The Mediterranean Diet and Inflammatory Bowel Diseases

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The Mediterranean diet is considered one of the healthiest dietary patterns worldwide, thanks to a combination of foods rich mainly in antioxidants and anti-inflammatory nutrients. Many studies have demonstrated a strong relationship between the Mediterranean diet and some chronic gastrointestinal diseases, such as inflammatory bowel diseases.

Keywords: Mediterranean diet ; inflammatory bowel disease

1. Introduction

The Mediterranean diet (MD) is a term coined by Ancel Keys in the 1960s, describing the dietary pattern of the people living in the Mediterranean area, which is structured on a daily consumption of specific food groups included in a standardized food pyramid [1]. The MD is characterized by a high intake of vegetables, fruits, nuts, legumes, low processed cereals, whole grains, and olive oil, as well as a moderate consumption of fish and poultry, and a low intake of sweets, red meat, and dairy products, especially in the form of aged-cheeses [2][3][4]. The proportionally low content of saturated lipids as well as the high content of monounsaturated fatty acids and omega-3 polyunsaturated fatty acids, due to the use of olive oil as the main seasoning, make the MD a dietary pattern with anti-inflammatory and antioxidant properties [2][5][6][7]. Butyrate and other short-chain fatty acids produced from fibres and starches found in fruits and vegetables, which are prevalent in this type of diet, have a key role in downregulating inflammation and promoting innate immunity [3][8][9]. On the other hand, a low-fibre diet can in fact damage the mucous layer, leading to an increased barrier permeability and direct bacterial translocation across the epithelial membrane [3][8][10]. Moreover, the MD is a low-sugar, low-saturated-lipid, and almost additive-free diet, which t avoids dysbiosis and induces a reduction of the levels of plasmatic inflammatory markers, such as tumour necrosis factor-α, interferon-y and high sensitivity C-reactive protein (hs-CRP) [3][8][9]. On the other hand, the Western diet, with its high-fat intake can worsen the damage, especially in the overweight and obese patient. Indeed, adipose tissue has been demonstrated to be an important source of pro-inflammatory cytokines, which can sustain inflammation in many organs, including the gut [1][3]. Inflammation is the natural immune response to tissue damage in the human body [11]. It is initially protective for the removal of the injurious stimuli and damaged tissues, as well as the initiation of tissue healing [11]. However, it becomes problematic when there is overnutrition, which makes inflammation chronic. This is because the nutrition from the degradation of the damaged tissue, together with the excessive nutrition, will be mostly turned into lipid intermediates and deposited in healthy non-adipose tissues, causing lipotoxicity and further tissue damage [12][13]. Thus, over-nutrition will lead to a vicious cycle of excessive lean mass (such as protein) broken down and lipid intermediates piling up, fueling chronic inflammation. For its positive influence on gut microbiota and the immune system, the MD is now proposed not only as a potential tool in the management of different medical conditions, but also for health promotion and prevention globally [14]. Epidemiological evidence, in fact, has demonstrated that adherence to the MD can greatly reduce the risk of overall mortality and the incidence of many conditions such as cancer, diabetes, respiratory and cardiovascular diseases [15][16], inflammatory and functional diseases and obesity [17][18].

2. The Mediterranean Diet and Inflammatory Bowel Diseases

Inflammatory bowel diseases (IBD) are chronic autoimmune disorders characterised by chronically relapsing–remitting inflammation of the gastrointestinal (GI) tract [19]. The prevalence of IBD exceeds the 0.3% in Oceania, North America and in many European countries, and the incidence of these diseases has been substantially increasing in the last decades, principally in industrialised countries, making IBD an important burden on health systems [3][19].

The etiology of IBD is still unknown; in fact, it is a multifactorial disease [19]. Recent evidence indicates that a combination of susceptible genes, environment, altered microbial flora and inappropriate immune responses might be factors involved and functionally integrated in the pathogenesis of IBD [19]. As IBD incidence and prevalence both in the adult and in the paediatric population are constantly increasing [20], new data emerging from developing countries and migration studies suggest that environmental factors might play a major role [21]. Therefore the identification of IBD environmental risk factors and new therapies remain subjects of intensive research, and diet is one of the best candidates [3][19]. The intestinal microenvironment is indeed normally influenced by many factors in which diet plays a vital role, as it impacts its function, the gut epithelial-mucosal layer, the microbial composition, and the immune homeostasis by direct and indirect mechanisms [8]. It is known that diet can play a role in the generation of inflammation, by modulating the microbiome, the function of the intestinal barrier and the mucosal layer [22]. Several epidemiological studies discuss a positive correlation between the “Western diet”, with high amounts of unsaturated fatty acids, proteins, high sugar loads and a low vegetable and fruit intake, and the risk of developing IBD [22][23]. The components of the Western diet such as animal fats, sugars, wheat proteins, emulsifiers and maltodextrins, can determine an altered bacterial clearance at the intestinal level, promoting bacterial adhesion and penetration and subsequent intestinal inflammation [23]. Roberts et al. recently highlighted a clear correlation between the annual emulsifier consumption (in food and beverages) and the incidence of IBD [24].

A paediatric study recently confirmed a profound imbalance in fat, vegetables, and fruits consumption and the development of CD, favouring this hypothesis [25]. In IBD the nutritional approach represents a valid therapeutic option by regulating the inflammatory mechanisms [26]. Exclusive enteral nutrition (EEN) is the first-line treatment for induction of remission in patients with Crohn’s Disease [26]. The latest ESPGHAN guidelines show that the patient with IBD must not be subject to particular food restrictions and that an individual diet must be assessed on the basis of the nutritional imbalances of the individual patient, in order to avoid aggravating the symptoms [26]. Several other diets have been suggested for management of IBD, including the low-FODMAPs diet, a gluten-free diet, and a vegan diet [26]. Nevertheless, none of these diets should be recommended to children and adolescents with IBD at present [26]. On the other hand, in recent years, much attention has been given to the role of MD in IBD [19][21][26].

Multiple research studies agree on its preventive and therapeutic role [9][27][28][29][30][31][32]. Initial interest in this diet scheme arose from the observation of lower rates of chronic and degenerative diseases, such as IBD, in the Mediterranean region compared to Western countries [9]. There are several proposed mechanisms of action to explain the association between IBD and MD. These proposed mechanisms involve the direct effect of dietary antigens, the alteration of gut permeability, and the autoinflammatory response of the mucosa due to changes in the microbiota [27]. Several papers analysed the connection between single dietary elements and IBD development; to summarise, many studies agreed that a high intake of animal protein, linoleic acid and sweets and a low intake of fruits and vegetables were all risk factors for IBD development [28][29][30]. However, only a few of the studies focused their attention on the role of specific dietary patterns, such as MD in IBD prevention [28][29][30]. In 2016, the Epic Study was the first major European case-control study to analyse the link between adherence to the Mediterranean diet and the risk of developing UC or CD [31]. Between 1992 and 2000, the EPIC-IBD study gathered a group of 366,351 healthy people (male and female, aged 20–80 years) from seven European countries [31]. During the follow-up, which lasted from 2004 to 2010, incident cases of IBD were tracked down, and for each case, four controls were chosen [31]. For all the people enrolled, food-frequency questionnaires were administered at baseline, and an adapted Mediterranean-diet score (aMED) was calculated, to establish MD adherence [31]. Three distinct dietary patterns were separately generated for UC and CD [31]. The study showed that a diet rich in sugar and soft drinks was directly associated with UC risk when the disease was diagnosed after at least two years of diet recording; nevertheless, this bond failed if the vegetables intake was high, as if they offset each other [31]. On the other hand, the study was not able to prove any connection between diet and CD risk [31]. Subsequently, Khalili et al. gathered a group of 83,147 Swedish middle-aged male and females born between 1914 and 1952 and calculated for each of them a modified Mediterranean-diet score (mMED); incident cases of UC and CD were verified from the Swedish Patient Register [9]. Statistical analysis of this prospective cohort study showed that a higher mMED score was linked to a lower risk of developing CD ($p = 0.02$). Moreover, the relationship between diet and CD was confirmed, as people with poor adherence to the MD had an adjusted population-attributable-risk of 12% for later onset CD [9]. However, contrary to the work of Racine et al., no association was demonstrated between the mMED score and UC [9][31]. In addition to disease prevention, the MD seems to play a pivotal role in the management of the disease itself [32]. Its anti-inflammatory and antioxidant properties and its capacity to downregulate inflammatory pathways led researchers to investigate its effect on plasmatic and faecal inflammatory markers, such as CRP, FC and interleukins [32]. Several studies confirmed an anti-inflammatory role for MD in the healthy population, as observed in the study by Sureda et al., which concluded that a high adherence to the MD pattern was directly associated with a better profile of plasmatic inflammatory-markers (higher levels of adiponectin and lower levels of hs-CRP, TNF-α, leptin and PAI-1), particularly in

healthy male adults [33]. In a six-week pilot study, Marlow et al. highlighted a small reduction of established biomarkers, such as CRP (statistically non-significant) and an altered expression of 3551 genes analysed by transcriptomics [34]. Other interesting data that emerged from this manuscript was the fact that MD could influence the microbiota composition, leading to an increase in *Bacteroidetes* and *Clostridium* clusters and to a decrease in *Proteobacteria* and *Bacillaceae*, as was seen in the normal microbiome of non-IBD patients [34]. Regarding this last topic, Illescas et al. also confirmed the protective role of the microbiota associated with the MD [35]. They concluded that following an MD lead to an increase in beneficial anti-inflammatory bacterial species, in contrast to what happens in IBD patients [35]. Moreover, Chicco et al. evaluated the impact of a short-term dietary intervention based on the adoption of the MD in 142 adult patients with a diagnosis of IBD for at least 6 months and in active follow-up [36]. After six months of a hypocaloric MD properly prescribed by a nutritionist, they observed a statistically significant reduction in BMI (UC patients $p = 0.002$, CD patients $p = 0.023$), waist circumference (CD patients $p = 0.04$) and a substantial improvement of liver steatosis (UC patients $p = 0.016$ and CD patients $p < 0.001$). Interestingly they also noticed a reduction of inflammatory markers such as CRP (UC patients $p = 0.013$, CD patients $p = 0.035$) and FC (UC patients $p = 0.049$, CD patients $p = 0.035$) [36]. This prospective interventional study also highlighted an important increase in quality of life ($p < 0.001$), which is often compromised in IBD patients. Accordingly, an MD has also been associated with an improvement in nutritional status and with a reduction of pro-inflammatory visceral fat, when associated with energy restriction [36]. This feature can be very interesting, considering that IBD patients have been shown to have an increased risk of developing non-alcoholic fatty liver disease (NAFLD) and metabolic syndrome. The MD could also have a therapeutic role in the post-surgical phase of UC patients who undergo pouch surgery. In fact, as shown in the study of Godny et al., high adherence to an MD was directly associated with lower faecal-calprotectin levels and, in the long run, lower risk of developing pouchitis [37].

Other studies focused instead on the self-perceptive quality of life of IBD patients and its correlation with a healthy and balanced lifestyle which includes adherence to the MD [5][10]. For example, Ruano et al. reported a firm association between MD adherence and some aspects of a self-perceived mental and physical quality of life [38]. The latter can also be explained by the fact that a reduction in BMI, waist circumference and a controlled healthy lifestyle might influence the perception of quality of life of these patients. A recent study by Papada et al. tried to analyse the relationship between adherence to an MD and the quality of life of IBD patients. In a cross-sectional study, they used the MedDiet score to assess patients' dietary habits and highlighted a statistically significant correlation between adherence to an MD and improved quality of life; collaterally they also noticed an improvement in intestinal symptoms correlated with IBD ($p = 0.008$) [5]. Following a healthy lifestyle such as the MD might lead to an improvement of life quality, but can also determine a mortality reduction in patients affected by CD and UC, as seen in the work of Lo et al. [10]. Similarly, Vrdoljak et al. investigated the adherence to an MD in 94 patients aged between 18 and 65 years with an IBD-diagnosis for at least 1 year. They observed that only nine participants fulfilled the criteria for MD adherence, and all of them were male ($p = 0.0021$) [19]. On the other hand, most of the population (90.4%) considered that proper nutrition might play an important role in their health and agreed that a more controlled and better diet could reduce their IBD symptoms [19]. Indeed, most of the participants expressed their will to expand their nutritional knowledge if proper educational programs were proposed [19]. Following this example, Taylor et al., in their single-centre cross-sectional analysis, suggested the use of an MD-adherence questionnaires, such as the thirteen-item PREDIMED Mediterranean diet score to identify pro-inflammatory dietary schemes, in order to modify the patient's dietary scheme and ameliorate their dietary intake [39]. Although many studies have been published for the adult population, little is known about the paediatric population. D'Souza et al. analysed the preventive role of diet in the paediatric population in their case-control study, trying to determine the connection between certain dietary patterns and risk of CD in Canadian children [40]. In this published paediatric case-control study, a positive association with CD was found in girls with a diet rich in meats, fatty foods, and desserts, whereas a high intake of vegetables, fruits, olive oil, fish, grains, and nuts was inversely associated with CD in both sexes [40]. One published manuscript focused on the role of environmental factors in IBD and showed that the Mediterranean dietary pattern may exert a protective role in the development of IBD [41]. Researchers found that low adherence to an MD was higher for CD and for UC when compared with controls [41]. In addition, El Amrousy et al. proved that the reduction of inflammatory biomarkers in the paediatric population was similar to the adult one if adherence to MD was high [42]. They analysed the positive effects of an MD in IBD patients with active CD and UC; after a 12-week diet, the clinical remission rate, as well as most inflammatory markers (CRP, calprotectin, TNF- α, IL17, IL 12 and IL13) were significantly improved, in contrast to the patients who followed their regular diet [42]. Researchers investigated the relationship between inflammation and dietary behaviours in IBD children, in particular adherence to an MD, in comparison with a healthy control group [43]. It is observed that there was a different kilocalorie intake between IBD patients and the control group ($p = 0.024$), and comparing UC to CD, there emerged a significant difference in protein intake ($p = 0.047$), iron intake ($p = 0.023$) and vitamin D ($p = 0.044$), which was higher in CD patients. Interestingly, researchers found a significant association between adherence to an MD and a lower level of FC in IBD patients ($p = 0.027$) [43].

Table 1 summarizes the main studies regarding the impact of the MD on IBD.

Table 1. Main characteristics of the studies regarding the impact of a Mediterranean diet on Inflammatory Bowel Disease.

Study	Type of Study	Population	Aim	Results
Marlow et al. [34], 2013	Prospective study	Eight adult patients with active stable Crohn's disease (six females and two males, aged between 31 and 60 years).	Evaluation of changes in inflammation and in the gut microbiota after administration of a 6-week Mediterranean-inspired diet.	Small reduction of inflammatory biomarkers (non-statistically significant). A total of 3551 genes had significantly ($p < 0.05$) altered expression as a result of the dietary intervention. Normalising trend of the microbial gut composition.
Racine et al. [31], 2016	Prospective study	A total of 366,351 adult patients (20–80 years). During the follow-up, 117 patients developed CD, while 256 developed UC.	Evaluate the connection between adherence to the MD, assessed by an adapted Mediterranean diet score (aMED), and the risk of developing UC and CD.	A diet rich in sugar and soft drinks was positively associated with UC, when diagnosed at least 2 years after diet recording. No association between any dietary pattern and CD risk.
Sureda et al. [33], 2018	Observational study	A total of 598 healthy patients (364 adolescents and 234 adults).	Evaluate the connection between inflammatory biomarkers and MD adherence (using food-frequency questionnaire (FFQ) and two 24 h diet recalls).	High adherence to the MD was associated with a better inflammatory-biomarker profile.
Godny et al. [37], 2019	Prospective observational study	A total of 153 adult patients with UC, who underwent pouch surgery.	Evaluate the connection between adherence to the MD, using FFQ and inflammatory markers (CRP and faecal calprotectin) and pouchitis-disease-activity index (PDAI).	MD-adherence was higher in patients with inactive disease. High MD-adherence was inversely associated with elevated calprotectin and lower risk of developing pouchitis in the years after surgery.
Papada et al. [5], 2019	Cross-sectional study	A total of 86 CD adult patients (45 in remission and 41 in relapse).	Evaluate the adherence to MD in patients with CD and assess the role of MD in improving intestinal symptoms and inflammatory markers.	Adherence to MD was greater in patients with inactive disease. The MedDiet score correlated positively with the inflammatory bowel disease questionnaire (IBDQ), and negatively with disease activity.
Khalili et al. [9], 2020	Prospective study	A total of 83,147 patients.	Evaluate the connection between MD adherence, using semiquantitative food-frequency questionnaire (SFFQ) and IBD risk.	A higher mMED score was linked to a lower risk of developing CD. People with poor adherence to an MD had an adjusted population-attributable risk of 12% for later onset CD. No association was proved between UC and mMED.

Study	Type of Study	Population	Aim	Results
Vrdoljak et al. [19], 2020	Cross-sectional study	A total of 94 adult patients (44 in the UC group and 50 in the CD group) with IBD diagnosed for at least 1 year.	Investigate nutritional habits and dietary attitudes in IBD patients, in addition to assessing their adherence to the MD.	Only nine participants fulfilled criteria for MD adherence, all of them male. A total of 86.2% of subjects considered certain foods as responsible for exacerbating their gastrointestinal symptoms. A strict correlation between Mediterranean diet serving score (MDSS) and HDL cholesterol levels was observed. Most of the population (90.4%) considered that proper nutrition plays an important role in their illness and quality of life, and considered that a more controlled and better diet could reduce their IBD symptoms.
Chicco et al. [36], 2021	Prospective, Interventional study	A total of 142 patients (18 years old and older) with diagnosis of IBD for at least 6 months in active follow-up.	Impact of short-term dietary intervention based on the adoption of MD on anthropometric parameters, serum lipid profile, liver function and intestinal disease activity.	Improvement of anthropometric measures (BMI and waist circumference reduction), decrease in fat body mass and increase in lean body mass (no statistical significance). Significant improvement of liver steatosis and liver function (reduction of alanine aminotransferase and gamma-GT within the reference range). Improvement of inflammatory biomarkers and of quality of life.
Taylor et al. [39], 2018	Single-centre cross-sectional study	A total of 67 patients affected by inactive CD (mean age of 45).	Investigate micro- and macronutrient intake and dietary attitudes in CD patients, including their adherence to the MD, and compare them to a representative of healthy individuals.	Patients with CD had multiple vitamin and micronutrients deficits and lower MD adherence, compared with healthy controls.
D'Souza et al. [40], 2008	Case-control study	A total of 149 cases of children (2.6–20 years) with CD, 251 controls.	Obtain gender-specific dietary patterns and calculate their associated risk for CD.	Dietary pattern rich in vegetables, fruits, dairy products, eggs, olive oil, dark breads, grains, fish and nuts was negatively associated with CD, for both boys and girls.
Strisciuglio et al. [41], 2017	Case-control study	A total of 264 patients (1–18 years); 102 children with CD and 162 children with UC, and 203 healthy controls.	Evaluate the role of environmental factors in IBD development. *	Low adherence to MD was higher for CD and for UC when compared with controls.
Strisciuglio et al. [43], 2020	Single-centre cross-sectional study	A total of 125 children with a diagnosis of IBD in clinical remission and 125 healthy controls.	Assess dietary intake through a 3-day food diary and Mediterranean-diet-quality index for children and adolescents (KIDMED); evaluate their adherence to MD and investigate the relationship between inflammation and dietary behaviours.	IBD patients and healthy controls had an intermediate adherence to MD. IBD group had a higher kilocalorie intake. Significant association between adherence to MD and a lower level of FC in IBD patients. In comparing CD and UC, a higher intake of protein, iron and vitamin D in CD patients emerged.

Study	Type of Study	Population	Aim	Results
El Amrousy et al. [42], 2022	**Prospective randomised study**	**A total of 100 patients (12–18 years) with mild-moderately active CD or UC. Group I (26 patients with active CD and 24 patients with active UC) received Mediterranean Diet for 12 weeks. Group II (28 patients with active CD and 22 patients with active UC) followed its regular diet.**	**Evaluation of clinical remission, clinical scores (PCDAI and PUCAI) and inflammatory biomarkers (CRP, calprotectin, TNF-alfa, IL17, IL12, IL13).**	**Most of the patients reached clinical remission after a 12-week diet. Clinical scores (PCDAI and PUCAI) and inflammatory markers were significantly improved in patients in Group I (all cytokines were decreased, except IL10).**

* Among the various areas examined in the study, researchers focused on dietary habits.

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