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Review Article

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The Role of the Mediterranean Diet in Reducing Inflammation and Enhancing Patient Outcomes in Inflammatory Bowel Disease

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Introduction

Inflammatory Bowel Disease (IBD) encompasses two primary chronic inflammatory conditions of the gastrointestinal tract: Crohn's disease (CD) and ulcerative colitis (UC). Both conditions are characterized by relapsing and remitting inflammation, leading to symptoms such as abdominal pain, diarrhea, weight loss, and fatigue. The exact etiology of IBD remains unclear, but it is understood to involve a combination of genetic predisposition, environmental triggers, gut microbiota dysbiosis, and immune system dysregulation [1].

Management of IBD typically includes pharmacological approaches such as aminosalicylates, corticosteroids, immunomodulators, and biologic therapies. However, there is growing interest in dietary interventions as adjunct therapies due to their potential to modulate gut inflammation and improve patient outcomes [2]. Among these, the Mediterranean diet (MD) has garnered significant attention due to its anti-inflammatory and gut microbiome-modulating properties [3].

The Mediterranean diet is traditionally consumed by populations residing in countries bordering the Mediterranean Sea and is rich in plant-based foods, including fruits, vegetables, whole grains, legumes, and nuts, as well as healthy fats, particularly olive oil. It is also characterized by moderate consumption of fish, poultry, and dairy products, and low intake of red meat and processed foods. Numerous studies have linked this dietary pattern to reduced incidence of chronic diseases such as cardiovascular disease, diabetes, and certain cancers [4,5]. Recently, attention has turned to its potential role in managing autoimmune and inflammatory diseases, including IBD.

In this review, we will explore the existing literature on the Mediterranean diet's role in managing IBD. We will examine the underlying mechanisms through which this dietary pattern may influence IBD progression and evaluate clinical studies that have investigated its impact on disease activity, and quality of life in patients with Crohn's disease and ulcerative colitis.

Mechanisms of Mediterranean Diet in Reducing Inflammation

The Mediterranean diet (MD) has been recognized for its anti-inflammatory effects, which are particularly relevant in the context of inflammatory bowel disease (IBD). The components of the MD, including omega-3 fatty acids, polyphenols, fiber, and antioxidants, are believed to exert protective effects on the gut through multiple mechanisms. These mechanisms include modulating the immune response, enhancing gut microbiota diversity, improving intestinal barrier function, and reducing oxidative stress, all of which play crucial roles in managing IBD (Figure 1).

1) Omega-3 Fatty Acids: Modulating the Immune Response

A hallmark of the Mediterranean diet is the high intake of omega-3 fatty acids, particularly from fish and olive oil. Omega-3 fatty acids, especially eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are known to have potent anti-inflammatory properties. They compete with omega-6 fatty acids in the production of eicosanoids, leading to the generation of less inflammatory mediators such as prostaglandins and leukotrienes. These mediators play a crucial role in the inflammatory pathways of IBD, where pro-inflammatory cytokines like tumor necrosis factor (TNF)-α and interleukin (IL)-6 are often elevated during disease flares [6].

Several studies have demonstrated the beneficial role of omega-3 fatty acids in IBD management. A systematic review of randomized controlled trials (RCTs) showed that omega-3 supplementation, as part of a Mediterranean-style diet, helped reduce disease activity and improve clinical outcomes in patients with Crohn's disease and ulcerative colitis [7].

2) Polyphenols and Antioxidants: Reducing Oxidative Stress

The Mediterranean diet is rich in bioactive compounds such as polyphenols, particularly from olive oil, fruits, vegetables, and red wine. Polyphenols are powerful antioxidants that scavenge free radicals and reduce oxidative stress, which is a critical driver of inflammation in IBD. In IBD patients, increased oxidative stress leads to mucosal damage and exacerbation of inflammation, making the antioxidant properties of polyphenols highly relevant.

Oleuropein, hydroxytyrosol, and resveratrol, which are abundant in olive oil and red wine, have shown specific anti-inflammatory effects by inhibiting the production of inflammatory cytokines and modulating immune responses [8]. These compounds suppress the activation of nuclear factor-kappa B (NF-κB), a key transcription factor that regulates the expression of pro-inflammatory genes. Additionally, they enhance the activity of anti-inflammatory mediators such as IL-10, further contributing to the resolution of inflammation in the gut mucosa.

Recent studies highlight the role of polyphenols in altering gut microbiota composition, promoting the growth of beneficial bacteria such as *Lactobacillus and Bifidobacterium*, which are essential for maintaining gut homeostasis. By improving gut microbial diversity, polyphenols may indirectly reduce

intestinal inflammation and improve mucosal healing in IBD patients [8-10].

3) Dietary Fiber and Gut Microbiome: Enhancing Gut Health

Fiber, a cornerstone of the Mediterranean diet, has a profound impact on gut microbiota, a key factor in IBD pathogenesis. Soluble fiber from fruits, vegetables, and legumes is fermented by gut bacteria, producing short-chain fatty acids (SCFAs) like butyrate, propionate, and acetate. These SCFAs are essential for maintaining the integrity of the gut barrier and exerting anti-inflammatory effects. Butyrate, in particular, serves as a primary energy source for colonic epithelial cells and has been shown to suppress the activation of inflammatory pathways by inhibiting histone deacetylase (HDAC) and reducing the release of pro-inflammatory cytokines [11].

Dysbiosis, or imbalance in the gut microbiota, is a common feature in IBD, where harmful bacteria often dominate, and beneficial bacteria are depleted. The Mediterranean diet, through its high fiber content, promotes the growth of beneficial bacteria such as *Faecalibacterium prausnitzii* and *Akkermansia muciniphila*, which are known for their anti-inflammatory properties. These bacteria help restore gut homeostasis, reduce gut permeability, and improve the immune response, thus contributing to better disease control in IBD patients [11-13].

Recent studies emphasize the potential of the Mediterranean diet to increase microbial diversity and improve the Firmicutes-to-Bacteroidetes ratio, which is often disrupted in IBD. 13 This rebalancing of gut bacteria is associated with reduced intestinal inflammation and improved clinical outcomes.

4) Improving Gut Barrier Function

A disrupted intestinal barrier, or "leaky gut," is a common feature in IBD, where increased intestinal permeability allows pathogens, toxins, and antigens to penetrate the gut lining, leading to inflammation. Components of the Mediterranean diet, particularly fiber and polyphenols, have been shown to strengthen the gut barrier by enhancing tight junction integrity between epithelial cells and promoting the production of mucins that protect the gut lining [14].

Research suggests that the Mediterranean diet increases the expression of tight junction proteins such as occludin and zonulin, which prevent the translocation of harmful substances into the bloodstream [11,14]. This improvement in gut barrier function helps to reduce the inflammatory burden in IBD patients and may contribute to longer periods of remission.

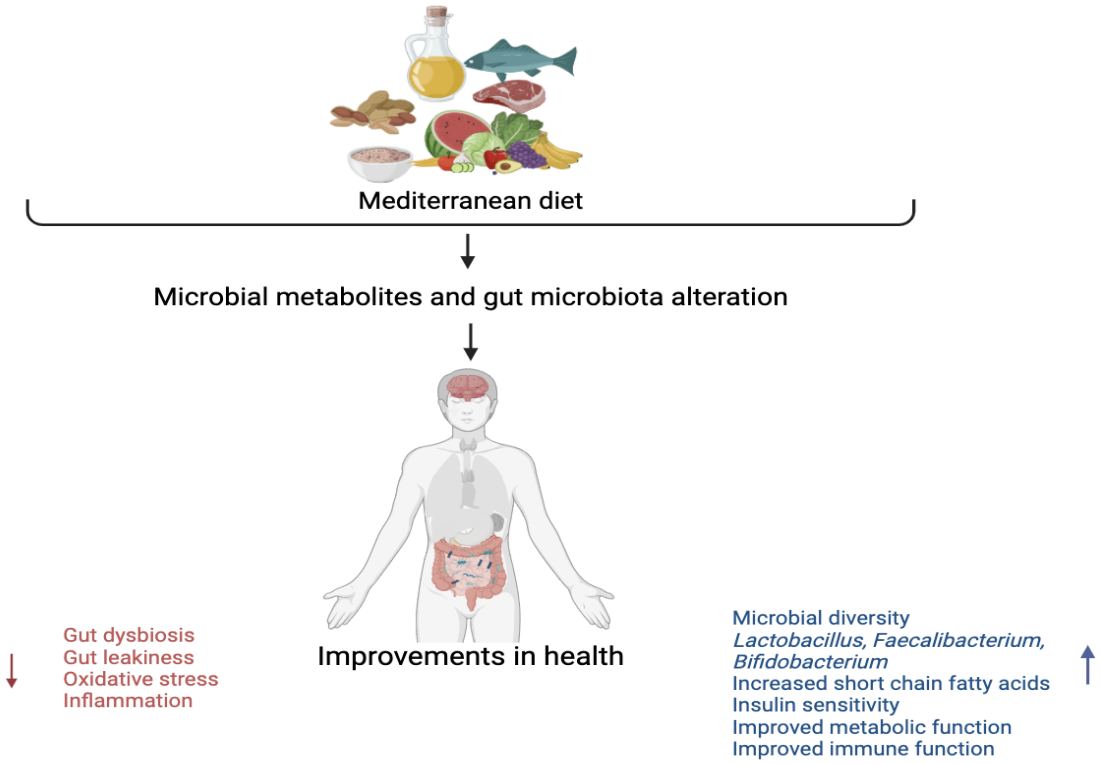

Figure 1: Demonstrates role of Mediterranean diet in health and disease (Image created with Biorender).

Expanded Clinical Evidence on the Role of the Mediterranean Diet in IBD

Numerous studies consistently highlight the Mediterranean diet (MD) as an effective intervention for reducing inflammation in inflammatory bowel disease (IBD), which includes both Crohn's disease (CD) and ulcerative colitis (UC). The anti-inflammatory and gut microbiome-modulating properties of the MD are well-supported by recent findings.

1. Studies Demonstrating Long-Term Benefits:

In a prospective cohort study involving 83,147 participants, adherence to the MD was associated with a decreased risk of developing Crohn's disease over time (p=0.03). This study points to the potential of the MD as a preventive dietary approach in populations at risk of IBD [15].

The benefits of MD were further demonstrated in a study by Godny et al, [16] where researchers found that patients with UC who underwent pouch surgery and adhered to the MD exhibited

significantly lower levels of inflammatory markers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and fecal calprotectin. Furthermore, a subgroup of patients with higher adherence to the MD experienced a reduced risk of developing pouchitis, suggesting that the MD can help modulate intestinal inflammation.

Chicco et al enrolled about 142 patients with IBD (84 with UC and 58 with CD) in their study that followed the MD for six months, during which their body mass index (BMI), body composition, liver steatosis, serum lipid profiles, and inflammatory markers were assessed. The study reported significant improvements in BMI (UC p=0.002; CD p=0.032) and waist circumference (UC p=0.037; CD p=0.041) at six months. Additionally, the number of patients affected by liver steatosis was reduced in both UC (36.9% vs. 21.4%, p=0.0016) and CD (46.6% vs. 31.0%, p<0.001). Importantly, the number of patients with active disease and elevated inflammatory biomarkers significantly decreased after six months of MD adherence [17].

2. Randomized Controlled Trials and Case-Control Studies:

The Diet to INduce Remission in Crohn's Disease (DINE-CD**)** trial [18] compared the Mediterranean diet to the Specific Carbohydrate Diet (SCD) in 194 adults with Crohn's disease over 12 weeks. Both dietary groups achieved similar clinical remission rates (SCD 46.5% vs. MD 43.5%; p=0.77), and fecal calprotectin response was also comparable between the two diets (SCD 34.8% vs. MD 30.8%; p=0.83). The trial concluded that although neither diet was superior in inducing clinical remission, and both decreased overall inflammatory burden. The researchers concluded that MD offers additional health benefits and is easier to follow, making it a more practical option for many patients with Crohn's disease.

The Mediterranean diet's efficacy also extends to pediatric populations as well. A study assessing 100 adolescents (aged 12-18) with mild to moderate IBD, half of whom were assigned to the MD for 12 weeks, revealed significant reductions in both clinical disease scores (PCDAI for Crohn's disease and PUCAI for ulcerative colitis) and inflammatory markers such as CRP, fecal calprotectin, TNF-α, IL-17, IL-12, and IL-13, compared to those who followed their usual diets [19].

Another study involving pediatric IBD patients in clinical remission, compared to healthy controls (HCs), evaluated adherence to the MD using a 3-day food diary and the Mediterranean Diet Quality Index for Children and Adolescents (KIDMED). The results showed that IBD patients had a significantly higher intake of calories (p=0.012), carbohydrates (p=0.015), and protein (p=0.024) compared to HCs. Although both groups demonstrated intermediate adherence to the MD, higher protein, vitamin D, and iron intake was observed in Crohn's disease patients compared to those with UC [20]. Furthermore, in IBD patients, greater adherence to the MD was significantly associated with lower fecal calprotectin levels (p=0.027), indicating a direct link between dietary adherence and reduced intestinal inflammation. This highlights the potential of the MD as a therapeutic dietary intervention even in younger populations, offering an avenue to improve both disease activity and overall nutrition.

Conclusion

The current literature demonstrates the wide-ranging benefits of the Mediterranean diet for patients with IBD. The MD not only helps reduce systemic and intestinal inflammation but also promotes better nutritional intake and quality of life. Its ease of adherence, compared to more restrictive diets like SCD, makes it a feasible option for patients with Crohn's disease and ulcerative colitis, both in pediatric and adult populations. Given these advantages, the MD represents a valuable dietary strategy in the holistic management of IBD, contributing to reduced disease activity, improved nutritional status, and enhanced long-term outcomes.

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