced nutrient profile resonates with diverse cultural and regional preferences. The flexibility and adaptability of the MED allow individuals from different backgrounds to incorporate their traditional foods while adhering to its core principles. This makes it a practical and sustainable dietary approach for people in different regions and cultural settings.

An interesting aspect of MED, which has shown an association with reduced risk of developing IBD, is its potential to

The Mediterranean diet in IBD

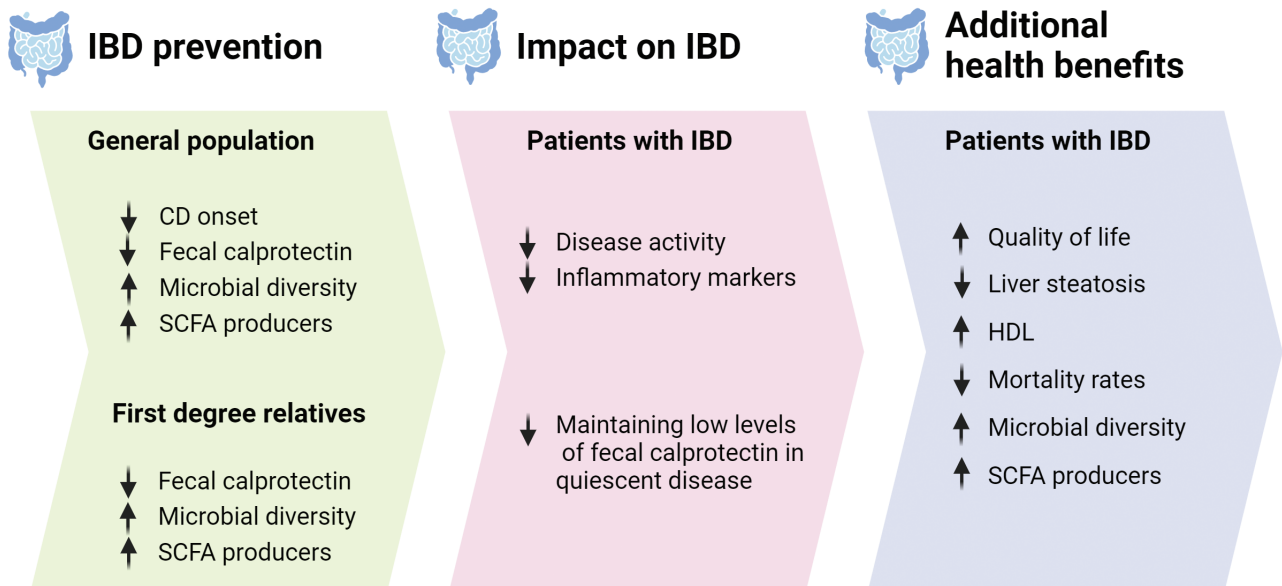


Figure 1. Role of the Mediterranean diet in the prevention and management of IBD. IBD, inflammatory bowel disease; CD, Crohn's disease; UC, ulcerative colitis; SCFA, short chain fatty acids. Created in BioRender.com.

extend beyond individuals and have a positive impact on their family members. The shared nature of dietary habits within households makes adopting MED a catalyst for a ripple effect and patients can influence the dietary choices and habits of their loved ones. This family-centred approach to nutrition creates a supportive environment and fosters lasting lifestyle changes that promote overall health and well-being for the entire family unit.

MED should be guided and supported by an IBD dietitian, as a part of an IBD multidisciplinary team. The expertise of a dietitian ensures personalized approach, addressing individual needs and challenges and considering factors such as nutritional deficiencies, food intolerances, specific symptoms, and preferences. By following the principles of MED and making necessary adaptations, patients can optimize their nutrition, alleviate symptoms, and improve their overall food-related quality of life. While the dietitian's role is crucial, there is a large gap and an unmet need in the delivery of dietary advice, as currently, access to an IBD dietitian is limited in many parts of the world. Increasing accessibility to IBD dietitians as well as increasing knowledge and endorsement of IBD practitioners on the importance of diet and lifestyle modification will contribute to improved, holistic patient care.

Overall, the evidence suggests that MED could be a beneficial dietary approach for IBD prevention and management, warranting further research and consideration in clinical practice.

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Conflict of interest

L.G.: Janssen, Takeda, Abbvie, Pfizer, Galapagos, Ferring, Gutreat, Food industries organization, Altman, Tnuva. I.D.: Janssen, Abbvie, Altman research, Takeda, Pfizer, Genentech/Roche, Arena, Neopharm, Eli-Lilly, Gilead, Galapagos, Celltrion, Ferring, Falk Pharma, Cambridge Healthcare, Sublimity, Nestle, Wild bio, Gutreat, Food industries organization, Athos, Iterative Scopes, Celgene/BMS, Abbott.

Data Availability

There are no data associated with this manuscript.

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